Frederic Shapiro

Pediatric Orthopedic Deformities

Volume 1

Pathobiology and Treatment of Dysplasias, Physeal Fractures, Length Discrepancies, and Epiphyseal and Joint Disorders

Springer

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To my wife. Carol Ann Satler

Preface

The current edition of *Pediatric Orthopedic Deformities: Basic Science, Diagnosis, and Treatment* has been increased to three volumes, updating and expanding the presentation of skeletal deformation in the growing child. It demonstrates throughout how specific biological and mechanical abnormalities can affect normal bone and cartilage development and lead to problematic deformation. The two main premises of the book remain the same however: (1) current orthopedic treatments of growth deformities of the developing skeleton are most effective when based on an understanding of and relationship to the underlying pathobiology and (2) future treatments can be developed best with deeper understanding of and more specific relationships to the underlying pathobiology.

Volume 1, Chap. 1 (Developmental Bone Biology) describes skeletal development as outlined by several investigational approaches including: histology at the light and electron microscopic levels; molecular biology outlining the wide array of gene and molecular controls for skeletal tissue differentiation, 3- and 4-dimensional limb bud axial differentiation and growth, and synthesis of structural macromolecules; mineralization; mechanical–biophysical effects on the developing skeleton; and radiological parameters of growth such as appearance of secondary ossification centers and times and patterns of physeal fusion.

Chapter 2 (Overview of Deformities) is new and describes: founders of the field of pediatric orthopedics, which essentially began with several individuals specifically addressing the major musculoskeletal deformities of the developing child; 34 basic principles regarding pediatric orthopedic deformity; descriptive terminologies for bone and joint deformities; correction of deformities by spontaneous, non-operative and operative means with an overview of each of the clinical methods and techniques used for the treatment groups; a detailed molecular and histological description of biological tissue repair mechanisms for direct, primary, and endochondral cortical bone repair, metaphyseal cancellous bone repair, articular cartilage (full and partial thickness) repair, and physeal cartilage repair; and derangements of the repair process. Tendon, muscle, and peripheral nerve are also discussed regarding structure and injury and repair mechanisms.

Chapter 3 (Skeletal Dysplasias) discusses the skeletal dysplasias concentrating on clinical and radiographic descriptions of the entities, molecular abnormalities, histopathology, the lethal variants, orthopedic deformities by region and by specific disease entities, and orthopedic treatments.

Chapter 4 (Bone and Joint Deformity in Metabolic, Inflammatory, Neoplastic, Infectious, and Hematologic Disorders) reviews entities known to be associated with pediatric orthopedic deformities from the perspective of: the pathobiology of the disorder, the pathoanatomy of deformation, and the principles of medical and orthopedic management. The epiphyseal, metaphyseal, and joint abnormalities are reviewed for: rickets, juvenile rheumatoid arthritis, benign and malignant neoplasms and pyogenic and tuberculous infections (which concentrate at the epiphyseal-metaphyseal regions), and hematologic disorders such as hemophilia.

Chapter 5 (Epiphyseal Growth Plate Fracture-Separations) describes the relationship of these injuries with the possible growth deformities. These represent the main subset of childhood fractures contributing in a major way to limb deformity.

The cell biology and histopathology of growth plate injuries are reviewed, the commonly used pathoanatomic classifications are explained, and the presence or absence of growth sequelae are outlined. Each major physis is reviewed regarding clinical management and results. A pathophysiologic approach is outlined which provides a more dynamic and biological understanding and classification of these injuries at the cell and the tissue level. Imaging modalities beyond plain radiographs, such as magnetic resonance imaging, computerized tomographic scanning, and ultrasound, provide information on blood supply and tissue injury planes, the main determinants of negative growth sequelae. Management is detailed to eliminate, minimize, or if necessary treat transphyseal bone bridges.

Chapter 6 (Lower Extremity Length Discrepancies) outlines: the natural history of specific disorders leading to discrepancies, negative sequelae of discrepancies, methods projecting eventual discrepancies at skeletal maturity, developmental patterns of discrepancies, and techniques and timing for shortening, lengthening. and bone bridge resection. Femoral overgrowth following diaphyseal fractures is reviewed and updated following immediate casting or intramedullary nailing.

Volume 2 will assess regional deformities of the developing lower extremity. The developmental biology and histopathology at each region are stressed and related to treatment interventions. Chapters are devoted to: Developmental Dysplasia of the Hip; Legg-Calve-Perthes disease; Slipped Capital Femoral Epiphysis (and other causes of coxa vara); Degenerative Joint Disease following childhood hip disorders (femoral-acetabular impingement); Developmental Disorders of the Knee; Club Feet (and other deformities of the foot and ankle); and Rotational and Angular Deformities of Femur and Tibia.

Volume 3 will outline the developmental biology and histopathology of the vertebrae, ribs and spinal cord. Chapters will assess: 1. Spinal Deformities including: (a) congenital and idiopathic scoliosis, (b) kyphosis, (c) spondylolisthesis and d) cervical abnormalities; and 2. Neuromuscular Disorders and their spinal, hip, and limb deformities for: (a) cerebral palsy, (b) the muscular dystrophies and structural myopathies, mitochondrial and metabolic myopathies, myotonic disorders, spinal muscular atrophy, Friedreich Ataxia, and the peripheral neuropathies, (c) spinal cord abnormalities of Meningomyelocele, diastematomyelia, transverse myelitis, tethered cord, and syringomyelia, and (d) brachial plexus injuries.

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Developmental Bone Biology

1

1.1 Overview of Bone Development

During the embryonic period, limb buds filled with undifferentiated mesenchymal cells form from the lateral side walls. The earliest sites of skeletal formation are characterized by condensation or close packing of mesenchymal cells followed by early cartilage differentiation. Each of the long bones is preformed as a cartilage model. Bone tissue is then deposited beginning in the middle of the model on the calcified cartilaginous core using the endochondral ossification mechanism and directly by the surrounding periosteum using the intramembranous ossification mechanism. Bone deposition progresses toward each end with intramembranous bone formation at the periphery slightly in advance spatially of internally or centrally positioned endochondral bone formation. The proportional involvement of each of the three regions of a developing bone—diaphysis, metaphysis, and epiphysis—is established by the early fetal stage and remains more or less unchanged until skeletal maturity. The central part of the bone is the diaphysis or shaft; the furthermost bone extension of the diaphysis is the metaphysis; and the developing cartilaginous end of each bone is the epiphysis.

Normal bone development occurs in conjunction with the proliferation and differentiation of cells, the synthesis and interaction of specific molecules, and the generation of intrinsic and extrinsic biophysical forces. Primary genetic blueprints and secondary epigenetic and inductive phenomena lead to the patterns characteristic of each bone throughout the skeleton. A developing long bone consists of the ***epiphyses*** and ***metaphyses*** at each end and the ***diaphysis (shaft)*** in between. These regions are established by the middle of the embryonic stage and go through proportional changes in size until skeletal maturity. The epiphyses are responsible for the transverse and spherical growth of the ends of the bone, the shaping of the articular surfaces, and the longitudinal growth of the metaphyses and the diaphysis. A small amount of longitudinal growth also occurs with interstitial expansion of the epiphyseal cartilage, including the undersurface of the articular cartilage. Each epiphysis, formed initially completely in cartilage, subsequently differentiates into three histologically distinct regions. These are: (i) the cartilage at the outermost boundary of the epiphysis adjacent to the joint space that is the ***articular cartilage***, (ii) the cartilage adjacent to the metaphysis that forms the ***physis (growth plate, epiphyseal growth plate)***, and (iii) the cartilage between the articular cartilage and the physeal cartilage referred to as the ***epiphyseal cartilage***, which will form a ***secondary ossification center*** after vascular and osteoprogenitor cell invasion. The cells and matrices of the ***perichondrial ossification groove of Ranvier*** (the terminal extension of the periosteum) surround the physis and part of the metaphysis and are an integral part of long-bone development.

The growth plate components go through a sequential process of cell proliferation, synthesis of extracellular matrix, cell hypertrophy, mineralization of the matrix, localized vascular invasion accompanied by osteoprogenitor cells, and apoptosis. These highly coordinated activities lead to longitudinal bone growth and bone formation at the physeal–metaphyseal region and encompass the mechanism of ***endochondral ossification***. The growth cartilage replenishes itself through the germinal zone and continually is replaced with bone at the physeal–metaphyseal junction. With these coordinated events, the length of the entire bone increases; the physes at either end are displaced progressively further away from the center of the bone, and the physis itself maintains the same height throughout the growth period. At the same time, there is radial growth of the diaphysis and parts of the metaphysis by ***intramembranous bone formation*** with direct apposition of cortical bone by osteoblasts from the inner cambial layer of the periosteum. This is coordinated closely with resorption of bone by osteoclasts on the inner cortical endosteal surfaces and lateral metaphyseal surfaces to maintain the relative proportions of the marrow cavity to the cortices and the overall shape of the bone as it grows. We have outlined 16 stages with several additional substages of long bone and

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Table 1.1 Early observations on bone growth

1727	Bones grow in length by the addition of new tissue at their ends. (Hales)
1731–1736	There are two mechanisms of bone formation, one occurring directly in a membrane (intramembranous ossification) and one via pre-existing cartilage (endochondral ossification). Vascularization immediately precedes bone formation in cartilage. (Nesbitt)
1736	Growing bone is stained red by madder (alizarin) in diet. (Belchier)
1739–1743	A long bone grows in length from its ends and in thickness by formation of new bone on its outer surface. The osteogenic function of the periosteum thickens the bone on its outer surface, based on madder feeding studies. (Duhamel)
1740	Increased diameter of marrow cavity with growth is due to absorption of pre-existing bone internally. Bone development includes both bone deposition and bone absorption. (Hunter)
1815	Interplay of cartilage and bone formation in long bone development. Cartilage vascular canals in epiphyses. Gross and crudely magnified evidence of physeal cartilage. Vascularization of inner periosteum precedes earliest site of bone formation. Cartilage model determines the shape of the future bone and establishes ossification within it. Mechanical pressure variously modified is the principal agent in effecting progressive changes of structure in growing bone. (Howship)
1841–1847	Bone is formed in the periosteum, grows in thickness by superimposing new layers externally, grows in length by adding new layers at the growth cartilage at each end, and has the marrow cavity formed by resorption of the inner bone layers. There is formation–resorption– reformation of the bone with growth accompanied by constant change in bone substance. (Flourens)
1850	Resorption of bone as part of developmental sequence is mediated by osteoclasts. (Kolliker)
1852–1853	Tissue at epiphyseal–diaphyseal (metaphyseal) junction is characterized by differing layers as determined by careful gross and early lower power microscopic examination. (Broca; Tomes and de Morgan)
1858	Detailed microscopic–histologic structural recognition of physeal layers and endochondral sequence. (Müller)
1860	Bone description as a **tissue** (bone cells plus calcified matrix) and as an **organ** (encompassing bone tissue, marrow, periosteum, articular and epiphyseal cartilage, vessels, and nerves). Detailed cellular description of physeal sequence including hypertrophic chondrocyte fate. (Virchow)
1864	Bone forming cells first referred to as osteoblasts (Gegenbaur)

epiphyseal development to show the timing and coordination of the growth process. The endochondral and intramembranous ossification sequences are involved together not only in long bone formation but also in formation of the pelvis, vertebrae, sternum, ribs, scapula, and clavicle. Skull and facial bone formation and repair are similar but have slight differences owing to origin from differing embryonic lines and are outside the scope of this review. An overview of early observations on bone growth is presented in Table 1.1.

1.1.1 Epiphysis

The term epiphysis refers to the entire developing end of the bone [1, 2]. The epiphyses are responsible for long bone longitudinal growth, for transverse growth at the ends of the bone, and for the shape of the articular surfaces. This region is formed initially completely in cartilage and subsequently subdivides during development into three histologically distinct regions: (a) the cartilage immediately adjacent to the joint, referred to as articular cartilage; (b) the cartilage adjacent to the metaphysis, referred to variously as the growth plate, the epiphyseal growth plate, or the physis. It is the functionally and cytologically specialized region where the bulk of longitudinal growth occurs and encompasses the area from the reserve zone of cells to the end of the hypertrophic cell layer; and (c) the cartilage between the articular cartilage and the growth plate cartilage, referred to as the epiphyseal cartilage. This is eventually transformed entirely into bone and marrow following the appearance and enlargement of what is variously referred to as the secondary ossification center, the bony nucleus, the ossific nucleus, or the bony epiphysis (Fig. 1.1). The epiphysis is sometimes referred to as the chondroepiphysis, but use of this term should be restricted to the time prior to formation of the secondary ossification center.

1.1.2 Metaphysis

The metaphysis lies between the lower part of the physis and the outer reaches of the diaphysis. It is the area where the endochondral ossification process leads to bone tissue formation. Cells and capillaries penetrate through the metaphysis, entering into the spaces at the lowermost 3–4 levels of hypertrophic chondrocytes of the physis, forming in older terminology the “osteogenic–degenerative zone of the physis” or currently the osteogenic–apoptotic zone. Undifferentiated mesenchymal cells, preosteoblasts, and osteoblasts accompany the vessels, forming a cellular layer on the remaining calcified longitudinal septae of cartilage, covering them with osteoid tissue as part of the bone synthesis process. The metaphyseal cortical bone is formed by the

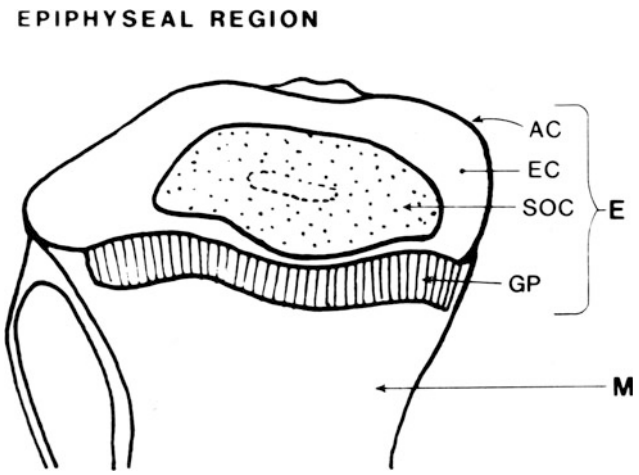


Fig. 1.1 The histologic structure of the epiphysis of the proximal tibia is illustrated. The entire developing end of the bone from the articular cartilage surface to the last cells of the hypertrophic zone of the growth plate is the epiphysis (*E*). This encompasses 3 regions that are initially cartilage: (a) the articular cartilage (*AC*), (b) the growth plate (*GP*), also referred to as the epiphyseal growth plate or the physis and (c) the epiphyseal cartilage (*EC*) which refers to the cartilage mass between the articular cartilage and the growth plate cartilage. It is within the epiphyseal cartilage that the secondary ossification center (*SOC*), also referred to as the bony nucleus, the ossific nucleus, or the bony epiphysis, forms and expands. (Reprinted with permission from Shapiro F, Epiphyseal Disorders. New Engl J Med. 1987;317:1702–1710. Copyright 1987 Massachusetts Medical Society)

coalescence of peripheral endochondral trabecular bone from the physis with intramembranous bone from the inner osteogenic (cambial) layer of the periosteum.

1.1.3 Diaphysis

The diaphysis lies between the two metaphyses and is the shaft of the bone. During the early stages of development it is composed within of endochondral bone but eventually with growth and resorption the marrow space predominates. The outer part of the diaphysis is composed of cortical bone. The cortex is formed and widened by the inner cambial layer of the periosteum and maintains its relative thickness by resorption by osteoclasts on its inner surface.

1.1.4 Bone Tissue Formation

In bone tissue formation osteoblasts synthesize and deposit type I collagen, the main protein constituent of bone matrix, in only two basic conformations, ***woven*** and ***lamellar***. In woven bone the collagen fibrils are randomly oriented while in lamellar bone they are clustered in parallel arrays. The fibrils in lamellar bone are not invariably parallel to each other and to the longitudinal axis; rather they alternate in adjacent layers between longitudinal and circular orientations in an orthogonal pattern. These matrix orientation processes are repeated in normal bone development, in bone repair utilizing any of several mechanisms, and in several pathologic conditions. Bone is formed by two mechanisms, endochondral ossification and intramembranous ossification.

1.1.4.1 Endochondral Ossification

The cartilage models of a developing bone and ultimately the epiphyses form bone by a mechanism referred to as endochondral bone formation. The major characteristics of this mechanism of bone formation involve growth of the cartilage by interstitial expansion involving chondrocyte proliferation, matrix formation, and chondrocyte hypertrophy. At a certain stage of development, the cartilage matrix adjacent to the hypertrophic cells mineralizes, there is vascular invasion of the lacunae in which the hypertrophic cells reside, and this vascular invasion is accompanied by mesenchymal cells which shortly differentiate to osteoblasts and synthesize a bone matrix on the calcified cartilage cores. The calcified cartilage is thus serving as a scaffold on which bone is deposited initially at the center of the developing cartilage model of the bone at the primary center of ossification, eventually at the lower regions of the physis merging into the metaphysis and within the epiphyseal cartilage where the bone formed is referred to as the secondary ossification center. The epiphyseal cartilage immediately surrounding the secondary ossification center and undergoing chondrocytic hypertrophy is referred to as the physis of the secondary ossification center.

1.1.4.2 Intramembranous Ossification

Bone formation is also characterized by a mechanism referred to as intramembranous ossification which occurs in long bone formation from the surrounding periosteum. In this mechanism, bone tissue is formed directly from mesenchymal cells without the mediation of a cartilage scaffold phase. The periosteum has a specific structure with two layers, an outer fibrous layer and an inner osteogenic or cambial layer. The inner cambial layer also displays an organized cellular differentiation pattern although it is not as structurally specific as the physis. The outermost part of the inner layer is composed of undifferentiated mesenchymal cells; these then begin to secrete and surround themselves with an osteoid matrix as they differentiate from pre-osteoblasts to osteoblasts; further toward the cortex, osteoblasts line the surface of the bone to synthesize osteoid preferentially on the bone surface. When the osteoid matrix surrounds a cell completely and then becomes mineralized, that cell is referred to as an osteocyte.

1.1.5 Perichondrial Ossification Groove of Ranvier

In all long and most flat bones both mechanisms of bone formation, endochondral and intramembranous, are present. They relate intimately and specifically to one another at the periphery of the growth plate in a region referred to as the perichondrial ossification groove of Ranvier (Fig. 1.2). The tissues comprising the intramembranous ossification mechanism circumferentially ensheathe and support the physeal cartilage at this area. A circumferential groove indenting the cartilage is present whose deepest part is opposite the epiphyseal cartilage/physeal cartilage junction. It contains three tissue components: (a) an outer fibrous layer which is continuous with the outer fibrous layer of the periosteum and inserts beyond the physeal region into the epiphyseal cartilage; (b) a zone of densely packed cells which is a continuation of the inner cambial layer of the periosteum and is present into the depths of the groove as far as the resting zone of physeal cartilage. This collection of dense cells synthesizes osteoid and intramembranous bone directly; and (c) a collection of loosely packed cells between the outermost reaches of the zone of dense cells and the fibrous tissue layer that adds chondrocytes to the periphery of the epiphysis just beyond the physis itself. The intramembranous bone synthesized by the tissues within the groove region is sometimes referred to as the bony bark of Lacroix. It is frequently discontinuous with the cortical bone of the diaphysis and metaphysis in those areas where the metaphyseal cutback zone is extensive. The perichondrial ossification groove of Ranvier with its fibrous, chondroprogenitor, and osteoprogenitor cells is an integral part of the epiphyseal region [1].

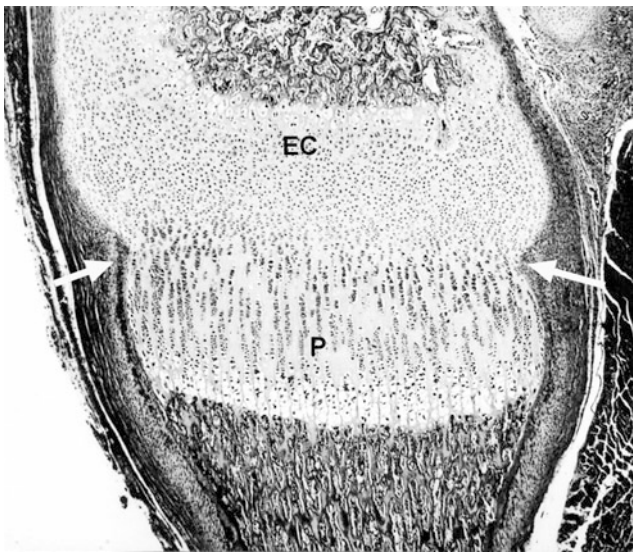


Fig. 1.2 Photomicrograph of the developing end of a rabbit metatarsal is shown. The secondary ossification center is shown centrally at the *top*. EC-epiphyseal cartilage; P-physeal cartilage. The two closed white *arrows mark* the perichondrial ossification groove of Ranvier. Just below the *arrows* at the periphery of the physeal cartilage is the terminal extent/origin of the cortex which is formed by the intramembranous ossification mechanism. The metaphyseal bone just *below* the physis is formed by the endochondral ossification mechanism as is the bone of the secondary ossification center. (Reprinted with permission from Shapiro et al. Organization and cellular biology of the perichondrial ossification groove of Ranvier. J Bone Joint Surg Am. 1977;59A:703–723)

1.1.6 Cellular Components

A brief definition of the cells present in bone follows.

1.1.6.1 Undifferentiated Mesenchymal Cells

The developing tissues of the skeleton form from undifferentiated mesenchymal cells. These are present initially in the limb buds prior to any histologic developmental differentiation. They are uniform appearing cells histologically with a nucleus and cytoplasm not yet surrounded by any specific matrix. They have the potential for differentiation with the appropriate stimulus along various tissue producing lines including becoming chondrocytes to produce cartilage, osteoblasts to produce bone, fibroblasts to produce fibrous tissue, adipocytes to produce fat, or myoblasts to produce muscle.

1.1.6.2 Osteoblasts

Osteoblasts are active bone forming cells. They are characterized by an abundant cytoplasm filled with rough endoplasmic reticulum at the ultrastructural level. Some refer to the cell intermediate between the undifferentiated mesenchymal cell and the osteoblast as a pre-osteoblast. The cells are responsible for synthesizing large amounts of collagen primarily of the type I variety which accumulate to form the matrix of bone. We refer to two types of osteoblasts based on their topography [3]. The ***mesenchymal osteoblast*** is surrounded completely by randomly oriented collagen fibrils and is thus responsible for the synthesis of woven bone. The ***surface osteoblast*** lines up along the surface of pre-existing bone tissue and synthesizes collagen fibrils along the pre-existing surface in parallel array. The surface osteoblast is thus involved in the direct synthesis of lamellar bone. As bone synthesis proceeds the osteoblast becomes completely surrounded by matrix referred to as osteoid and when that matrix becomes mineralized, the encased cell is referred to as an osteocyte. An osteoblast-specific transcription factor has been identified [4–6]. The first osteoblast-specific transcription factor is Runx2 (Cbfa1), one of thethree vertebrate homologs of the drosophila runt and lozenge proteins. Cbfa1 appears to have features specific for early differentiation along the osteoblast line. Cbfa1 expression is initiated in the

mesenchymal condensations of the developing skeleton, is strictly restricted to cells of the osteoblast lineage, and is regulated by BMP7 and vitamin D3. These transcription factors are increasingly referred to as runx2 and runx3.

1.1.6.3 Osteocytes

Osteocytes are mature bone cells [7]. They reside in spaces referred to as lacunae and their cell processes are connected to one another with the processes being present in canals passing through the matrix and referred to as canaliculi. Each osteoblast and osteocyte has numerous cell processes passing from it which serve to relate to cell processes from adjacent osteoblasts and osteocytes. These cell processes link up via the gap junction mechanism.

1.1.6.4 Chondroblasts and Chondrocytes

Chondroblasts and chondrocytes are cells responsible for the synthesis and maintenance of cartilage tissue. The transcription factor Sox9 is required for mesenchymal differentiation into chondrocytes and subsequent maintenance and maturation of chondrocytes. It is considered to regulate the earliest stage of the chondrocyte line. The cells surround themselves with a matrix composed primarily of type II collagen although there are also considerable amounts of type IX, X, and XI collagens and a large array of proteoglycans. Cartilage has a high proportion of water which composes approximately 80 % by volume of the tissue mass. It is difficult to make a histologic differentiation between chondroblasts and chondrocytes since both cell types are surrounded by cartilage tissue which unlike bone does not, except in rare incidences, mineralize. The chondroblast or chondrocyte has an oval shape with an appearance of the cytoplasmic wall by ultrastructure of mild scalloping. The collagen fibrils in cartilage are randomly arrayed and tend to be much thinner than those in bone averaging 10–20 nm in diameter.

1.1.6.5 Fibroblasts and Fibrocytes

These connective tissue cells are found in bone in the outer fibrous layer of the periosteum. They primarily synthesize type I collagen, although this does not mineralize.

1.1.6.6 Osteoclasts

The cell type responsible for resorption of bone and cartilage tissue is the osteoclast. It is not part of the mesenchymal series but has its origin from the hematopoietic system. The osteoclast is derived from hematopoietic cells of the monocyte–macrophage line. The osteoclast is a large, multinucleated cell formed by fusion of circulating monocytes. The same cell type can resorb cartilage or bone. If the cell is relating to cartilage exclusively then the term chondroclast can be used although the tendency is to simply use the term osteoclast in relation to resorption of either bone or cartilage. The osteoclast attaches itself to the underlying tissue by a characteristic structural mechanism evident only by ultrastructural assessment. The cell surface has a circular region free of organelles, which is referred to as the clear zone. This serves to attach the cell in a donut-like fashion to the underlying bone and cartilage. The cell surface within the rim of the clear zone is then thrown into innumerable folds or outpouchings forming what is referred to as the ruffled border. This mechanism serves to allow for increased secretion of lytic enzymes by the cell, with the extreme increase in extent of the cell border being caused by the ruffling phenomenon. The circumferential clear zone seals the environment and allows the lytic enzymes to be present in high concentration. It is these enzymes that are responsible for resorption of the underlying mineral and then matrix of the cartilage and bone.

Several factors affect osteoclast formation at differing stages of their development [8]. Transcription factors needed are Pu.1, an ETS domain-containing transcription factor expressed in the myeloid and B-lymphoid lineages; c-Fos, a protooncogene; and nuclear factor κB (NF-κB) [9]. Signaling molecules needed are M-CSF (macrophage colony-stimulating factor) and RANKL (receptor for activation of nuclear factor κ-B = RANK, L = ligand). The two major molecules exclusively essential for osteoclast function are macrophage colony-stimulating factor (M-CSF) and receptor for activation of nuclear factor κ-B (RANK) ligand, (RANKL), also known as osteoprotegerin ligand (OPGL) [8, 10]. The latter is a tumor necrosis factor family molecule identified as an osteoclast differentiation factor. Hematopoietic stem cells differentiate to monocyte/macrophage cells with the help of Pu.1 and M-CSF. The macrophages become monocular osteoclasts under the influence of C-Fos, NF-κB, M-CSF, and RANKL. RANKL stimulates both the fusion of mononuclear osteoclasts into multinuclear osteoclasts and their activation to resorption, with the latter activation also aided by microphthalmia transcription factor (MITF). Another molecule involved in the sequence is osteoprotegerin (OPG), a soluble receptor member of the tumor necrosis factor (TNF) receptor family. OPG actually inhibits osteoclast differentiation. Its ligand RANKL is a membrane bound TNF. RANKL binds to OPG allowing for osteoclast activation. RANK, a member of the TNF receptor superfamily, binds to RANKL and induces osteoclast differentiation.

1.1.7 Gap Junctions Linking Bone Cells

Gap junctions serve as areas for direct cell–cell communication either by electrical coupling or as points of passage for small low molecular weight messenger molecules [11]. They are intercellular channels formed by different membrane spanning proteins called connexins. Gap junctions are

observed linking the cell bodies of surface osteoblasts, linking surface osteoblast processes passing through newly synthesized osteoid with osteocyte processes, and linking osteocyte processes of adjacent cells within bone. Gap junctions are arranged in five basic shapes as defined by thin section transmission electron micrographs. These appear as linear, stacked linear, curvilinear, oval, and annular. Light microscopic sections of bone show the osteocytes to be present in round- to oval-shaped spaces in the bone referred to as ***lacunae*** which are linked to adjacent lacunae by multiple small canals referred to as ***canaliculi*** [11–16].The lacunae house the osteocytes and the canaliculi contain the ***osteocyte cell processes***. The lacunar–canalicular intraosseous system plays a key role in the transfer of nutritive fluid from blood vessels to bone cells. The common technique used for assessing bone by light microscopy involves hematoxylin and eosin staining of paraffin embedded sections. This technique does not demonstrate the lacunar–canalicular system well, and frequently scarcely shows it all. Plastic embedded, toluidine blue-stained sections outline well the organized lacunar-canalicular system in cortical bone [16]. The canaliculi link osteocytes and blood vessels extensively. A canaliculus passes into or away from a lacuna by a mean distance of 1.9 μm over the entire osteocyte perimeter [16]. Undifferentiated mesenchymal cells have no processes, as seen by transmission electron microscopy, but soon sprout a florid array of processes as differentiation to early mesenchymal osteoblasts proceeds. Osteoblast and osteocyte cell processes are packed with ***actin*** (7 nm) and ***intermediate filaments*** (10–11 nm) including vimentin that are continuous with those in the cell bodies [17]. Intercellular ***gap junctions*** are seen between surface osteoblasts, between osteoblasts and underlying osteocytes, between osteocyte cell processes in the canaliculi, and between osteocytes and the intracortical blood vessels. The woven bone canaliculi pass into the matrix in irregular, poorly defined pathways, but once cortical lamellar bone is formed, the canaliculi assume a more regular orientation passing between osteocytes either perpendicular or parallel to the longitudinal bone axis.

1.2 Embryology of the Limbs

1.2.1 Timing and Staging of Human Limb Development

The limb buds form as outpouchings of the embryo lateral plate mesoderm mass and are composed initially of undifferentiated mesenchymal cells uniformly packed throughout the entire extent of each bud and continuous with the undifferentiated mesenchyme of those regions which will become the shoulder and pelvis. There is a craniocaudal differential time gradient in development with the upper limb buds appearing in the lower cervical region in the human on day 24 and the lower limb buds in the lower lumbar region on day 28. By 33 days the hand plate is seen and by the end of the 6th week all upper and lower limb segments can be seen. Digital rays appear in the upper limb during the 6th week and in the lower limb during the 7th week. By the end of the 8th week components of each of the upper and lower limb bones are formed in cartilage. The embryonic period comprises the first eight post-ovulatory weeks with limb morphogenesis in the human occurring between the 4th and 8th weeks. At 8 weeks ossification of the humeral diaphysis begins, a time at which embryonic development is arbitrarily considered to be over and fetal development, which involves growth of fully established models, begins [18–23].

Embryonic staging terminology. The human embryonic phase is divided into 23 stages using the Carnegie system. This system, adopted in the early 1970s, is a refinement of what were previously referred to as Streeter's horizons. Much human embryologic and fetal study is categorized on the basis of the crown-rump length expressed in millimeters. The Carnegie staging system incorporates 23 stages and relates them to crown-rump length and age in post-ovulatory days. It is given in Table 1.2 listing some general correlations in the human embryonic periods along with developmental features particularly related to limb development. A more detailed outline of human limb development is listed in Table 1.3.

O'Rahilly [23] makes several points in terms of previous descriptions referable to embryonic staging in the human. These include: (1) The term horizon used by Streeter is no longer used and has been replaced by the term stage; (2) Roman numerals from the old Streeter classification have been replaced by Arabic numerals to denote what are now referred to as the Carnegie stages; (3) The most useful single measurement of an embryo or a fetus is the crown-rump (C-R) length which is expressed in millimeters (4) The crown-rump lengths used by embryologists agree closely with those determined ultrasonically; (5) The length of an embryo is not a stage and when used in a descriptive mode should simply be reported as, for example, 15 mm; (6) Stages within the embryonic period are expressed as post-ovulatory weeks or days; (7) Ages previously described by Streeter are incorrect for the human; and (8) the 23 stages of the Carnegie system refer to the embryonic period only, that is the 1st eight post-ovulatory weeks; no widely accepted staging system has been devised for the fetal period.

Table 1.2 Correlation of timing systems used for human embryos (Weeks 1 through 8)

Week	Day	Length (mm)	Carnegie stage	Features
1	1	0.1–0.15	1	Fertilization
	1-5-3	0.1–0.2	2	First cleavage divisions (2–16 cells)
	4	0.1–0.2	3	Blastocyst free in uterus
	5–6	0.1–0.2	4	Blastocyst hatches, begins implanting
2	7–12	0.1–0.2	5	Blastocyst fully implanted
	13	0.2	6	Primary stem villi appear; primitive streak develops
3	16	0.4	7	Notochordal process forms; gastrulation commences
	18	1–1.5	8	Neural plate and neural folds appear; primitive pit forms; vasculature begins to develop in embryonic disk
	20	1.5–2.5	9	Caudal eminence and first somites form; neuromeres appear in presumptive brain vesicle; primitive heart tube forming
4	22	2–3.5	10	Neural folds begin to fuse; cranial end of embryo undergoes rapid flexion; myocardium forms, and heart begins to pump; first two pharyngeal arches and optic sulci form
	24	2.5–4.5	11	
	26	3–5	12	Primordial germ cells begin to migrate from wall of yolk sac; cranial neuropore closes; optic sulci form
	28	4–6	13	Upper limb buds appear; caudal neuropore closes; urorectal septum begins to form; pharyngeal arches 3 and 4 form
				Dorsal and ventral columns begin to differentiate in mantle layer of spinal cord and brainstem; lower limb buds appear; septum primum and muscular ventricular septum begin to form in heart; spleen appears; ureteric buds appear; otic vesicle and lens placode appear; motor nuclei of cranial nerve appear
5	32	5–7	14	Spinal nerves begin to sprout; semilunar valves begin to form in heart; metanephros begins to develop; lens pit invaginates into optic cup; cerebral hemispheres become visible
	33	7–9	15	
				Hand plate develops; arterio-ventricular valves and definitive pericardial cavity begin to form; lens vesicle forms and invagination of nasal pit creates medial and lateral nasal processes; cranial nerve motor nuclei appear in ventral column of brainstem; sensory and para-sympathetic cranial nerve ganglia begin to form
6	37	8–11	16	Foot plate forms on lower limb bud; major calyces of kidney begin to form and kidneys begin to ascend; genital ridges appear
	41	11–14	17	Finger rays are distinct; bronchopulmonary segment primordia appear; septum intermedium of heart is complete; subcardinal vein system forms; nasolacrimal groove forms; cerebellum begins to form
7	44	13–17	18	Skeletal ossification begins; elbows and toe rays appear; intermaxillary process and eyelids form on face
	47	16–18	19	Trunk elongates and straightens; pericardioperitoneal canals close; septum primum fuses with septum intermedium in heart, minor calyces of kidneys are forming; urogenital membrane ruptures
8	50	18–22	20	Upper limbs bend at elbows
	52	22–24	21	Hands and feet approach each other at the midline
	54	23–28	22	Eyelids and auricles are more developed
	56	27–31	23	Definitive superior vena cava and major branches of the aortic arch established; gut tube lumen almost completely recanalized

Derived from Larsen (Ref. [19]) and O'Rahilly (Ref. [23])

1.2.2 Outline of Embryonic Development of Long Bones

Mesenchymal condensation has outlined the scapula and humerus of the upper limb and the pelvis and femur of the lower limb by the end of the 5th week. By early in the 6th week the developing models of the more distal limb bones are seen and chondrification has begun in humerus, ulna, and radius; by late in the 6th week carpal and metacarpal chondrification has begun; by mid-6th week femur, tibia, and fibula chondrify with tarsals and metatarsals by late 6th week; by the end of the 7th week all upper extremity

Table 1.3 Stages at which developmental features appear and events occur in human limbs

Feature	Stage for upper limb	Stage for lower limb
Limb bud	12	13
Length: width = 1.1	14	15
Apical ectodermal ridge	14–17	15–18
Hand plate/foot plate	15	16
Mesenchymal skeleton	15	16
Mesenchymal scapula/hip	16	15–18
Mesenchymal humerus, radius, ulna/femur, tibia, fibula	16	17
Chondrifying humerus/femur	16–17	17–18
Chondrifying radius/tibia	17	17–18
Chondrifying ulna/fibula	17–18	17–18
Finger rays/toe rays	17–18	18
Chondrifying metacarpus/metatarsus	17–18	18–19
Chondrifying carpus (except pisiform) tarsus	18–19	18–19
Chondrifying scapula/hip	18	19
Chondrifying proximal phalanges	18–19	19–21
Homogeneous shoulder and elbow/hip and knee	19	19
Homogeneous wrist/ankle	?	21
3-layered elbow/knee	?	21
Chondrifying middle phalanges	19–20	21
Chondrifying distal phalanges	20–21	21–23
3-layered wrist/ankle	21	23
Ossifying humerus and radius/femur and tibia	21–23	22–23
Ossifying ulna/fibula	22–23	23
Cavitation in shoulder and elbow/hip and knee	23	23
Cavitation in wrist/ankle	23	?

Derived from O'Rahilly and Gardner (Ref. [22])

bones are chondrifying as are all bones of the lower extremity except the distal phalanges which do so in week 8. Appearance of the diaphyseal primary ossification centers also follows a regular sequence: clavicle, early 7th week, followed by humerus, radius, ulna; femur and tibia, 8th week; scapula and ilium, 9th week; ischium, 15th week; calcaneus, 16th week and pubis, 20th week.

The developing model of each long bone is preformed in cartilage [18, 24, 25]. The undifferentiated mesenchymal cells, which have undergone condensation and started to outline specific bone shapes, then differentiate, surround themselves with a cartilaginous matrix, and take on the conformation of round chondrocytes. Histochemical stains, such as Safranin O-fast green, show the pinkish development of the matrix indicating the presence of glycosaminoglycans [26]. When the cartilage model of each of the long bones has been formed, the region where the joint will eventually be present is still filled with cells and is referred to as the interzone area. Early shaping of the epiphyseal ends of the bone occurs prior to necrosis and resorption of cells in the interzone area. When the latter occur, the joint cavity is formed and the complete model of the developing bone and joint has been formed. The cartilage model of the developing bone then increases in size by both interstitial and appositional growth of the chondrocytes. At a certain stage of development, the primary center of ossification forms. There is some confusion in the literature as to the exact meaning of this term. It can refer to the circumferential mid-diaphyseal rim of periosteum which synthesizes the initial bone of the cortex using the intramembranous mechanism without the mediation of a cartilage phase. It can also refer to mid-diaphyseal endochondral ossification within the cartilage model. Contemporaneous with the periosteal new bone formation, there is hypertrophy of cells in the mid-diaphyseal region of the cartilage model, calcification of the cartilage matrix, and vascular invasion of the hypertrophic cell lacunae accompanied by undifferentiated pre-osteoblast cells which then synthesize bone on the scaffold of the calcified cartilage matrix. The vascular invasion occurs in the areas of hypertrophic cells and serves to remove these and replace them with marrow cells and newly synthesized bone. The zone of hypertrophic cells or ossification front is then extended toward either end of the long bone.

The central replacement of hypertrophic chondrocytes with deposition of bone on the calcified cartilage cores encompasses what is referred to as the endochondral mechanism. In the periosteal region intramembranous bone formation extends the periosteal new bone sleeve. The periosteal development is always spatially somewhat more advanced toward either end of the bone than the central endochondral development. As this developmental sequence works its way toward either end of the bone, the cartilage forms itself into a specifically structured region referred to as the epiphyseal growth plate. This is characterized by specific conformations of the chondrocytes and serves as a functionally specialized region responsible for longitudinal growth.

1.3 Early Scientific Understandings of Bone Growth

Investigations to clarify mechanisms of bone growth began to show definitive advances early in the eighteenth century [27–38] (Table 1.1).

1.3.1 Theories of Embryogenesis. Preformationism and Epigenesis

Prior to the nineteenth century the main theory of embryogenesis was preformationism, the doctrine that the entire adult individual was present in miniature in the egg or sperm and development simply involved an increase in size. With more detailed observation however the concept of development by epigenesis became widely accepted. Epigenesis, as used in an older terminology, refers to the sequential development of morphological complexity in the embryo by the gradual and progressive differentiation of homogeneous material; each stage in development is considered to be dependent on and directed by its immediately preceding stage. The term epigenesis took on more specific meanings in the mid- twentieth century and now itself has evolved into a specific scientific discipline integral to biologic development (as discussed in Sect. 1.12.1 below).

Caspar Friedreich Wolff [39], Pander [40], and Karl Ernst von Baer [41] established the scientific validity of development by epigenesis. Wolff, in 1759, reported his observations on hen's egg development which showed blood vessels appearing where none previously existed and intestine forming from a flat plate. He concluded that epigenesis was real; "each part is first of all an effect of the preceding parts, and itself becomes the cause of the following part."

The structural basis of embryogenesis was more clearly revealed by Pander who defined the three germ layers in 1817 and then by von Baer [41], considered as the founder of embryology. von Baer performed elaborate descriptions of chick embryo development and its similarity to development of several other vertebrate types in 1828 and 1837. He recognized the significance of the three germ layers in development in all vertebrates and the epigenetic mechanism of development from the general to the specific. He recognized that the general path of differentiation proceeds in three sequential stages: the primary formation of the germ layer, histologic differentiation of cell and tissue types within the germ layers, and morphological differentiation to early organ formation. The mode of development is from simple to complex and from undifferentiated masses to new organs. Biological development involved progressive differentiation of the homogeneous, coarsely structured, general to the heterogeneous, finely structured, specific.

It is now recognized that much of development occurs in a self-assembly or "automatic" mode based on chemical and biophysical phenomena. Development is epigenetic in the sense that only early pre-patterns are rigidly determined after which each subsequent step is a combination of gene synthesis and automatic self-assembly based on the physical presence of certain molecules. Genes give approximate direction only. The detailed structure of multicellular organisms occurs on the basis of many intermediate levels of interaction each with its own immediate properties such that the edifice is virtually entirely epigenetic.

1.3.2 Hales, Belchier

Stephen Hales in 1727 showed that the bones grew in length by the addition of new tissue at their ends rather than interstitially [35]. He measured the leg bones of a young chicken twomonths after drilling two holes in the shaft to act as markers. The holes were no further apart although the bone itself had lengthened considerably. John Belchier [27], a London surgeon, observed that the bones of growing pigs and fowl which had been fed on madder were subsequently colored red. It soon became evident that red staining occurred only of the bone added while the animal was on the madder diet. By alternating periods of time on and off the diet (usually of a few weeks' duration) investigators were able to assess regions of bone deposition by studies after sacrifice. [Madder is a red dye (*Rubia tinctorum*) present in the roots of a plant.] The vital staining dye of the madder plant was subsequently recognized as alizarin [42]. The alizarin red stain is still used today in whole mount embryo studies. Staining with alcian blue outlines cartilage structures while alizarin red stains the bone [43, 44]. Subsequent studies by Duhamel, [30–34] Hunter [36], and Flourens [45–49] further demonstrated that bones grew in length by continuous increments at the ends.

1.3.3 Nesbitt

The formation of bone by the two now familiar endochondral and intramembranous mechanisms was noted early. Robert Nesbitt (1736) is recognized as being the first in describing the two methods of ossification in human fetal bone, one occurring directly in a membrane and the other via pre-existing cartilage [29, 38]. In his book Human Osteogeny published in 1736 he indicated that he would "show the ancient and common notion of all bones being originally cartilaginous to be a vulgar error." There were two methods, or species in his terminology, of ossification. "The bony particles in the fetuses begin to be deposited or to shoot either between membranes or within cartilages."

Nesbitt clearly noted that "the periosteum is a delicate fine and strong membrane which is spread on and covers not only all the bones in general but is also continued over the cartilages that have any connection with them; where from its situation it acquires the name of perichondrium". By formation of bone and membrane he was referring to periosteal new bone formation. He also recognized both the

inner and outer layers, or strata as he referred to them, of the periosteum. While bone formation from pre-existing cartilage models had previously been appreciated Nesbitt also showed that "some bones begin and continue to increase until they arrive at maturity without the least appearance of cartilage in or around them." The first species of ossification therefore was intramembranous bone. "The texture of that species of ossification which is produced between membranes by a careful and proper examination may be seen to be of small particles so conjoined together as to form fine bony threads or fibres which are disposed differently according to the particular formation of each bone and its several parts. This is most visible in thin and broad bones, especially in some of those which form the cranium." He noted that "you may observe the bony particles to be gradually multiplied and so conjoined in contact as to produce the appearance of small fine bony threads or fibres which then appear a little like radii shooting from a centre". With time there was an increase in the number of bony fibers which became "pressed so close together to form a single lamina or plate of bone." Membrane bone was that type formed in the cranium and it was also seen in cylindrical bones. He defined well the periosteal intramembranous bone sequence by noting that "their ossifications begin while the circumference of the part is not larger than a small pin in the form of a broad flat ring which surrounds the internal periosteum and is surrounded by the external. As these rings increase in breadth their fibres shoot toward both extremities of the part, not always in straight lines, but according to the particular figure the bone is designed by nature to be." He was aware that "the other species of ossification which first appears within a cartilage begins late …" Bone formation occurred in close association with blood vessels. He described formation of the secondary ossification centers and noted that vascularization immediately preceded bone formation in the epiphyseal cartilage. "The first small corpuscles of bone which become visible are always in that part of the cartilage which has the greatest quantity of red fluid appearing in it and they are not always placed close together but often at small distances from each other." In many diagrams Nesbitt indicated that "there are often 3 or more very considerable vessels going to and penetrating the ossifications" and commented that "near the ossification you will rarely miss feeling by the point of a knife bony particles." In drawings of the formation of the secondary ossification center of the distal femur he notes in one early section that vessels only are seen in the cartilage and in others as ossification increases centrally various additional vessels appear. Thus, even before the development of the cell theory there were clear descriptions involving transformation of cartilage to bone and the close relationship of vascularization to bone formation.

1.3.4 Duhamel

Henri-Louis Duhamel of France demonstrated from 1739 to 1743 that madder colored only those parts of the skeleton which were being formed at the time of its administration [30–34]. When madder feeding had been suspended for several weeks before sacrifice, the bone at the extreme ends of the shafts of long bones was uncolored as was that of the most peripheral cortical bone surrounding the mid-shaft region. By varying the time of madder feeding, he inferred that a long bone grew in length from its ends and in thickness by the progressive development of new bone on its outer surface. The discovery of the osteogenic function of periosteum is credited to Duhamel based on his interpretation of madder feeding and subsequent patterns of bone staining. Duhamel also found that bone grew in length at its extremities by drilling two holes at a measured distance in the shaft of a growing bone, filling them with metal plugs, and finding no difference in their position with time. He was unable to explain the increasing width of the marrow cavity with growth.

1.3.5 Hunter

The biologic mechanism of the increased diameter of the marrow cavity with growth was first understood by John Hunter who from 1740 onwards recognized both the growth of bone in length at its ends and the deposition of new bone by the periosteum on the outer surface of the shaft, but also the absorption of pre-existing bone which must occur within the marrow cavity as well as on the external surface of the expanded metaphyses [36]. He referred to this phenomenon as "modeling absorption" and clearly expressed the dynamic component of bone formation. Hunter used madder staining and diaphyseal hole drilling approaches to assess subsequent bone growth in pigs and fowls. He also discussed the modeling of the head and neck of the femur. Based on his madder studies of the proximal femur in growing pigs he recognized that "the addition of new matter was made to the upper surface, and a proportional quantity of the old removed from the lower, so as to keep the neck of the same form, and relatively in its place." [36] He established the principle that bones grow by two processes going on at the same time and assisting each other; the arteries bring the supplies to the bone for its increase; the absorbents at the same time are employed in removing portions of the old bone, so as to give to the new bone the proper form. "By these means the bone becomes larger, without having any material change produced in its external shape." [36] His work was the first which clearly recognized that absorption of bone was as essential to overall bone growth as deposition of bone.

1.3.6 Howship

Howship demonstrated the interplay of cartilage formation and bone formation in human and animal embryos based on studies with a solar compound microscope [50]. His text and illustrations presented in 1815 defined the embryonic 8 week human hand showing the primary ossification "rings of bone" of the metacarpals and phalanges. He identified cartilage canals in the epiphyseal ends of the bones and was able to outline the laminar structure of cortical and trabecular bone tissue. In a remarkable tissue section of the distal femur of a newborn child the epiphyseal–metaphyseal junction was magnified. The edge of the newly formed bone, by which he refers to the metaphyseal region, "exhibited an appearance of small short pointed villi shooting forward from the surface of the bone into the substance of the cartilage." He noted that "all sections exhibited an apparent alteration in the texture of the cartilage upon the surface connected with the bone. In many instances the cartilage seemed to be more opaque here than elsewhere, this slight opacity forming a line equal to 120th of an inch in breadth." This latter reference is to the physeal cartilage which indeed can be distinguished from the adjacent epiphyseal cartilage at low powers of magnification.

Howship further studied the cartilage–bone junction in a distal femur from a 3-week-old child. He examined the bone from the diaphyseal region toward the growth region. "It was observed that in proceeding from the middle of the cylindrical bones, where the medullary spaces are larger and the cancellated structure stronger towards the more recently formed extremities of the bone, the ossific masses become more numerous, of a lighter substance, and a thinner texture; the same gradation being continued up to the margin of the newly ossified surface, where the structure is most curiously wrought, and so exquisitely fine as scarcely to admit a description." His description clearly relates to the changes at the lower end of the physis and the furthest reaches of the adjacent metaphysis. "It was ascertained that the first and earliest state in which the particles of ossific matter become apparent, after they have formed a mass by their cohesion, may be considered as an assemblage of the finest and thinnest fibers, molded into the form of short tubes, arranged nearly parallel to each other, and opening externally upon the surface connected with the cartilage. These tubes appeared to correspond in number to the villi noticed in the last examination." Similar studies were also performed in animals. Howship clearly defined cartilaginous canals within the cartilage tissue at the ends of the bone. He noted that the principle of bone formation involving the appearance of the cartilage and ossifying bones "was in every respect precisely similar" in many species and that "the same purpose of ossification is accomplished by one and the same means." Howship concluded that the first rudiments of ossification in the long bones were associated with vascularization and occurred "upon the internal surface of the periosteum, which produced a portion of a hollow cylinder; this form of bone having been found antecedent to the evolution of any cartilaginous structure."

Howship mentioned the importance of the circulation both for cellular growth and for providing the means of calcification. He noted the value of the cartilaginous mode of bone formation indicating that "at a certain stage of the process the mode of operating is changed in order that it may proceed more expeditiously. A cartilage is formed, which, by the nature of its organization, and by admitting of a specific provision of cavities and canals lined with vascular membranes, which secrete an abundant store of gelatinous matter, is adapted to this particular purpose; while at the same time it serves to determine the future figure of the extremity of the bone by establishing and conducting the ossification within its own substance". He indicated that "from the period when the ossification proceeds in the mode above described by the medium of cartilage the process is continued in the same uniform manner until it has completed the growth of the bone. The growth of the epiphyses at the ends of the bone is also effected by the same means." He also noted the simultaneous formation of bone peripherally in cylindrical bones being "deposited primarily in the form of fine thin tubular plates: a mode of deposition of all others the most favorable for their being subsequently remodeled and for facilitating all the subsequent changes of structure they are destined to undergo."

He commented on the mechanical aspects of bone development noting that "the principal agent in extending the cylinder and in effecting the subsequent progressive changes of structure which in a growing bone are continually taking place appears to be simply the mechanical pressure exerted by the fluid secretions within the medullary cavities of bone, this power operating successively in different directions according to the particular determination given by the circulation." "The particular simplicity observable in the mode of production of the bones of the skull affords a strong argument in favor of the opinion that pressure variously modified constitutes one of the most efficient instruments in the hand of nature."

1.3.7 Flourens

Flourens also emphasized that longitudinal growth of the long bone took place at the ends (Fig. 1.3a). He outlined six major principles of bone growth based on extensive reference to the work of Duhamel as well as his own experiments

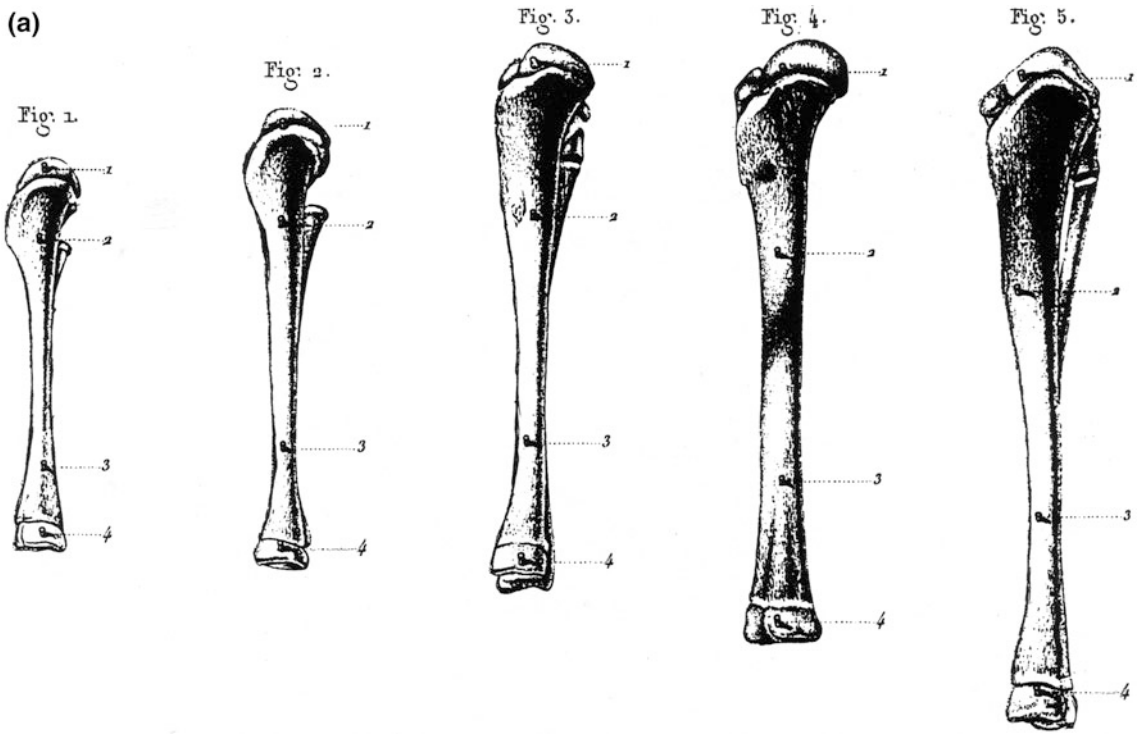


Fig. 1.3 (continued)

[45–49]. His six principles of bone formation follow: (1) bone is formed in the periosteum; (2) bone grows in thickness by superimposing new layers externally; (3) bone grows in length by adding layers at each end; (4) the medullary cavity grows by resorption of the inner layers of bone; (5) the ends of the bone are first formed and then resorbed and then reformed as the bone grows; and (6) bone development is accompanied by a constant change in the bony substance with the gaining of new molecules and loss of older molecules. Ollier also demonstrated the principle of long bone longitudinal growth from either end (Fig. 1.3b) [51].

1.4 Bone Development at the Light Microscopic Level Following Delineation of the Cell Theory and Advances in Microscopy and Histochemistry

Although early studies clearly established that growth in long bones occurred by means of the cartilages at either end, progress was slower in elucidating the structure of the growth cartilage itself. With the development and widespread acceptance of the cell theory dating from 1838, combined with advances in microscopy techniques, the structure and function of the growth apparatus became clearer.

1.4.1 Kolliker (1850)

Kolliker illustrated the sequential findings in growth of a long bone from embryonic to mature phases showing the upward and outward deposition of tissue and the need for both cell deposition and cell resorption during the process [52, 53]. He initially identified and described the functions of the osteoclast as the cell responsible for tissue resorption. Gross examination of a neatly cut longitudinal section of a developing bone showed tissue and vascular differences between the epiphyseal cartilage area and the metaphyseal/diaphyseal regions which had been appreciated long before the era of microscopy.

1.4.2 Broca

Broca defined these regions structurally both on the basis of gross inspection and with the early use of histologic sections which began to outline the phenomenon down to the cellular level [54, 55]. He was able to observe five layers at the physeal and peri-physeal regions. The first was the “couches

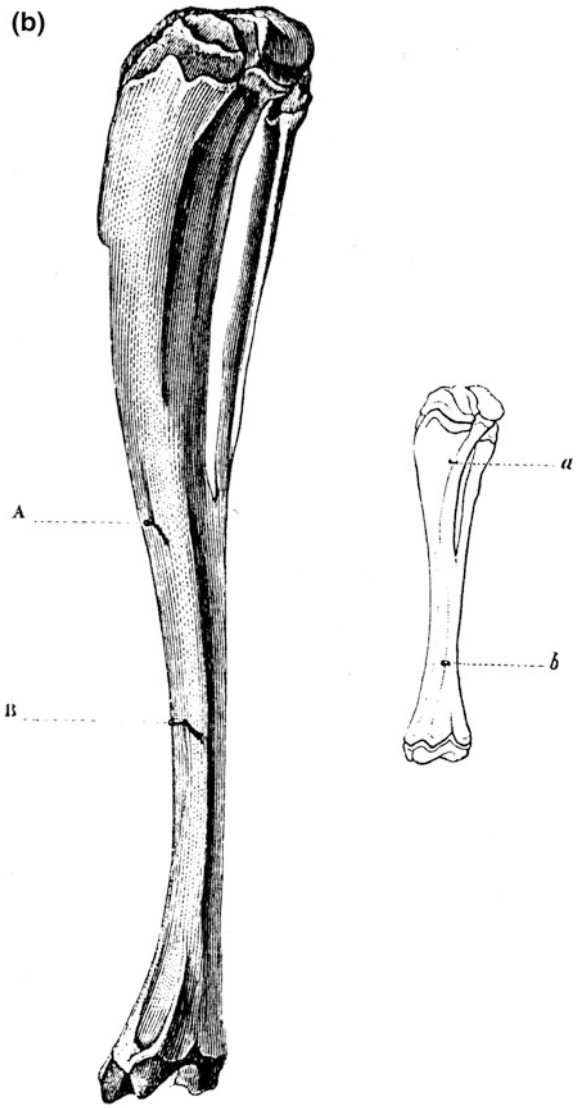


Fig. 1.3 Early experimental illustrations showing that long bones grow in length from their ends. **a** This reproduction of an illustration from Flourens [48] depicts studies showing long bone growth following insertion of two metal pins in the diaphyseal region and one in each epiphysis of the rabbit tibia. The distance between diaphyseal pins 2 and 3 always remains the same while the distance between epiphyseal–diaphyseal pins 1 and 2 (proximal) and 3 and 4 (distal) progressively increases with time. The upper and lower sets are initially equidistant. If the images are printed at a magnification where the distances between 1 and 2 and 3 and 4 are both 9 mm, by *Fig. 5* the distance is 28 mm above and 23 mm below indicating not only that growth in length has occurred at each end but that proximal growth activity is slightly greater than distal. These studies along with those done earlier by Hales, Duhamel, and Hunter led to the realization that bone grows in length by the addition of tissue at either end rather than interstitially. As the bone grows in length, the distance between the two diaphyseal pins remains the same but the distance between the diaphyseal pins and those in the epiphyses continually increases. **b** An illustration from Ollier [51] demonstrates the same principle with the 2 diaphyseal pins remaining the same distance apart even though extreme growth in length of the rabbit tibia has occurred

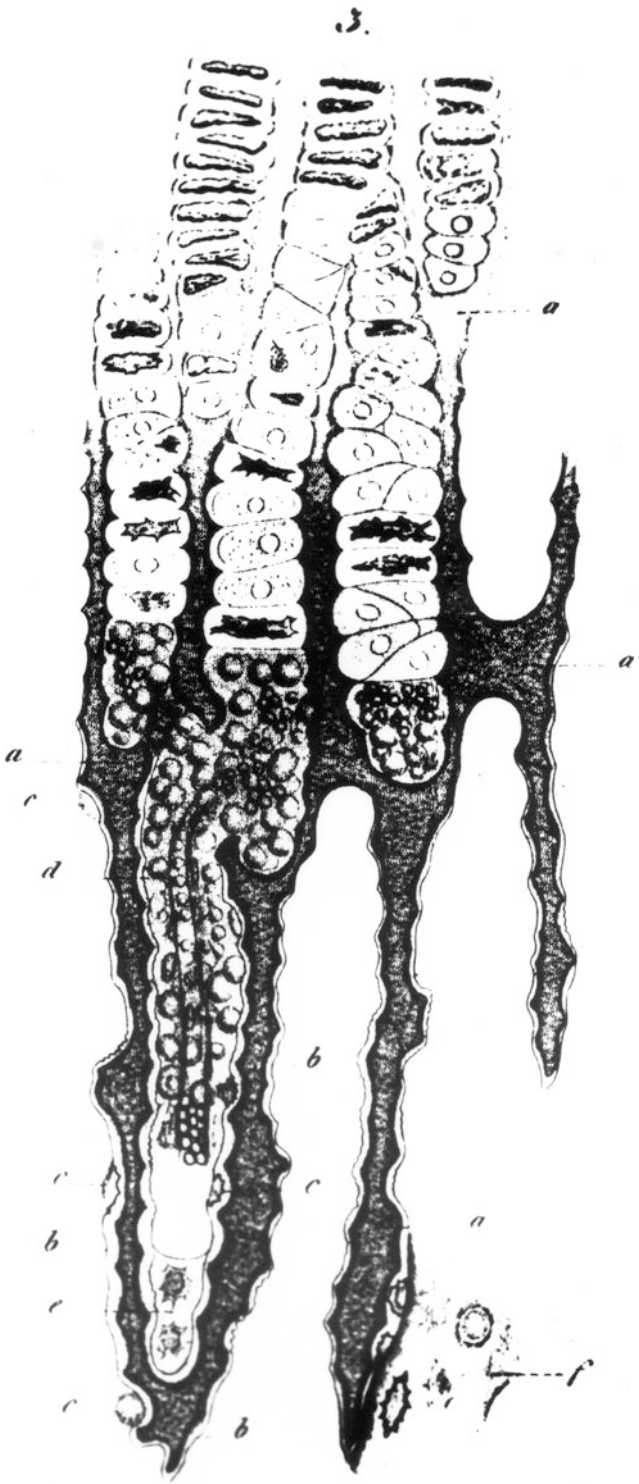


Fig. 1.4 This histologic illustration of the growth plate from Mueller's 1858 Article [57] shows his accurate depiction of the specific structures

cartilaginous"; the second a bluish region of the epiphyseal cartilage referred to as the "couches chondroid" which corresponded at the histologic level to the columnar cell region

or the "cartilage series"; the third toward the diaphysis, called the "couches chondro-spongioid" since it had gross appearing characteristics both of the chondroid layer above and the spongioid below; the fourth with a yellowish tinge referred to as the "couches spongioid" which in histologic terminology represented the hypertrophic cell zone including the area of calcified cartilage; and the fifth referred to as the "tissue spongieux" which represented the metaphyseal bone and was red in appearance. Tomes and de Morgan also described and illustrated the growth plate sequence [56].

1.4.3 Heinrich Mueller

Heinrich Mueller in 1858 provided detailed descriptions of epiphyseal cartilage development including the earliest description of the growth plate mechanism, which reached a coherent understanding at the light microscopic level [57]. His illustrations of the growth plate apparatus depicted the cell structure of the epiphyseal growth plate and the epiphyseal–metaphyseal junction in great detail and in a way fully consistent with observations made today (Fig. 1.4). He clearly illustrated the palisading or proliferating cell zone of the growth plate and its transformation over a few cells to the hypertrophic zone. The calcified cartilage matrix of the hypertrophic cell region was identified as was the invasion from below by vessels and bone forming cells, the deposition of new bone on the cartilage cores, the presence of osteocytes adjacent to the new region of bone formation, and the diaphyseal (metaphyseal) marrow. Mueller provided a series of illustrations of transverse cuts through the growth plate region of a human embryo three months of age. The first cut passed through the upper layer of small cartilage cells of the physis; the second through the region bordering the calcified cartilage where the cartilage cell cavities were somewhat larger; the third through calcified cartilage with large chondrocyte cavities (the hypertrophic zone); and the fourth through a zone characterized by central cores of cartilage trabeculae, surrounding bone, and cellular marrow. Mueller recognized the structural changes at both cell and matrix levels in the physeal regions. In his illustration of the outer reaches of the diaphysis, he showed both vessels and red cells. He concluded from his structural observations that elements of the marrow could be regarded as derivatives of young generations of cartilage cells which could transform themselves into bone cells. Mueller was described by Retterer [58] as showing "no doubt on this point: the elements or cells of the bone marrow and even the bone cells (osteoblasts) are derived from cartilage cells." He felt that the cell division was so rapid that it was impossible to observe. On the other hand, many cartilage cells died by being included in the calcified matrix. His work stood as the standard for explaining and illustrating growth plate morphology over several decades in the latter part of the nineteenth century.

Kolliker reproduced the drawings of Mueller accepting the transformation of cartilage cells into bone cells. Much later, in 1889, he utilized the same drawings but admitted the decline or decay of the cartilage cells and the budding of the perichondrial tissues providing a source of new cells [53].

1.4.4 Virchow (1860)

Virchow made the important distinction between **bone as a tissue** which he defined as the bone corpuscles or cells plus the calcified intercellular substance and **bone as an organ** which encompassed not only the osseous tissue, but also the medullary marrow tissue, the periosteum, articular cartilage, and all vessels and nerves [59]. It would also encompass the epiphyseal cartilage in a growing child. Long bones grew in length from cartilage and in thickness from periosteum. He described the endochondral sequence in excellent detail. In reference to the cartilage cells, "the greater the number of cells which undergo this change, the larger the cartilage will become and the height to which any one of us attains essentially depends upon the extent to which growth occurs in the individual groups of cartilage cells." The enlarged cartilage cells (of the hypertrophic region) "may be converted by a direct transformation into marrow-cells and continue as such; or they may first be converted into osseous and then into medullary tissue; or lastly, they may first be converted into marrow and then into bone." He was aware of the calcification of cartilage in the endochondral mechanism indicating that "what first takes place in the course of these processes is not the production of real osseous tissue, but only the deposition of calcareous salts …. There first of all takes place in the immediate vicinity of the border of the bone a calcification of the cartilage which gradually advances …. So that every individual cartilage cell is surrounded by a ring of calcareous substance. This is not yet bone, it is nothing more than calcified cartilage …." Bone tissue can arise out of marrow cells or directly from cartilage cells.

Virchow indicated that "it is no doubt true that in the case of the normal growth in length of bone, most of the bone-corpuscles do not directly proceed from cartilage-corpuscles, but are immediately derived from marrow-cells…but it is just as true that cartilage-cells can also be transformed straightway into bone-corpuscles." The isolated transformation of single cartilage cells into bone corpuscles was an accurate observation and of great importance to the cell theory in general. This direct

transformation was not associated therefore with death of the cartilage cell and its subsequent replacement. At that time, a cartilage corpuscle was considered to be composed of the cartilage cell and a surrounding membrane which was an integral part of it whereas a bone corpuscle referred only to a bone cell with the lacunar or canalicular wall representing the end point of the adjacent matrix. He pointed out that the conversion of cartilage into osteoid tissue directly was clearly evident at points of transition from cartilage to bone where the boundaries of the different forms of tissue are "completely obliterated and all sorts of transitions between round (cartilaginous) and jagged (osteoid) cells are seen."

1.4.5 Gegenbaur (1864)

Gegenbaur was a morphologist whose studies involved comparative anatomy, embryology, and histology. In studies on the development of primary and secondary bone he indicated that the tissue eventually formed was the same, even though the site of bone formation and the tissue replaced differed. He defined the cell most closely involved in bone formation as the osteoblast [60].

1.4.6 Ollier (1867)

Ollier wrote a classic treatise on bone development and regeneration [51]. This extensive experimental work defined the role of the periosteum in bone formation. He also demonstrated that bone irritation increased the rate of growth at the epiphyseal lines and that damage to the epiphyseal lines inhibited growth. He was the first to study the variable amounts of bone growth at the proximal and distal epiphyses. He also repeated the experiments of Duhamel and Flourens showing that growth in length took place only at the epiphyseal lines [51, 61, 62].

Growth plate structure and development were further described beginning in the late nineteenth century with particularly excellent presentations by Waldeyer [63], Schafer [64], and Bidder [65]. A brief review of some of the major landmarks in bone growth research is presented in Table 1.1. It was some time after the work Nesbitt published in 1736 before the two modes of bone formation, intramembranous and endochondral, were more widely appreciated. Kolliker wrote on the morphologic significance of membrane and cartilage bone. Russell [40] noted that Reichert (1849) and Mueller (1858) [57] had pointed out that there was no essential difference in the eventual histologic structure of bone whether it had been formed initially in cartilage or in membrane, a view still held today.

1.4.7 Retterer (1900)

Retterer described the development of bone by the endochondral mechanism in "The Development of the Transitional Cartilage" [58]. The various developmental phases from the embryonic limb bud onward were defined. Growth of the cartilage model was accomplished both by interstitial and appositional mechanisms in which the perichondrium contributed to the growth in width of the cartilage. Light microscopy showed that the matrix, referred to as the "fundamental substance," had many components among them connective tissue fibrils, collagens, which were very fine in nature and immersed in a matrix with acid-like chondroitin, also referred to as chondromucoid. Virchow is credited with being the first to describe the cartilage cell in hyaline cartilage which was formed of a central nucleus, a surrounding cell body, and a capsule. Retterer concluded that the cartilage hyaline or fetal cell was composed of a large nucleus and a cell body with many organelles leading to a peri-nuclear granular chromophilic appearance. Regarding transport mechanisms for nutrition within cartilage, it was evident that a diffusion process was available with evidence from many experiments that it occurred by diffusion from the synovial cavity (as we accept today) while others implied that it passed from cell to cell along cell processes.

Retterer assessed the epiphyseal growth plate and the transformation of cartilage to bone. A major unresolved question at that time was what became of the cartilage cells at the lower part of the growth plate, with the question raised as to whether they atrophied and died or survived and were transformed to other cellular elements. This question has not been totally determined almost 100 years later with recent work on the hypertrophic cell interpreted by some as a continuing functional role in some instances. He demonstrated the cartilage model of the developing bone, the flattening of chondrocytes in the transverse plane at the early regions of physeal differentiation, and the swollen cartilage cells centrally which were much larger than other cells. He gave to this region the name of hypertrophic cartilage ("cartilage hypertrophic"). It was in this zone that the calcium salts were deposited in the matrix leading to the term calcified cartilage.

A 4-zone region of cartilage cell transformation was recognized. In the first zone the flattened cells of the cartilage were referred to as "cartilage series." The cartilage cells in this region were flattered in the transverse plane where they were 15–20 μ wide and only an average 9 μ thick. The flattened cells were disposed in groups separated by matrix whose long axis was parallel to the long axis of the developing bone. The second zone was the hypertrophic cell zone

with calcified cartilage matrix. The cartilage cells enlarge in this region being larger than in the adjacent zones and either round or polyhedral in shape. The question was raised as to whether the modifications of the hypertrophic cells represented a progressive or regressive phenomenon, and as to whether the cells of this zone were preparing to ultimately evolve or to perish. Some of the cells appeared histologically to be undergoing atrophy and most observers felt that the cells of the hypertrophic zone were undergoing death. Retterer felt that if the cartilage was prepared for histology in a different way, and serial sections were done, the hypertrophic zone often showed intact cells rather than empty cell spaces. He felt he could demonstrate intact cells with cytoplasmic elements in place demonstrating results "entirely different from those announced classically." The third zone, the "cartilage hyperplasie," included the medullary space created by the entrance of blood vessels and red blood cells through the transverse septae into the lower hypertrophic cell lacunae. In the fourth zone, there were trabeculae of bone representing the upper portion of the diaphyseal "spongieuse" ossification region. Retterer thus established a 4-zone region of transformation with zone 1 being his "cartilage serie"; zone 2, the hypertrophic-calcified region; zone 3, the zone of the initial medullary space (zone hyperplasia); and zone 4, the zone of ossification. The terminology current at that time was such that the physis was generally described as being diaphyseal owing to its position at the extreme extent of the diaphysis while the term metaphysis was not used.

Retterer was able to distinguish clear zonal differentiations within the physis in particular with transverse sections slightly oblique to the horizontal axis which showed adjacent regions shading into one another. He was able to show smaller cell components invading the hypertrophic cell lacunae. Some of the cells were red blood cells associated with the vascular invasion. The hyperplastic zone was characterized by multiple cell types which merited the name of a zone of metamorphosis though he indicated it would be too confusing to introduce yet another term to this complex region. Some cartilage cells passed through the hypertrophic zone without degenerating and then transformed in the upper regions of the medullary zone. Some of these he felt became multinucleated. Calcium was deposited in the matrix trabeculae of the hypertrophic zone and no cell division had been noted in the hypertrophic zone. The hypertrophic zone did not consist only of an increase in the volume of pre-existing cells, but rather, the cells were also involved in a formative process which created both nucleus and cytoplasm different from those of the mother cell. He raised an issue which is not totally understood even today. He describes the invasion of the lower parts of the hypertrophic zone by vascular tissue, the development of capillaries carrying blood cells, and the resorption of transverse cartilage trabeculae. He concluded that it was the metamorphosis of the cartilage cell which represented the initial phenomenon of endochondral ossification and indicated that "the transformation of the cartilage cell led to the development of a reticular and vascular tissue analogous to that of the perichondrium; these 2 tissues are capable subsequently of elaborating bone."

Retterer also described the development of bone within the epiphysis where the cartilage was transformed centrally to begin formation of the secondary ossification center at a later stage. He observed that "the evolution of cartilage tissue of the epiphysis is in every point analogous to that which we have studied in the diaphysis in the developing skeleton of young embryos." Vascular canals were present within the epiphyseal cartilage. He felt that the cartilage canals formed directly within the cartilage model itself rather than being derived from the perichondrial vessels.

1.5 More Detailed Studies of Bone Formation

1.5.1 Overview of Bone Growth

By the first third of the twentieth century there was good conceptual understanding of what needed to be studied to advance the field of bone biology. Brash stated that "since bone is infinitely reparable, and repair is growth, the bone problem is a growth problem pure and simple" [66]. His studies assessed the increase of bone by surface accretion (addition of material) and its decrease by absorption and the relation between these which results in the enlargement of a bone as a whole while it retains its characteristic shape. He recognized the interdependence of cellular, chemical, and mechanical influences on growth and characterized any study as being one of "developmental mechanics" or "developmental physiology". As early as 1934 he was recognizing the successive phrases of the problem (or study) of osteogenesis passing from the histological phase to the surgical and experimental phase to the developing direct attack on the problem by the chemical phase. He reviewed experimental work on the importance of genetic factors which showed bones to be self-differentiating structures. Genetic patterning was shown by embryologic transplant and in vitro experiments where bones developed independent of mechanical factors. With time however, mechanical adaptation of form became important (structure of proximal femur; trabeculae of cancellous bone) and was primarily dependent on controlled absorption of bone to model internal as well as external bone architecture.

Brash outlined the classical features of bone growth relevant today: (i) diaphyses of long bones grow in length by

cartilage replacement of their ends only; (ii) long bones grow in width by surface accretions; (iii) long bones maintain their shape by modeling absorption principally toward their ends; (iv) interstitial expansion of bone (carefully distinguished from interstitial changes in bone) does not occur; and (v) no feature of a bone can be assumed as "fixed" for the purpose of comparing different growth stages. Brash pointed out that bone growth and the molding of bone form are surface phenomena exclusively. Much of his work also utilized madder vital staining alternating periods of use and non-use to assess growth deposition regions. He pointed out that the madder method also assessed the contribution to the length of the limb bones by growth of the epiphyses themselves. The madder method as applied to the pig by Payton allowed for quantitation of the amounts of growth at each end of the bone and between specific time periods [67, 68]. Femur and tibia grew in length more at the knee region while humerus and radius/ulna grew more at shoulder and wrist ends. The epiphyses were seen to grow primarily adjacent to the undersurface of the particular cartilage.

The final concept stressed by Brash was that "bone growth and bone absorption are always and solely surface phenomena". This had been first clearly raised by Hunter as the marrow cavity was widened by absorption from within but surface absorption also occurred at any bone surface wherever situated (including subperiosteal) to allow bones to retain their shape with growth ("modeling absorption"). The enlargement of all cavities in bone must be due to the process of absorption. Shaping of external form and orientation of internal architecture (e.g. bone trabeculae) are enhanced by surface absorption. Surface resorption also correlates with osteoclasts (as defined by Kolliker), with the varying relation of red and white areas with madder bones, and overlay comparison of serial radiographs of the developing ends of the same bone in a growing child where outer surface resorption is needed to maintain shapre after preceding outer outer surface accretion. In conclusion "all bone growth is by way of accretion of surfaces whether they be external or internal, the walls of larger cavities or the surfaces of the trabeculae of cancellous tissue; and that any of these surfaces wherever situated may melt away by the reverse process of absorption.—plates of bone which appear to be stationary (may) be—moving steadily by a process of reformation." Future work would be needed (and is still being done) to outline the cellular means and controlling factors coordinating these morphological ends. This "obvious universal co-ordination of accretion and absorption in the growth of bones" is currently studied as the concept of coupling of bone synthesis and resorption.

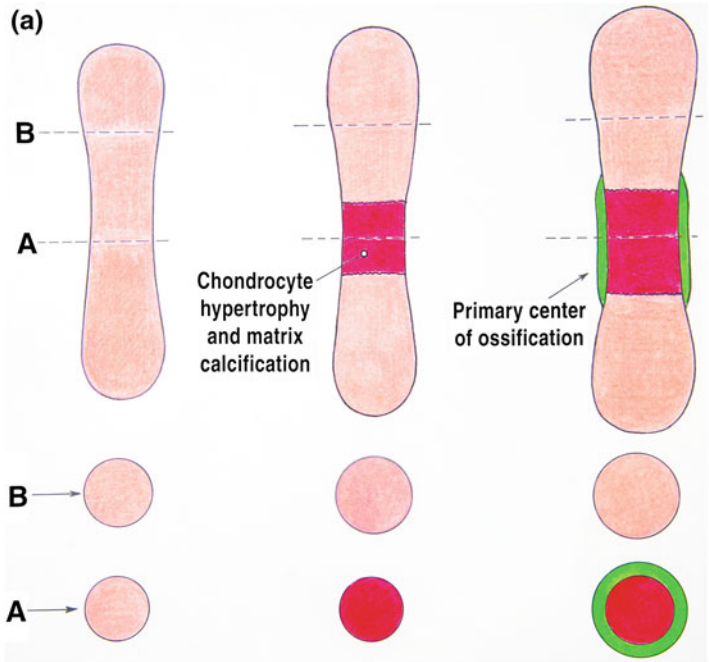
The pattern of long bone development encompassing both endochondral and intramembranous mechanisms is illustrated in Fig. 1.5a–e.

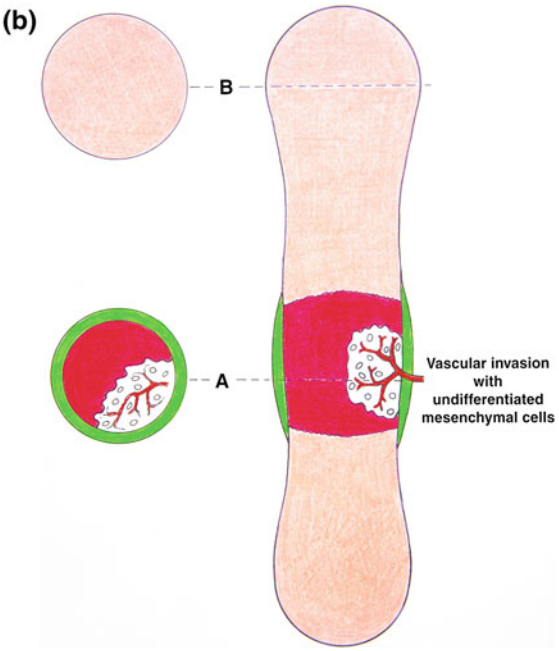
1.5.2 Histogenesis of Bone

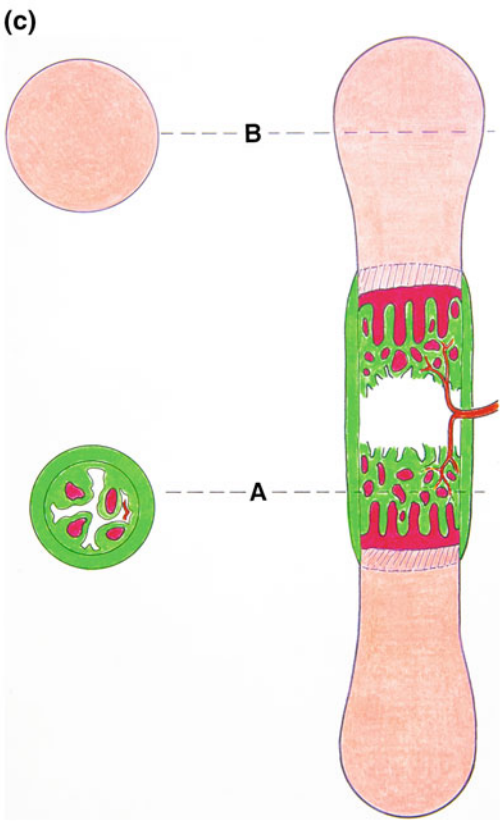
The histogenesis of bone was studied in detail by Stump (1925) including both the endochondral and intramembranous mechanisms [69]. Certain differences from current terminology must be recognized in reading earlier work on developmental bone biology; even as late as 1925, mention is rarely made of the metaphysis and indeed the growth plate is referred to by Stump as the "diaphyseal plate." His descriptions of the developmental sequences raised several points still pertinent to our understanding. The work included the concepts of bone as a tissue growing by apposition and cartilage by interstitial proliferation and of the perichondrium evolving into the periosteum "concurrently with changes in the sub-adjacent mesenchyme." Stump indicated in his discussion of the cartilage growth plate that the measure of its growth depended not only on the rate of division in forming the chondrocyte groups, but also on "the velocity of enlargement of the cells collectively." The enlargement of cells is primarily in reference to the hypertrophic zone. Persistence of the cartilage cell after its hypertrophy was sought but not found and he concluded that the hypertrophic chondrocytes "persistently showed the appearance of old mature cells with all the signs of structural degeneration." Calcification of the longitudinal cartilage trabeculae of the hypertrophic zone was defined as was its scaffold function. The hypertrophic cell region was invaded by vessels and undifferentiated mesenchymal cells, soon to become osteoblasts. This invasion occurred into the lower regions of the hypertrophic cell mass with evidence that the transverse, thin, non-calcified septae were readily resorbed but that osteoclasts or chondroclasts were not involved in this particular phase of development. Endochondral bone was transitory in nature, "serving to increase the stability of a bone at the site of its growth. It undergoes absorption, extending the area of the medullary cavity toward the diaphyseal (which we now describe as epiphysial) cartilage." In the epiphysis itself, cartilage and bone deposition was more a feature of growth than absorption, although replacement of all minute trabeculae to meet new tension and pressure stresses was a continuous process.

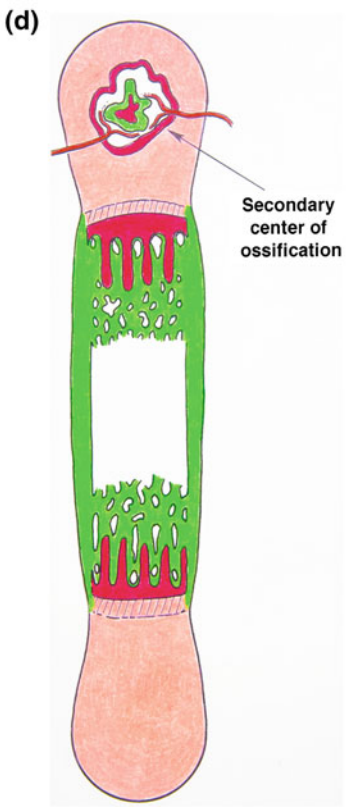
1.5.3 Chondrocyte Shape and Orientation in Epiphyseal and Physeal Cartilage; Cell, Matrix, Mineralization, and Vascularization in the Endochondral Sequence

Dodds: Dodds was one of the earliest to focus on specific cellular orientations within the epiphyseal growth plates


(a)
B
A
Chondrocyte hypertrophy and matrix calcification
Primary center of ossification
B
A


(b)
B
A
Vascular invasion with undifferentiated mesenchymal cells


(c)
B
A


(d)
Secondary center of ossification

(e)
Articular cartilage
Calcified cartilage

[70]. He was particularly interested in longitudinal row formation of chondrocytes and their gradual enlargement toward the metaphyseal region. He described the early epiphyseal cartilage structure (as distinct from the physeal structure) at either end of a long bone as the endochondral sequence worked its way from the diaphysis toward its ultimate epiphyseal position. He summarized as follows: "In the cartilaginous ends (the epiphyseal regions) of young bones, before the appearance of the epiphyseal centers, the condition of the cartilage is that of a primitive type of hyaline cartilage, such as would be found elsewhere in the body, with no relation to the process of ossification. The cells are small and all very much of the same size. They have a rounded form. They are undergoing mitotic divisions which take place in all planes. Following the divisions, the pairs of daughter cells slowly migrate apart and soon come to occupy separate lacunae. For this reason, the cells of this region occur singly, except for those, here and there, which, on account of recent division, occur in pairs. The growth of the cartilage in this region is not rapid, nor is it conspicuously greater in any one direction. It is simply sufficient in amount and of a suitable nature to keep the cartilaginous ends of the bones of proportionate size and of proper shape. This is the primitive type of cartilage-cell arrangement from which the (physeal) rows are derived. It might also be remarked, in passing, that in this region the cartilage also receives increments from the mesenchyme which underlies the perichondrium, as well as from the interstitial growth just described."

Dodds describes the development of the epiphyseal growth plate cartilage region, the cytologically and functionally specialized area of the epiphysis. He defines differentiating features from the primitive (epiphyseal) cartilage described in the paragraph above involving: (1) a definite orientation of the mitotic figures; (2) the two cells resulting from each division remain close together; (3) instead of retaining the primitive rounded form, the two daughter cells become greatly flattened assuming a discoid form; and (4) all of the pairs of flattened cells remain oriented in the same way with their widest diameters perpendicular to the long axis of the bone. These pairs of flattened cells are the beginning of rows of chondrocytes. This area of the physis is referred to by most researchers as the proliferating or columnar cell zone. The rows are built by the division of flat cells which

◀ **Fig. 1.5** The diagrams in this figure (**a**–**e**) illustrate the cell and tissue changes in long bone formation. **a** The cartilage model of the developing bone is shown at left (*pink*). *A* and *B* represent cross-sectional cuts of the developing bone with the tissue pattern illustrated *below*. In the diagram at far *left*, the tissue representations are the same (*pink*) since the entire model of the bone is still in a cartilage phase. In the central illustrations, chondrocyte hypertrophy and matrix calcification (*red*) are shown in the central or diaphyseal region. Chondrocyte hypertrophy starts as a central nidus both in the middle part of the shaft when considered in a longitudinal orientation and also in the central part deep within the cartilage when considered in the transverse orientation. This will eventually pass from one edge of the shaft to the other as is shown in the transverse section *A below*. At far *right*, the intramembranous bone formation (*green*) from the periosteum has begun surrounding the endochondral bone formation centrally. The two mechanisms of bone formation are most clearly illustrated in the transverse cut section *A* as seen at *bottom*. The initial formation of endochondral bone within (*red*) and intramembranous periosteal bone at the periphery (*green*) occurs at the same time. This initial area of bone formation is referred to as the primary center of ossification. It is unclear from the literature whether one site of bone formation precedes the other by a very short time interval. In a strictly technical sense, that region which formed first would be the primary center of ossification. This would have biologic significance but in a practical sense both mechanisms can be referred to as the primary center. An accurate observation, however, and one made by most observers is that the intramembranous or periosteal new bone formation is present spatially somewhat in advance of that occurring within the endochondral sequence centrally as bone formation passes from the primary center of ossification towards either end of the bone. This is seen in the top illustration at far *right*. This is a relationship which is maintained even in relation to formation of the physis and the perichondrial ossification groove of Ranvier. **b** Events surrounding the primary ossification center formation are detailed. Once the cartilage cells (chondrocytes) within the mid-part of the shaft have hypertrophied and the matrix has calcified (*red*), there is vascular invasion from the periphery (*green*) along with undifferentiated mesenchymal cells which shortly lay down bone on the calcified cartilage cores. Endochondral bone formation is underway. Intramembranous bone formation at the periphery occurs directly without the mediation of a cartilage phase. The intramembranous bone is spatially in advance of the more central endochondral bone. There are no vessels within the developing diaphyseal cartilage prior to its hypertrophy and matrix calcification. It is only when hypertrophy has occurred that vascular invasion from the adjacent perichondrium/periosteum occurs. There are thus no cartilage canals present in the diaphysis and metaphysis analogous to those seen later in the epiphysis. **c** Bone formation advances toward either end of the developing bone with a characteristic physeal orientation of the cartilage and endochondral sequence occurring. The physeal orientation is represented here by the slanted lines. The *solid* region (*red*) adjacent to both physes centrally represents the calcified cartilage of the lower part of the hypertrophic zone and the persisting cartilage cores in the metaphysis. Note the advance of the intramembranous bone formation (*green*) and its slightly greater peripheral extent than that of the endochondral bone within. **d** Formation of the secondary ossification center within the epiphysis above is shown. The endochondral sequence has moved the physes relatively closer to either end of the bone. The secondary ossification center has formed above while at the lower end it has not begun to form. This is a characteristic feature of long bones where one center, which can be at either end, forms before the other. Vessels passing from the periphery are present within the epiphyseal cartilage in cartilage canals for many weeks and sometimes for many months before formation of the secondary ossification center, a feature not characteristic of the endochondral mechanism at the primary center of ossification. **e** The secondary ossification center is now seen at the lower end of the developing bone where the physis (*oblique lines*) is still open. At the *upper* end, the physis has been completely closed and resorbed and there is continuity between metaphyseal and epiphyseal bone (*green*). The growth on the undersurface of the articular cartilage (*pink*) has also terminated and the innermost zone of articular cartilage (*red*) is now calcified

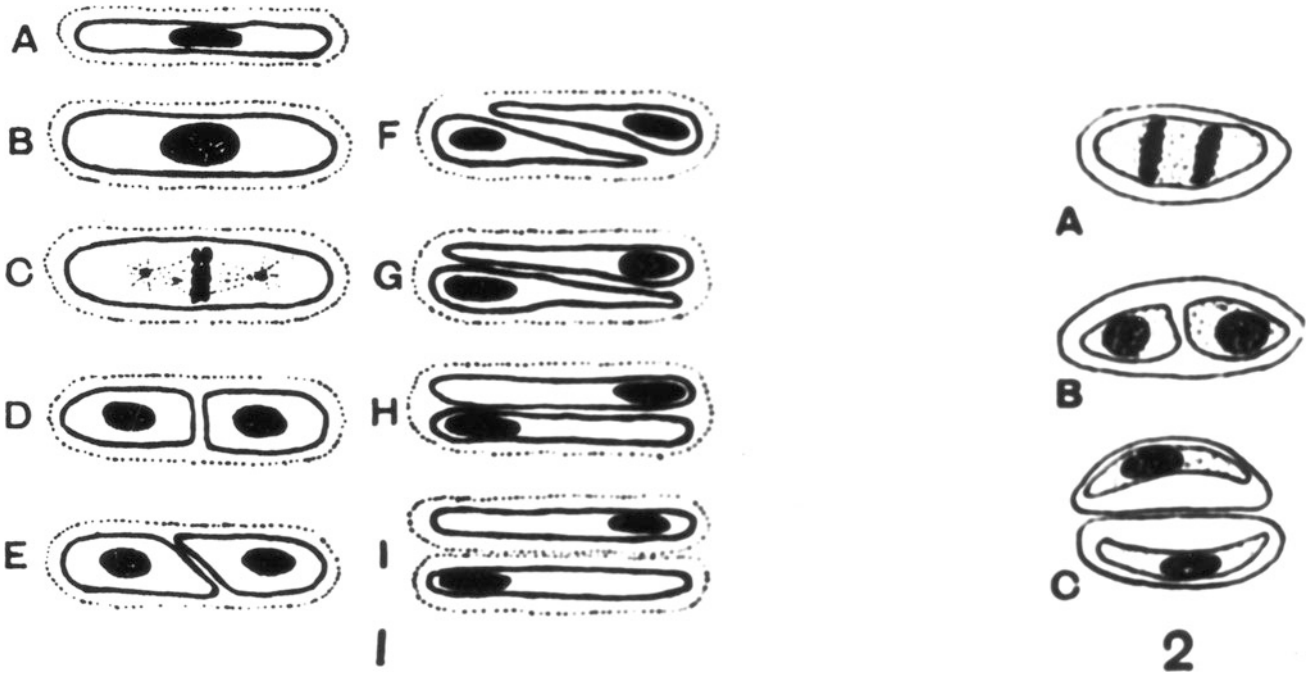


Fig. 1.6 Dodd's illustration of the genesis of row formation in the proliferating part of the cartilage growth plate from newborn dog metatarsal [70]. At *left* (*1*) the mode of cell division is shown beginning with a single cell (*A*) at *top left* and progressing to a flattened chondrocyte at *lower right* (*I*). At *right* (*2*) the beginning of a row of cells by division is shown. In part (*2*) *A* telophase; *B* two daughter cells just after division; and *C* = the two daughter cells after flattening and final reorientation. (Reprinted with permission from Dodds GS, Row formation and other types of arrangement of cartilage cells in endochondral ossification. Anat Rec. 1930;46:385–399. Copyright 1930 John Wiley and Sons)

following division retain a relation "like coins in piles" (Fig. 1.6). The number of cells in a row is constant for most epiphyses, but different regions have different characteristic numbers. These cell divisions increase the length of the rows of cells and thus are an important but not the only factor in the elongation of the bone. The increase in physeal width comes by multiplication of the number of rows caused by more numerous rows of mother cells produced by the epiphyseal cartilage. Some would refer to this process as occurring in the germinal or resting cell zone of the physis. Cartilage matrix forms in a thin septum between the two daughter cells with transverse partitions being much thinner than the longitudinal septae which intervene between adjacent rows. There is progressive hypertrophy of the cartilage cells. When the full number of cells in a row has been produced, the enlargement of the cells begins with the enlargement in general affecting the cells in sequence, beginning at the diaphyseal ends of the rows. The growth in thickness by the physis along its longitudinal axis is greater than that in width, a disparity which tends to turn the transverse flattened cells into more discoid cells. During growth of the cells, they remain in rows such that "elongation of the cartilage which was begun by the division of the flat cells in the rows, is continued with increased speed by the rapid enlargement of these same cells." Cells divide in the transverse plane and then rearrange in the longitudinal plane. The synthetic patterns of the chondrocytes during rapid growth of the cells in rows are recognized since there must be a consequent increase in the total length of the rows and a corresponding increase in the length of the longitudinal trabeculae between them. These happenings represent the actual elongation of the growing bone.

Dodds was one of the earliest to note that "when calcification of the cartilage matrix takes place, it affects only the longitudinal trabeculae, the transverse walls between the cells being unaffected by it. These thin, transverse, uncalcified walls are seemingly easily destroyed by the invading marrow as are also the degenerate cartilage cells within the lacunae so that the long parallel cylindrical holes are easily produced as lining on which the first bone matrix is deposited."

Formation of the primary center of ossification in each bone occurs by ossification in the central cartilage model following cell hypertrophy and vascular invasion. Dodds implies that bone formation centrally by the endochondral mechanism occurs "at about the time of the beginning of sub-perichondral ossification" by which he means the first evidences of deposition of periosteal intramembranous bone.

Physeal structure is further summarized by Dodds in another article dealing primarily with cartilage removal by

osteoclasts at the lower zone of the physis [71]. Mineralization of the cartilage matrix occurs along the longitudinal septae with essentially no mineralization of the narrow or transverse septae. Invasion of the hypertrophic chondrocyte lacunae is characterized by both undifferentiated mesenchymal cells and loops of capillaries. When the lacunae have been opened by a defect in the transverse septum, the marrow cells and capillaries advance into it beside the cartilage cell and immediately adjacent to the mineralized longitudinal cartilage core. "The primitive connective tissue cells of the marrow are seen to gradually develop into osteoblasts which begin at once to deposit bone upon the persisting, longitudinal, calcified cartilage walls surrounding the cylindrical holes." The osteoclasts which form also by a fusion of marrow cells are not found in the advancing capillary front but are closely behind it and are always applied to the persisting remains of the calcified longitudinal walls to resorb them. Osteoclasts can resorb both the bone spicules on the cartilage core or just the cartilage alone at which time they can also be referred to as chondroclasts. The osteoclast is present only on calcified material, be it bone or calcified cartilage.

1.6 Fate of the Hypertrophic Chondrocyte as Interpreted from Light Microscopic Studies

The fate of the hypertrophic chondrocyte is important and many views have been presented some of which continue to be debated. An important point concerning the technical preparation of histologic sections of bone and cartilage for light microscopic examination should be made. The techniques in use in the late 1800s and early 1900s in many instances allowed for the preparation of sections with better preservation of cell detail than paraffin embedded, hematoxylin and eosin-stained sections that characterized and continue to characterize much bone research of the past century. The drawings of cell and tissue appearances and the improving photo microscopy showed a degree of structural preservation supportive of some of the interpretations made. Retterer provided a detailed assessment of previous descriptions of cartilage transformation into marrow bone when he examined the fate of hypertrophic chondrocytes. He summed up the possibilities by which cartilage cells of the growth plate could subsequently be found in the medullary tissues of what we now refer to as the metaphysis. Many investigators of that era were comfortable in describing the transformation of at least some of the hypertrophic cartilage cells into bone cells with two distinct pathways occurring, one involving cell death or one involving cell transformation where the cartilage cell survived and underwent dedifferentiation and re-emergence as a bone forming cell. Owing to the current high-level interest in the fate of the hypertrophic chondrocyte, a review of previous morphologic findings and interpretations is interesting.

1.6.1 Chondrocyte Survival, Dedifferentiation, and Re-emergence to a Bone Forming Cell Line

Baur denied there was any direct transformation or metaplasia of cartilage cells to bone feeling that there was a survival and proliferation of the freed cartilage cells, many of which subsequently formed cells which constituted the embryonic marrow [72]. Ranvier also believed that there was no direct transformation of cartilage to bone, but rather, that cartilage cells, in particular young cells, divided extensively, and by what appears to have been a dedifferentiation, led to the formation of embryonic marrow [73]. Both observers felt that the medullary cells did derive directly from cells of cartilage after their surrounding pericapsular tissue dissolved. Ossification was not direct in a sense that cartilage cells did not lead directly to the formation of bone cells but underwent initial modification, or dedifferentiation, in which they lost their cartilage faculty. They then became embryonic marrow cells which eventually were able to form bone. Embryonic cells which had not yet taken a determined form could be seen in the development of bone from a cartilage model. The cells were thought to originate in the marrow of the bone under the influence of vessels. These vessels led the cartilage capsules to dissolve, the cartilage cells to be freed, and then to proliferate, following which they took on an embryonic character referred to as the medullary vascularized tissue and only later could these marrow cells align themselves along the walls or structures at which time they were referred to as osteoblasts. The general feeling of many observers therefore was that cartilage cells did not transform themselves directly into bone cells but rather that the bone forming cells develop from descendants of primordial cartilage cells. Mueller also stressed that bone cells were not derived directly from the cartilage cell capsules, but rather, from their young progenitors.

1.6.2 Direct Transformation of Cartilage Cells to Bone Cells

Virchow and Lieberkuhn [58, 74] stressed that cartilage transformed itself directly into bone. Bone cells were interpreted as being cartilage cells which survived and bone substance as cartilage matrix modified but not a new tissue. Schoney also thought that cells dedifferentiated in the

cartilage-to-bone formation phase although he did note that at the lower part of the growth plate, he had never seen a cartilage cell divide nor the protoplasm of a cartilage cell transform itself into an element of bony marrow [75]. Some histologists like Czermak [76] indicated that the connective tissues of bone and cartilage were similar and that they differed only slightly based on the nature of the surrounding matrices. Metaplastic changes therefore consisted only in a transformation of one matrix to another, with one of the subtle changes involving the ability of cells to secrete calcium salts and transform themselves into bony tissue. Leser [77] and each of Retzius, Brachet, and Retterer [58] described situations where growth plate chondrocytes survived and were transformed into either marrow medullary cells or osteoblasts.

1.6.3 Death of Cartilage Cells

An additional view, and one commonly held through most of the twentieth century, was expressed by Loven and others as early as 1863 favoring the destruction of hypertrophic chondrocytes and the development of bone without any participation of previous cartilage cells [58, 78]. He was impressed by the vesicular and swollen nature of the hypertrophic cartilage cells which occupy the calcified zone leading to the interpretation that the cells were degenerating and that calcification led to destruction of the cartilage cells which served to prepare a space where the bone tissue could invade and develop. He indicated that "it was the blood vessels coming from the perichondrium which contributed to the resorption of the cartilage tissue." He denied there was any participation of the cartilage cells in the development of the embryonic marrow. Stieda also published similar observations, namely that the marrow was a tissue whose origin was unique and not derivative from cartilage dedifferentiation [79]. Stieda was never able to see a direct passage of the cell line from cartilage to medullary elements and he felt that the medullary elements originated from the periosteal buds. It was the osteoblastic tissue of the embryonic state which invaded from the undersurface of the periosteum that formed the first bony deposits. Uranossow did not find continuity of cartilage cell division with that of the bone marrow and concluded that the medullary elements did not have their origin in cartilage [58, 80]. The cell masses which gave birth to endochondral bone derived originally from the cambial layer of the periosteum. He concluded that cartilage had only a passive role in the development of bone. Levschin denied any relationship between cartilage cells and the marrow elements of long bones [58, 81]. Retzius described the changes in cell shape and size as one proceeded toward the hypertrophic zone but felt that the cells were degenerating toward the ossification front [58]. Strelzoff indicated that for most bones, the cartilage was destroyed and bone itself occurred on the basis of osteoblasts derived from the periosteum [82]. In some regions, however, in particular in facial bones, ossification occurred wherein cartilage cells were transformed directly to bone cells.

An increasingly large number of observers thus defined the hypertrophic cartilage cells to be shriveled and withered while the osteoblasts brought in by the capillary vessels appeared healthy. Others adhered to the view that cartilage cells continued to be derived from the physeal cells, even though some were smaller at the lowest part of the hypertrophic zone. Seemingly all were in agreement that below the palisading layer of the cartilage, there were no longer any mitoses. Brachet indicated that while in the hypertrophic zone the cartilage cells seem to be degenerating, it was as though in the region of the resorptive zone they took on again a more embryonic form and that they subsequently became free in the marrow [83]. The question was how the cartilage cells which became hypertrophied and modified reached their ultimate goal. He noted that they disappeared essentially once the capsule had been opened and that osteoblasts filled the space along with vessels and chondroclasts. He indicated that he had never seen transitional forms between the modified chondrocytes and osteoblasts and at least stated in clear-cut fashion that "it is impossible for me to determine exactly the ultimate fate of these elements." Retterer felt that most views inclined to support the classic theory which attributed an extra-cartilaginous origin primarily from the blood vessels for the new osteoblasts.

1.6.4 Variable Responses

Not surprisingly, opinions persisted that there were variable patterns of occurrence in relation to the final state of the hypertrophic chondrocytes. Tschistowitsch [84] indicated that some of the hypertrophic cells degenerated completely and their space was invaded by vessels from the diaphyseal region which brought in cells of separate origin while other hypertrophic cells which appeared to be degenerating did not continue to final degeneration but persisted as pale transparent cells some of which appeared to regenerate and persist in medullary tissue. He was not able to follow the final evolution of the cells within the medullary tissue.

Almost 100 years later, many of the same questions as to the ultimate fate of the hypertrophic cell remain. With the onset of the identification of deposition of type X collagen within the hypertrophic zone matrix, and with definition by the ultrastructure of persisting organelles in the hypertrophic cells, the question has again been raised as to whether the swelling of the cells does or does not represent terminal degeneration. This phase is referred to today as apoptosis by

which is meant genetically determined or programmed cell death. While there appears to be little doubt that some and indeed most of the hypertrophic cells either die or are destroyed by the vascular invasion from below, the question remains as to whether or not some of the cells survive and go on to contribute both bone and perhaps even marrow elements to the metaphyseal region. In works by Gerstenfeld and Shapiro [85] and by Roach et al. [86] the opinions of current cell biologists as to possible lines of cell fate in this region were reviewed. (See also p. 43 below for discussion of the role of apoptosis and possible differentiation paths of hypertrophic chondrocytes.).

1.7 Structural Development of the Epiphyses, Metaphyses, and Diaphyses

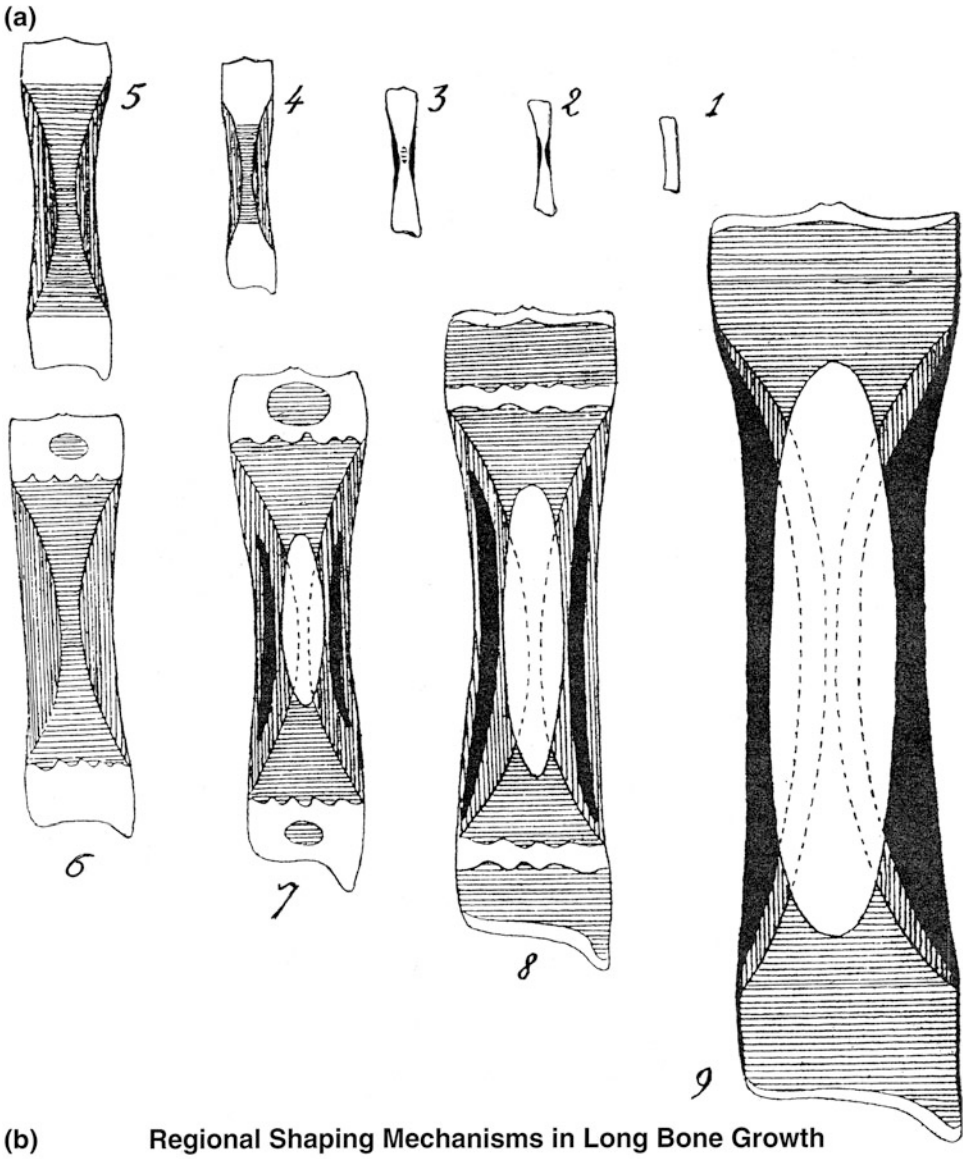
Series of histologic sections and diagrams outlining the cell and tissue development in long bone formation have characterized descriptions of bone formation since the late nineteenth century. These include the works of Mathias Duval, Schafer [64], Prenant, Maillard and Bouin [87], Renaut [88], Testut [89], Payton [67, 68], Maximow and Bloom [90], Nonidez and Windle [91], Dubreuil and Baudrimont [92], Ham and Cormack [93], and Krstic [94]. Figure 1.7a outlines an early accurate presentation of the dynamic aspects of the developmental sequence derived from M. Duval including the resorptive as well as synthetic phenomena in establishing bone shape and internal structure. The specific regional shaping mechanisms in long bone growth are outlined in Fig. 1.7a–d and in Tables 1.4 and 1.5. The structural features of long bone development are illustrated by light microscopic photomicrographs in Figs. 1.8a–j (limb bud and early endochondral and intramembranous bone formation), 1.9a–k (epiphyseal formation), and 1.10a–e (physeal and metaphyseal structure), and by electron micrographs in Fig. 1.11a–g (physeal structure).

1.7.1 Epiphyses

Once the primary ossification centers have formed and early endochondral and intramembranous bone formation has proceeded toward either end of the bone, it is at this stage that the entire cartilaginous region at the developing end of each long bone is referred to as the epiphysis. That part of the epiphysis adjacent to the joint is referred to as the articular cartilage. This merges in indistinguishable fashion histologically with the underlying epiphyseal cartilage and only reaches its definitive structure at skeletal maturity when the lowest zone of the articular cartilage calcifies persisting in the adult as the zone of calcified cartilage. The epiphyseal growth plate is the cytologically and functionally specialized region of the epiphysis responsible for most of the longitudinal growth of a long bone. Descriptions of its cell and matrix composition vary slightly between differing authors owing to the mixture of terms some of which are purely descriptive and others of which imply function. Table 1.5 outlines terminology for the layers of the physis which seems most consistent with current biological understanding and summarizes common terminology used by others. The cell layer at the outermost extent of the physis is composed of resting or germinal cells followed by the proliferating or columnar cell layer in which the chondrocytes line up in longitudinal array followed by the occurrence of the hypertrophic chondrocytes and below that the peripheral margins of the metaphysis. The epiphyseal growth plate, which is also referred to as the physis or simply the growth plate, maintains its height during growth as there is a symmetrical occurrence of cell proliferation at the upper margin allowing for longitudinal growth followed by resorption in the hypertrophic chondrocyte region allowing for formation of metaphyseal bone and marrow.

1.7.1.1 Secondary Ossification Center Formation

Cartilage canals which contain blood vessels are present within the epiphyseal cartilage from the early stages of epiphyseal development. At specific times, the chondrocytes within the central region of the epiphyseal cartilage undergo hypertrophy in association with mineralization of the cartilage matrix by a process felt to be entirely analogous to that occurring at the physeal–metaphyseal junction [95]. This is followed shortly with vascular invasion of the hypertrophic region from the adjacent cartilage canals, lysis of the hypertrophic chondrocytes, and the synthesis by osteoblasts, which accompany the vessels, of new bone on the calcified cores of cartilage. The initial positioning of the hypertrophic cells is uniform forming a 360° continuous arc of cells. As development proceeds, this circumferential arc of chondrocytes assumes a hemispheric shape with the hypertrophic chondrocytes forming in relation to the more peripheral articular surfaces, whereas the cartilage closest to the epiphyseal growth plate stops growing and the cell assumes the appearance of resting chondrocytes. The hypertrophic chondrocytes and the proliferating cells adjacent to them form what we refer to as the physis of the secondary ossification center. As growth continues the size of the cartilaginous epiphysis increases but there is a relative increase in the amount of secondary ossification center bone formation at the expense of the epiphyseal cartilage. For each epiphysis a point is reached in which the only cartilage persisting during the remainder of growth is the physis, the articular cartilage, and its under surface which is referred to by some as the mini-plate. By this stage, the secondary ossification center has almost completely replaced the epiphyseal



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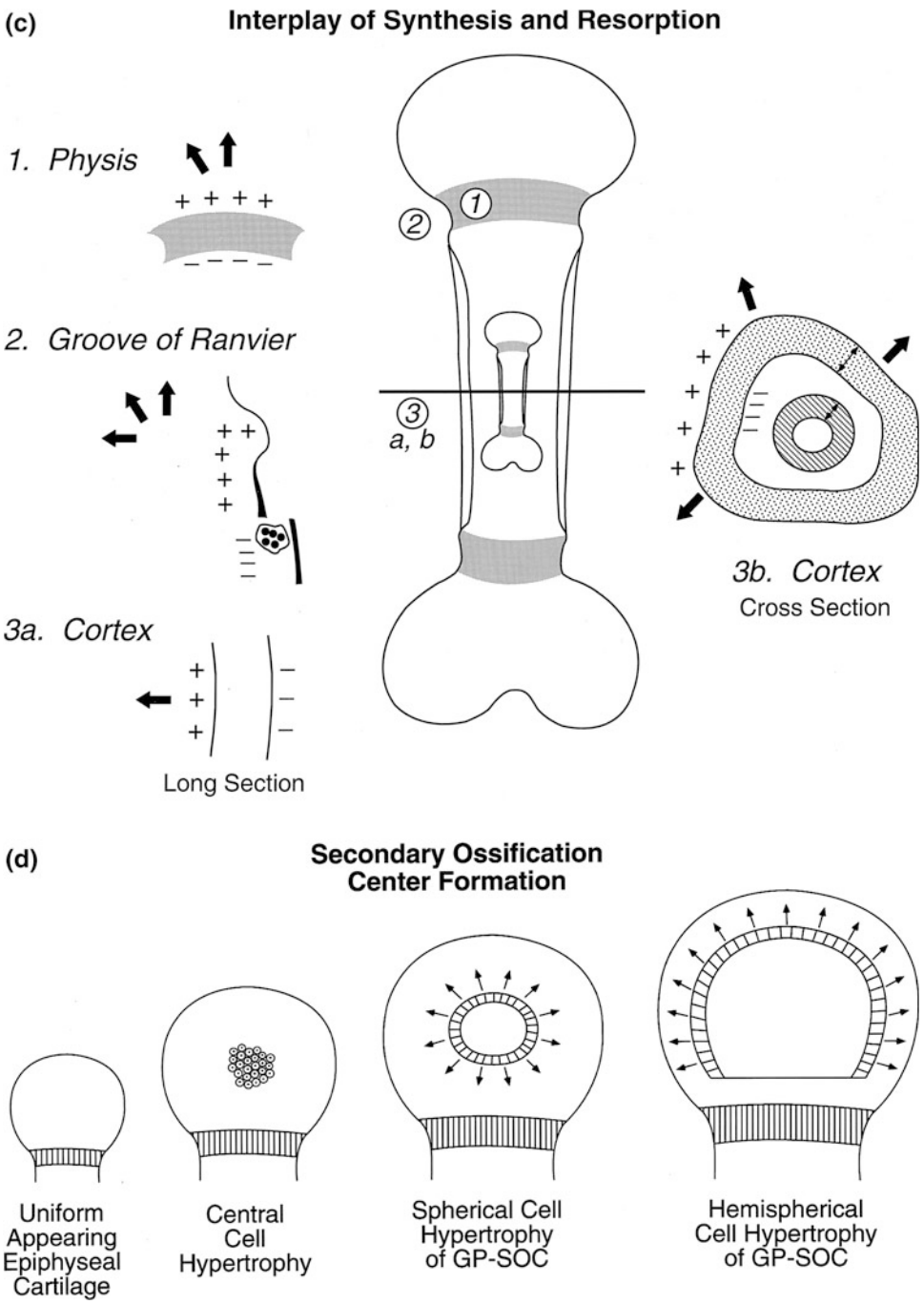


Fig. 1.7 Patterns and mechanisms underlying long bone growth are outlined. **a** These detailed illustrations show nine stages of growth and development of a long bone. Number *1* shows the cartilage model of the developing bone. Characteristic changes can then be seen progressing toward number *9*. Illustrations from number *4* on show periosteal bone indicated by the *vertical lines* and endochondral bone by the *horizontal lines*. The dense *black regions* of the cortex in *7*, *8*, and *9* represent compact cortical lamellar bone. In illustration number *6* the proximal secondary ossification center is shown while in number *7* both are present. The *dotted curved lines* in illustration numbers *7*, *8*, and *9* represent original cortical areas which have subsequently been resorbed to allow for marrow cavity formation. (Derived from M. Duval, modified from Prenant, Maillard and Bouin [87]). **b** Regional shaping mechanisms in long bone growth are shown. + = regions of outward tissue expansion; − = regions of tissue resorption. **c** Contributions of synthesis and resorption to long bone growth are shown. **d** Sequence of tissue changes in secondary ossification center formation and growth are shown

cartilage. We prefer the term physis of the secondary ossification center to mini-plate; it is more awkward but can be used to describe this specific region throughout the developmental cycle. The cartilage region closest to the main physis no longer undergoes proliferation and the secondary ossification center shows evidence of growth only adjacent

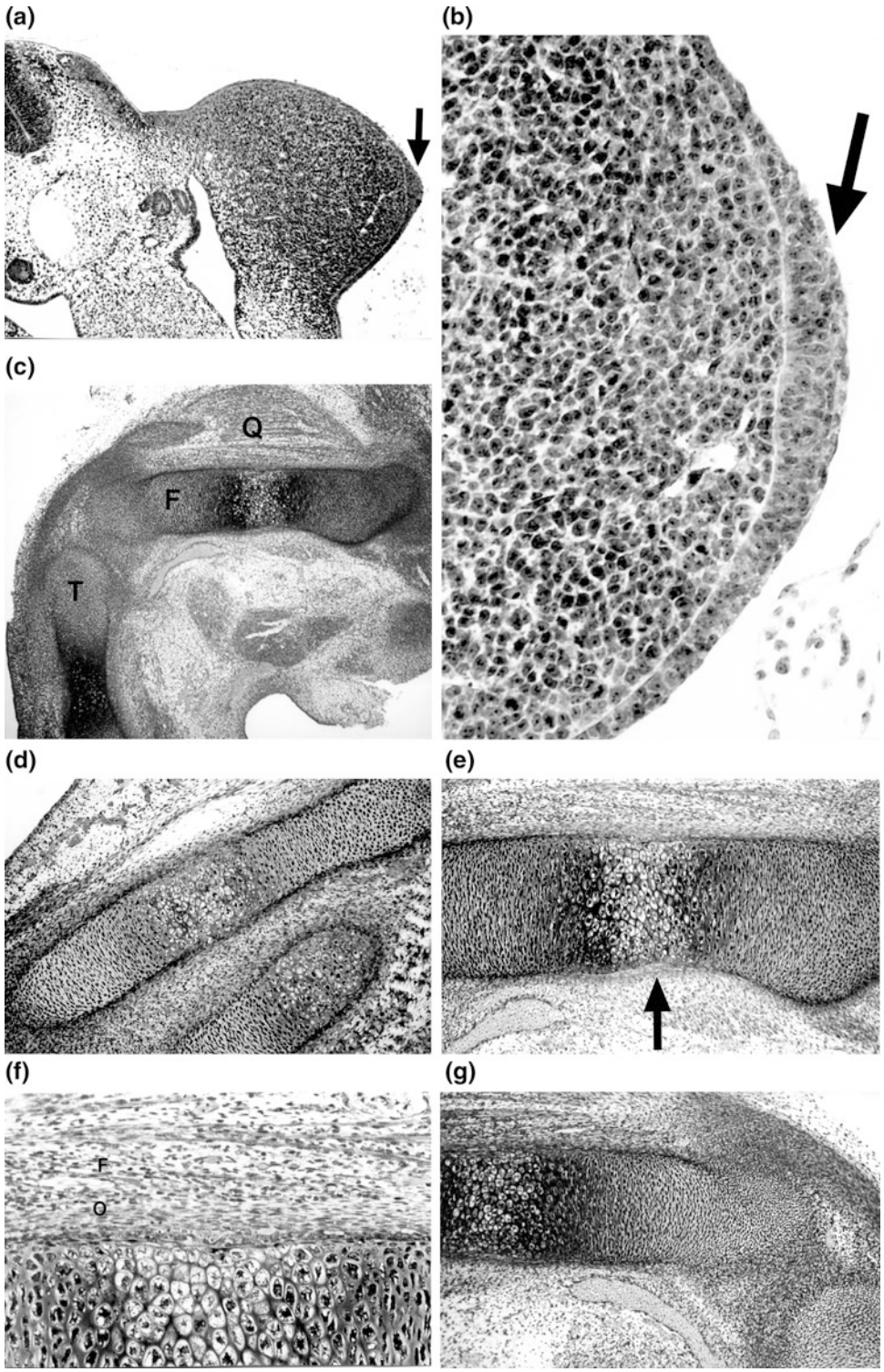
Table 1.4 Interplay between synthesis and resorption in long bone development

(i) *Articular–epiphyseal cartilage complex* synthesis/expansion by interstitial cartilage growth; resorption of bone/cartilage in secondary ossification center (to shape epiphyseal regions and articular cartilage surfaces)
(ii) *Growth plate* synthesis/expansion germinal to hypertrophic zones; resorption at lower hypertrophic zone/upper metaphysis (to maintain same growth plate thickness throughout most of the growth period.)
(iii) *Diaphyseal cortex* new bone formation by apposition on outer side by periosteum; resorption on inner side by osteoclasts (to maintain same relative extent of cortex throughout growth while allowing for progressive expansion of diameter of marrow cavity)
(iv) *Perichondrial groove of Ranvier* widening of physeal cartilage and furthest extent of periosteal new bone formation; resorption at lowermost groove region to remove bony ring (allows for metaphyseal funnelization)

Table 1.5 Structural terms for the epiphyseal growth plate or physis

Descriptive terms
1. Resting cell zone
2. Columnar cell zone
3. Hypertrophic cell zone
4. Metaphyseal bone
Functional terms
1. Germinal zone
2. Columnar cell zone
(a) Upper proliferating zone
(b) Lower maturation zone
3. Hypertrophic cell zone
(a) Upper part (4/5th), non-mineralized matrix
(b) Lower part (1/5th), mineralized matrix zone of provisional calcification
4. Metaphysis-outer reaches
Ham and Cormack (Ref. [93])
Zone of resting cartilage, Zone of young proliferating cartilage, Zone of maturing cartilage, Zone of calcifying cartilage, Developing trabeculae of metaphysis
Brighton (Ref. [98])
Reserve zone, Proliferative zone, Zone of maturation, Zone of degeneration → hypertrophic zone, Zone of provisional calcification

to the side walls of the epiphysis and to the undersurface of the articular cartilage. This is also reflected by changes in the structure of the secondary ossification center. At those regions immediately adjacent to the hypertrophic cell areas there is a continuing development of the endochondral sequence with new bone synthesized on cartilage cores. At that part of the secondary center adjacent to the physes where cell proliferation is no longer occurring bone is almost exclusively present with minimal to no traces of persisting cartilage cores. In association with this change in orientation of the physes of the secondary ossification center and its hypertrophic cell region, there is also a change in the marrow pattern. That marrow immediately adjacent to the hypertrophic zone always remains hematopoietic whereas the marrow in the regions closer to the epiphyseal bone plate demonstrates the area of earliest fatty change [96]. Toward the end of active epiphyseal growth there is a slowing down of the function of the physes of the secondary ossification center. Bone formation begins to predominate over the central cartilage cores since bone synthesis from the marrow cells continues. At skeletal maturation, the lowest level of the articular cartilage becomes calcified and this layer persists through adult life. A subchondral bone plate is formed. Virtually all the marrow is now fatty. The epiphyseal growth plate itself stops its proliferative function, is gradually resorbed from the metaphyseal side, and eventually completely disappears allowing for a continuity of the epiphyseal and metaphyseal bone marrow and circulations. The peripheral perichondrial ossification groove is an integral part of the epiphysis. The staging classification including all structural aspects of epiphyseal development as outlined by Shapiro and Rivas [97] is listed in Table 1.6.



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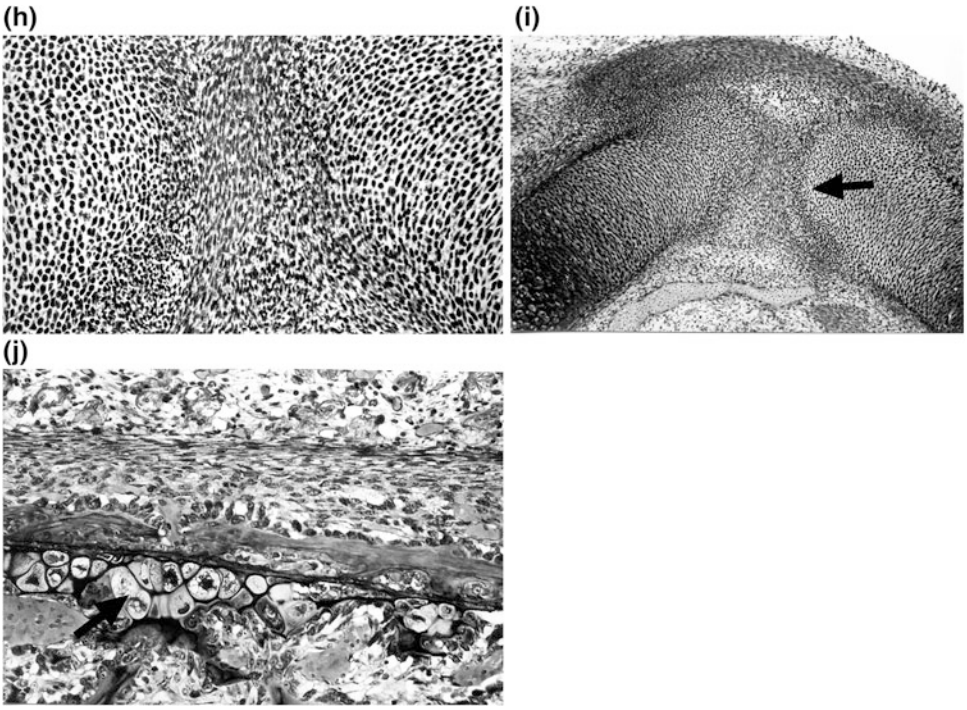
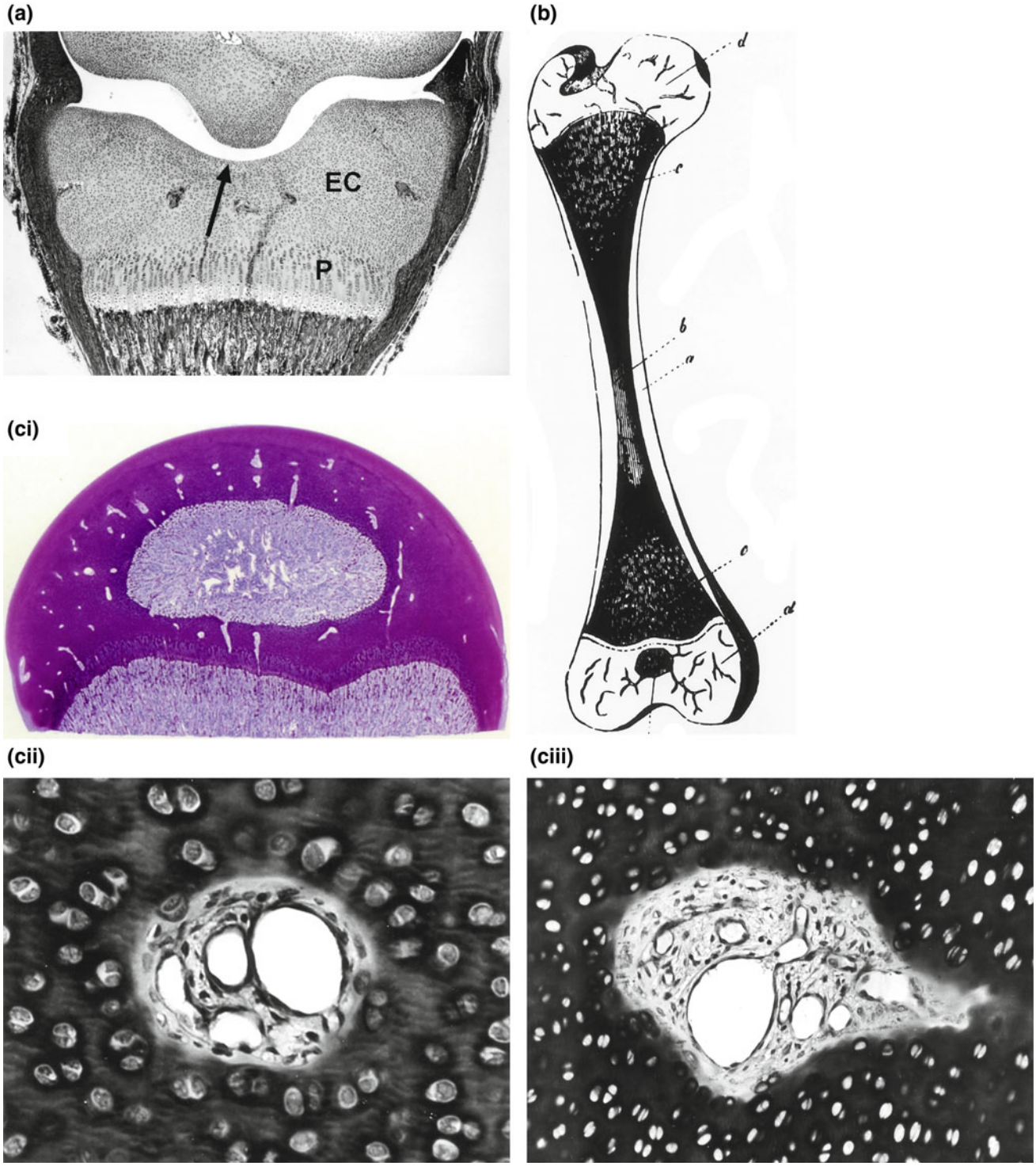


Fig. 1.8 This figure shows the histologic features of the intrauterine developmental sequence of the limb. These photomicrographs are from the developing embryonic and fetal limb of the rabbit although the histologic appearance in the human is the same. **a** The developing limb bud is shown at right along with the spinal cord at *upper left*. At this stage the limb bud is composed of undifferentiated closely packed mesenchymal cells with no histologic evidence of any structure. The densely packed cells of the apical ectodermal ridge are shown at far *right* (*arrow*). **b** A higher power view of the tip of the limb bud showing the mesenchymal cells and the apical ectodermal ridge (*arrow*). **c** A major segment of the developing lower limb is seen at a slightly later stage. The developing femur (*F*) and tibia (*T*) are shown, as is the quadriceps (*Q*) muscle mass. The central region of the femur shows the early changes of chondrocyte hypertrophy. These bones were initially formed completely in cartilage. **d** A slightly higher power view of a developing long bone, a metatarsal, shows the cartilage model and central regions of cell hypertrophy. **e** A higher power view of the femur shown in figure **c** highlights the hypertrophic region. There is also development of the intramembranous bone mechanism at the primary center of ossification (*arrow*). The popliteal artery is seen at *lower left*. Quadriceps muscle fibres are shown *above*. **f** The central hypertrophic cells of the femur are shown. The outer fibrous (*F*) and inner osteogenic (*O*) layers of the developing periosteum are seen. **g** The interzone region of the developing joint is seen at *right*. The cartilage models of the femur (*left*) and tibia (*lower right*) are shown. Cells completely fill the region between these two bone models indicating the relatively late time of formation of the joint. **h** A higher power view shows the dense cell accumulation within the interzone region. **i** The femoral cartilage is shown at *left* and tibial at *right*. The beginning *outline* of density of the articular cartilage surface of the tibia is seen (*arrow*). **j** At a slightly later stage of development the formation of the intramembranous bone sequence overlying the central endochondral sequence is seen. Endochondral bone formation is seen below and intramembranous bone *above*. Hypertrophic cells of the central endochondral sequence are seen to persist (*dark arrow*). The outer fibrous layer and the inner osteogenic layer of the periosteum are *above*. Surface osteoblasts overlying newly synthesized cortical bone are seen

1.7.1.2 Physis. Structure and Relation to Function

The cells and matrices of the epiphyseal growth plate have been well defined at the light microscopic and ultrastructural levels (Figs. 1.10, 1.11 and 1.12). The resting or germinal cell layer chondrocytes are round to oval in shape, and possess a central nucleus and a cytoplasm which is filled with abundant amounts of rough endoplasmic reticulum. The endoplasmic reticulum is mildly to moderately dilated, a finding considered to be consistent with synthesis of protein which in this instance is primarily type II collagen. There is also a well-developed Golgi apparatus which is responsible for processing the proteoglycans. The chondrocytes of the columnar or proliferating zone are markedly flattened and align themselves into columns. There is a marked tendency for these chondrocytes to be wedge shaped with the bases of the wedges alternating to allow the linear conformation to persist. The cells are also quite active in terms of mitoses in the proliferating upper part of the zone and in relation to protein synthesis showing abundant amounts of dilated rough endoplasmic reticulum in the lower or maturation part of this zone. In the hypertrophic zone a characteristic cell appearance is seen with the cell volume larger than in the above lying regions. The nucleus persists but there are many clear spaces within the cytoplasm. There is an apparent marked diminution of rough endoplasmic reticulum and by



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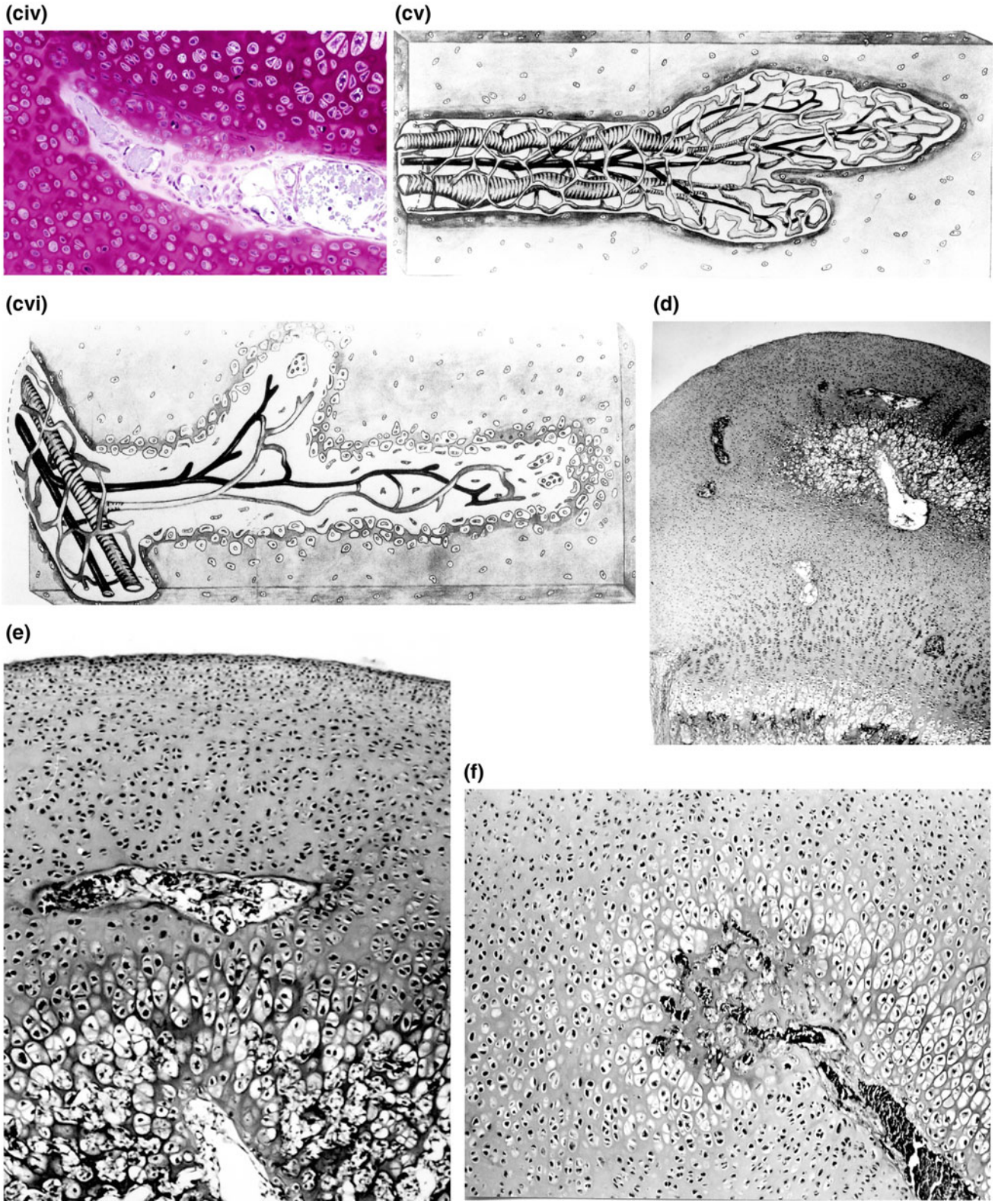

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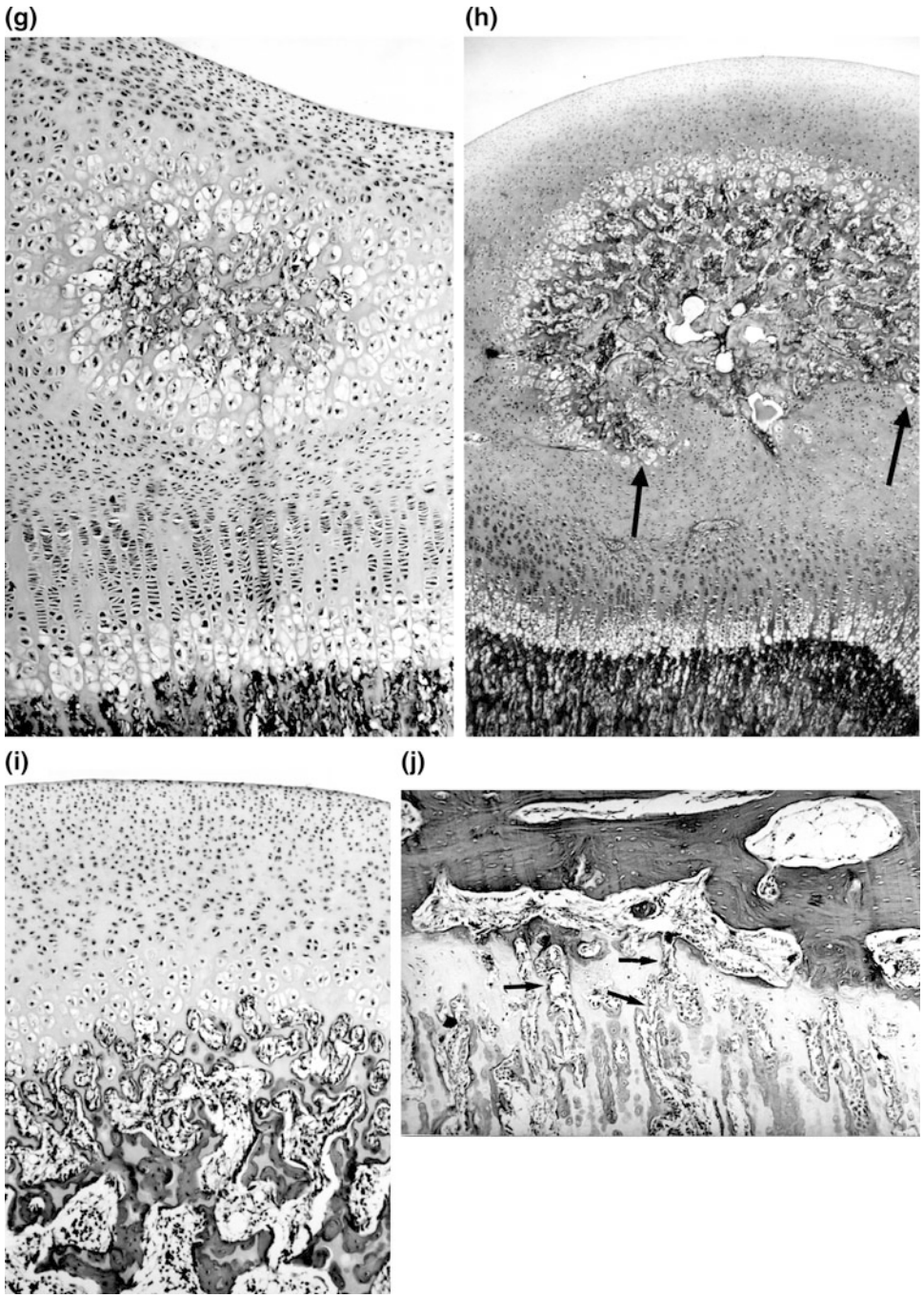


Fig. 1.9 (continued)

the time one examines cells at the lower margins of the hypertrophic zone, only scattered cisternae of endoplasmic reticulum persist. In the upper parts of the hypertrophic zone the cartilage matrix is not calcified. Calcification occurs in the matrix of the lower margins of the hypertrophic zone but involving almost exclusively the longitudinal septae along the long axis of the bone, whereas the transverse septae are either not mineralized or only slightly mineralized. The vascular invasion from below progresses two or three cells deep into the lower margin of the hypertrophic zone and in association with this vascular invasion of the hypertrophic cell regions there is deposition of bone by osteoblasts on the persisting calcified cartilage matrix. The sequence of events is illustrated in the adjacent figures and figure legends. Each level of the physis merges gradually with the level below; there are no sharp transitions. In addition, transitions of cell

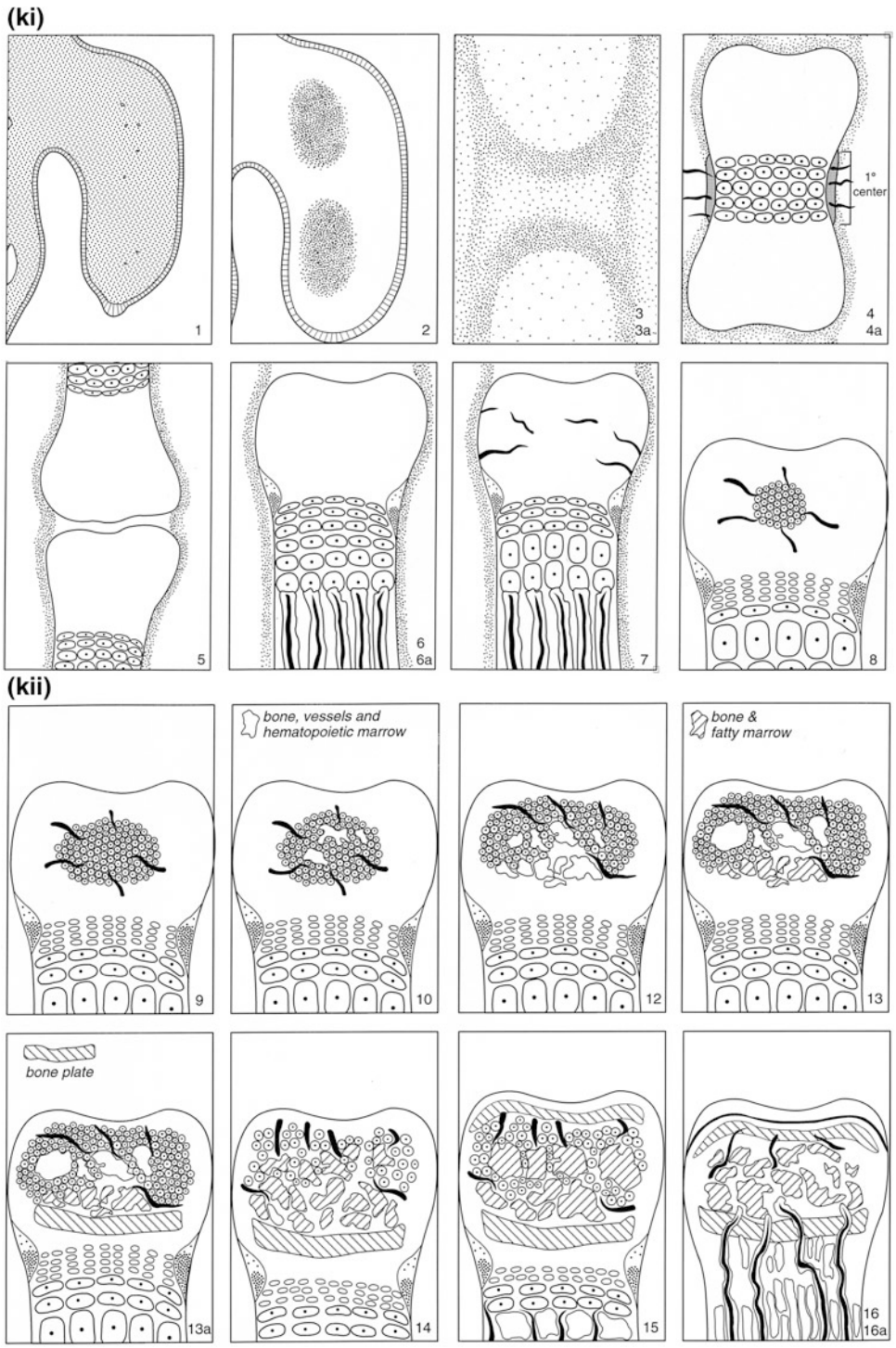


Fig. 1.9 (continued)

size, shape, and function occur sequentially even within each sub-region.

The resting or germinal cell layer does not contribute directly to longitudinal growth because the chondrocytes do not proliferate. [98, 99] (The two terms resting and germinal seem to be used interchangeably by many authors partly because they are not very distinct morpohologically compared with the layers below). The cells' high lipid vacuole contents indicate that they are a storehouse for nutrients [100]. The cells are similar to those of hyaline cartilage with small round or elliptical cells in an irregular distribution [101].

In the proliferating layer, the chondrocytes are arranged in columns parallel to the longitudinal axis of the bone and are separated from each other by matrices with large amounts of type II collagen. The number of cells in each column ranges from 10 to 20, according to the mitotic moment of the column. The more cells there are, the greater the physeal growth [101]. In the proximal portion of each column, multiple mitoses can be observed, even though each column behaves independently [101]. The chondrocytes only divide in this zone of the growth plate and the high degree of division makes the cells flat and slightly irregular in shape. The proliferating layer has high oxygen content, and the chondrocytes store large amounts of glycogen with raised mitochondrial ATP production [102]. It is in the lower half of the proliferating layer that matrix synthesis by the chondrocytes is extensive. Ultrastructural examination shows the chondrocytes with large amounts of rough endoplasmic reticulum.

Hypertrophic Chondrocytes: The function of the hypertrophic cell layer is not only to synthesize matrix but also to cause growth by cell expansion (hypertrophy) [85, 98, 103–112]. The hypertrophic chondrocyte, by the mechanism of swelling, is actually the principal engine of longitudinal bone growth. During the differentiation process, the chondrocytes increase their intracellular volume from 5 to 10 times, a sign of major activity in the intracellular organelles and cytosol. The hypertrophic chondrocyte is a viable master regulatory cell with an active metabolism. It prepares the matrix for calcification and vascularization. In this zone, collage Type X is synthesized as is vascular endothelial growth factor (VEGF) [113–116]. It directs the mineralization of the adjacent matrix and attracts vessels by producing vascular growth factors. Variation in the rate increase of hypertrophic chondrocytes has been regarded as the key to differences in the growth rate at different anatomic sites. According to Wilsman et al. [117] between 40 and 50 % of the differences between the growth rates of the different physes can be explained by differences in the degree of hypertrophy, the rest depending on matrix synthesis and the index of cell proliferation. The chondrocytes of the growth cartilage in rapidly growing bones such as the femur increase in size more than those of the slow-growing bones like the radius [106, 118]. When the skeleton is approaching growth maturity, the index of longitudinal growth drops and the chondrocytes in the growth plate proliferate less rapidly. The development of the chondrocytes from the germinal cell, proliferating cell, and hypertrophic cell zones down to the calcified matrix occurs in approximately 24 h (9).

The terminology used by Buckwalter et al. [119] to describe the physis is the reserve (germinal) zone, upper and lower proliferating zones, and upper and lower hypertrophic zones. Their histomorphometric studies of proximal tibial physes in mice of varying ages show that in transverse

◀ **Fig. 1.9** Some characteristic developmental features of epiphyseal formation are shown. Patterns in humans are similar to those seen in pig and rabbit. **a** The cartilaginous epiphysis at the developing end of a rabbit phalangeal bone is shown. At this stage, there is no formation of the secondary ossification center. The articular cartilage (*black arrow*), epiphyseal cartilage (*EC*), and physeal cartilage (*P*) are shown, as is the perichondrial groove of Ranvier (at the periphery of the physis). **b** Cartilage canals containing vessels have long been recognized as an integral part of epiphyseal development. They are responsible initially for nutrition of the cartilage and only later, often several months later, are they involved in the formation of the secondary ossification center. They are shown here within the cartilage at either end of the developing end of human bone from an illustration by Koelliker [52] over 160 years ago. **c** The cartilage canals (**i, ii, iii,** and **iv**) from a developing proximal femoral capital epiphysis in the newborn pig are shown. They are never present in the articular cartilage but often traverse the physis in the fetal and early post-natal time period. Vessels are present within a loosely packed connective tissue matrix. In figures (**v**) and (**vi**) Watermann [217] depicts vessel contents of a larger (**v**) and smaller (**vi**) canal. The striated structures are arterioles, the *dark solid structures* are venules, and the smaller structures are capillaries. (Reprinted with permission from Jaramillo et al. Gadolinium-enhanced MR imaging demonstrates abduction-caused hip ischemia and its reversal in piglets. Pediatr Radiol 1995;25:578–587. Copyright 1995 Springer and Watermann R, Gefassversorgung der distalen femurepiphyse. Z Orthop 1966;101:247–257. Copyright Georg Thieme Verlag). **d** Central cartilage hypertrophy is seen in early formation of the secondary ossification center from a rabbit proximal humerus. Adjacent cartilage canals are shown. Articular cartilage is at top while physeal and metaphyseal tissues are at *bottom of photograph*. **e–f** Cartilage matrix mineralization followed by vascular invasion has occurred in higher power photomicrographs. The vascular invasion has extended from the cartilage canals. (Matrix mineral is not seen since the specimens have been decalcified for better sectioning.) Early developing secondary ossification center shows a vessel at lower right passing into the center of the region (**f**). **g** Endochondral bone formation is now seen centrally in the proximal humeral epiphysis with new bone synthesized on cartilage cores and early evidences of marrow cavitation. The hypertrophic cells of the secondary ossification center are oriented in a 360° arc. **h** The secondary ossification center has increased in size in relation to the epiphyseal cartilage. At this stage the orientation of the hypertrophic chondrocytes of the physis of the secondary ossification center, mini-plate in some terminologies, has changed from a 360° orientation shown in figure **g** to an approximate 180° orientation here. The *two arrows* illustrate where the cell hypertrophy of this region ends with the area between the arrows no longer showing such changes. **i** At a slightly later stage of development the secondary ossification center moves progressively toward the articular cartilage surface. There is considerable cartilage however between the surface of the articular cartilage and the hypertrophic zone of the physis of the secondary ossification center. Endochondral bone is present now within the secondary ossification center with only small persisting central cores of cartilage seen. The marrow is hematopoietic. **j** Physeal closure shows disappearance of proliferating and hypertrophic zones and beginning transphyseal vessel communication (*arrows*). A continuous bone plate of mature lamellar bone is seen at *top* indicating complete replacement of the epiphyseal cartilage. **ki**, **ii** Epiphyseal development classification of Rivas and Shapiro [97]. Details are described in Table 1.6. (Reprinted with permission from Rivas and Shapiro, Structural stages in the development of the long bones and epiphyses. J Bone Joint Surg Am 2002;84A:85–100)

sections, cell profiles do not change within the same growth plate zones but in longitudinal sections the cell profiles and profile orientations differ significantly among zones. Cell profiles in the upper and lower proliferative zones are eccentric and highly oriented but they become more rounded and the degree of cell orientation decreases between the proliferative and hypertrophic zones. The degree of cell profile orientation decreases extensively in the upper and lower proliferative zones, less in the reserve and upper hypertrophic zones, and remains unchanged in the lower hypertrophic zones at varying ages. Changes in cell profiles and in the degree of proliferative zone cell profile orientation correlate with the rate of longitudinal bone growth. Chondrocytes prior to the appearance of a growth plate have rounded profiles with no apparent orientation. Questions remain as to what mechanisms give the cells of the proliferative zone their eccentric shape and high degree of orientation. A correlation is noted between the degree of chondrocyte flattening and the rate of proliferation with flatter cells proliferating more rapidly and less flattened cells decreasing their rate of proliferation. Others have suggested that the cell is flattened secondarily by the accumulation of matrix. Hypertrophic zone cells have a less eccentric shape and rarely if ever divide although they do enlarge. Their height in particular is increased in relation to their width which appears associated with the decreasing rate of DNA synthesis and proliferation. Cell swelling in the lower proliferative and upper hypertrophic zones tends to change the eccentrically-shaped highly oriented proliferative cell into the rounded and randomly oriented hypertrophic cell. Their height is increased relative to their width and it is felt that the growth plate matrix helps restrain transverse expansion. The flattest most highly oriented cells are those with the highest rate of proliferation while development of a more spherical shape and loss of orientation seem to be associated with a decreasing rate of proliferation.

A second assessment by Buckwalter et al. studied chondrocyte hypertrophy [104]. It is evident that in the hypertrophic zone, the chondrocytes enlarge and assume a more spherical shape. Morphometric analyses of electron micrographs show that between the upper proliferative zone and the lower hypertrophic zone, the cells increase their mean volume by more than 500 %. As the cells enlarge, the intercellular matrices change. The territorial matrix volume increases but the interterritorial matrix volume decreases. Between the upper proliferative zone and the lower hypertrophic zone, the absolute volume per cell of endoplasmic reticulum, Golgi membranes, and mitochondria increases 126 % while the volume of cytoplasm and nucleoplasm increases 779 %, apparently by the accumulation of water. Chondrocyte enlargement thus involves some increase in organelle synthesis, but the primary mechanism of cell enlargement is cytoplasmic and nuclear swelling. The chondrocytes enlarge primarily by accumulating water. The endoplasmic reticulum (ER) and mitochondria dilate, ribosomes dissociate from the endoplasmic reticulum, and distended fragments of ER or Golgi appear in the cytoplasm.

This work along with biochemical studies which identified type X collagen synthesis localized to the hypertrophic zone [120–122] raised again the question as to whether all

Table 1.6 The general plan of epiphyseal development (Rivas and Shapiro)

Stage 1	Limb bud formation. Uniform mesenchymal cell distribution. Apical ectodermal ridge
Stage 2	Mesenchymal condensation
Stage 3	Cartilage differentiation
Stage 3a	Interzone formation
Stage 4	Epiphyseal shaping
Stage 4a	Primary center of ossification
Stage 5	Resorption of joint interzone. Smooth articular cartilage surface
Stage 6	Physeal differentiation and peripheral groove tissue formation
Stage 6a	Furthest relative extent of epiphyseal/physeal position
Stage 7	Epiphyseal cartilage vascularization. Cartilage canals
Stage 8	Central chondrocyte hypertrophy to form spherical mass, development of growth plate completely surrounding secondary ossification center
Stage 9	Vascular invasion of developing secondary ossification center hypertrophic chondrocytes adjacent to mineralized cartilage matrix
Stage 10	Bone formation and marrow cavitation in secondary ossification center. Hematopoietic marrow
Stage 11	Increase in size of secondary ossification center, decrease in epiphyseal cartilage
Stage 12	Central chondrocyte hypertrophy/secondary ossification center growth plate change to hemispherical orientation
Stage 13	Fat in marrow. Hematopoietic marrow adjacent to secondary ossification center growth plate
Stage 13a	Epiphyseal bone plate formation
Stage 14	Fullest relative extent of secondary ossification center involvement in epiphyseal cartilage articular cartilage mini-plate formation
Stage 15	Thinning of the physis
Stage 15a	Articular cartilage mini-plate growth cessation
Stage 15b	Subchondral bone plate formation
Stage 16	Resorption of physis linking epiphyseal and metaphyseal circulations
Stage 16a	Calcification of lowest zone of articular cartilage and tidemark formation. All marrow fatty

From Rivas and Shapiro, J Bone Joint Surg Am 2002; 84–100; (Ref. [97])

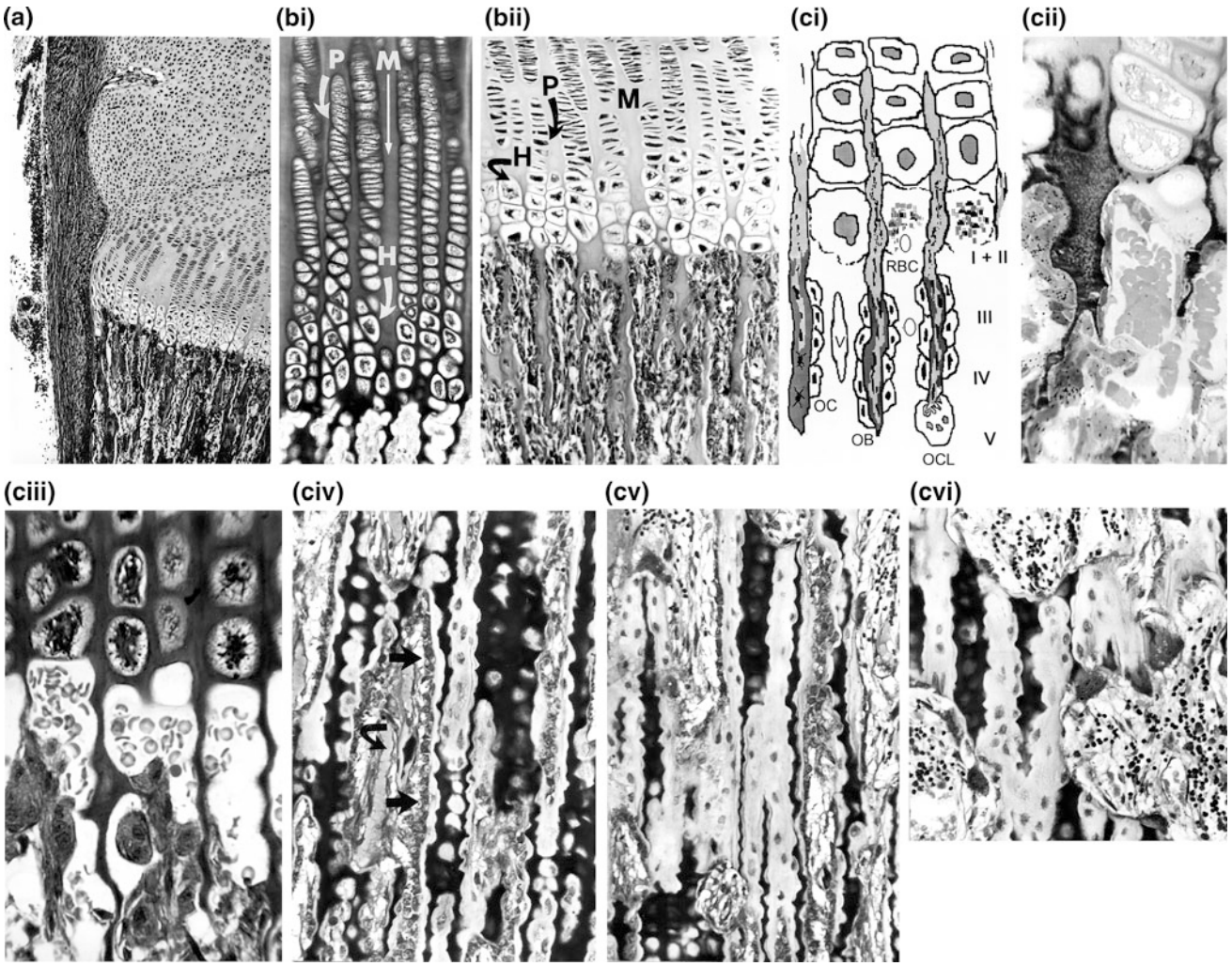


Fig. 1.10 (continued)

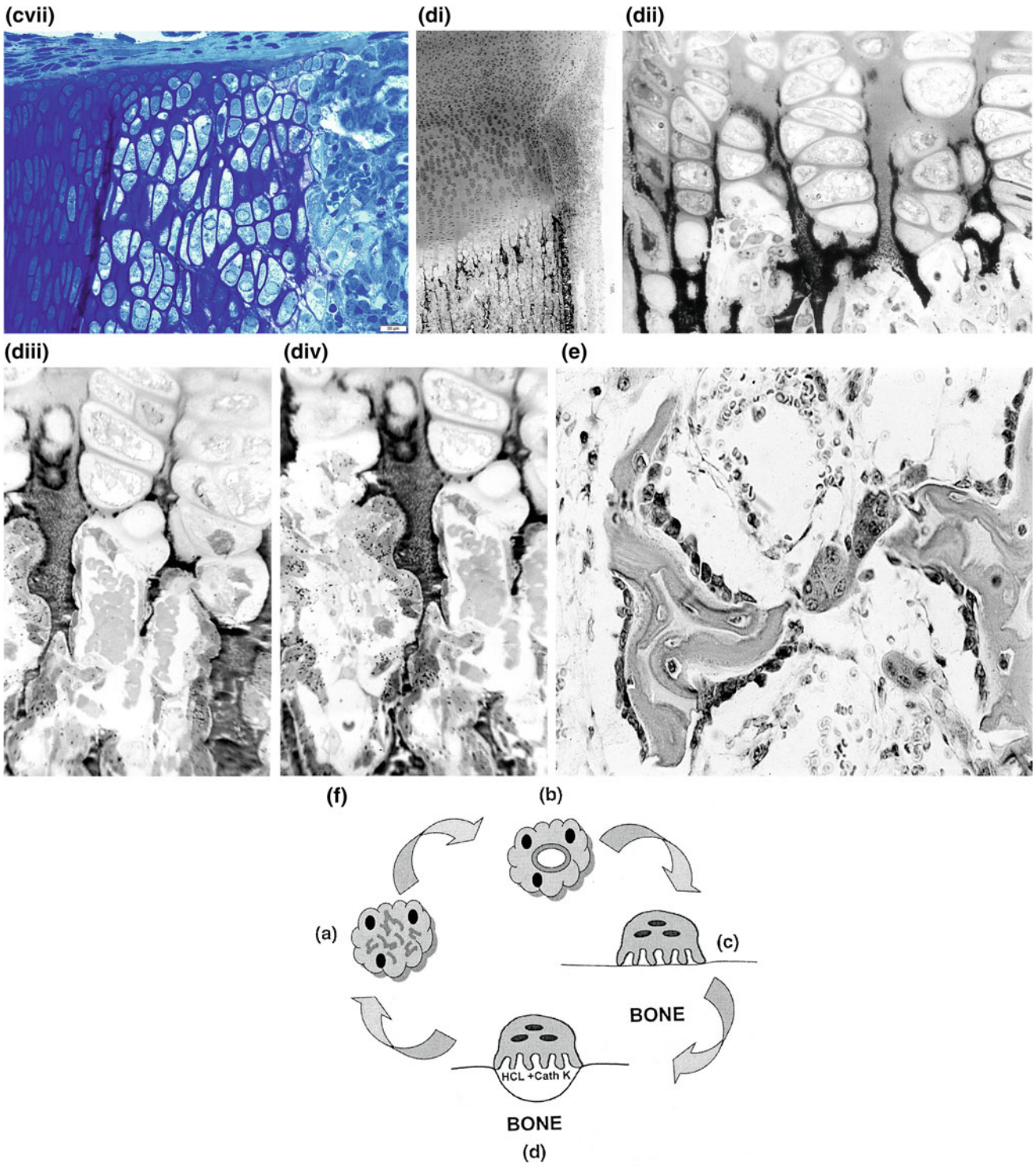


Fig. 1.10 (continued)

hypertrophic cells were degenerating or whether some, and perhaps a significant number, survived and functioned deep into the physeal region and perhaps beyond. The work reviewed above in Sects. 1.3 and 1.4 becomes relevant again.

Throughout most of the first half of the twentieth century the hypertrophic chondrocyte was considered to be a degenerating cell at the terminal end of the endochondral sequence. It was recognized that its swelling helped provide longitudinal growth, but that its degeneration coincided with vascular invasion of the hypertrophic cell lacunae following which bone was synthesized on the cartilage cores to form the metaphyseal trabeculae. Holtrop studied the hypertrophic chondrocyte at the ultrastructural level and concluded that "the results showed ultrastructural preservation of the cells that strongly suggest cell activity from the beginning of enlargement of the cell up to the stage where the lacunae breaks open" [123, 124]. She felt that a careful morphologic study did not confirm the long-accepted view of degeneration or cell death but was, rather, consistent with cell activity. Not only did the hypertrophic chondrocytes appear to play a role in the calcification of the matrix, which was being suggested by others, but she felt that they had the potential to become osteoblasts and osteocytes. Once again,

◀ **Fig. 1.10** Physeal and physeal–metaphyseal junctional tissues are detailed in this figure. All specimens except figure **e** are from the rabbit. **a** The resting germinal cell layer of the physis is not a particularly well-defined layer either by histologic or autoradiographic criteria being present between the epiphyseal cartilage and the proliferating cell layers of the physis. It is considered to become or serve as the germinal layer for the well-structured and clearly evident proliferating cell layer of the physis below. **bi**, **ii** are presented. The proliferating (*P*) or columnar cell layer of the physis is shown *above*; these cells then merge into the hypertrophic cell layer (*H*) as the cells increase in size. Cartilage matrix is labeled (*M*). The metaphysis is shown *below*. These various layers merge into one another with changes in cell activity and in cell size occurring gradually in progressive fashion. The proliferating cell zone is recognized in its *upper part* to undergo proliferation characterized by a high uptake of tritiated thymidine indicating DNA turnover. In its *lower part*, it is sometimes referred to as a zone of maturation in the sense that there is little cell turnover but the synthesis of proteoglycans, collagen, and non-collagenous proteins occurs actively. The hypertrophic zone region also can be subdivided into an upper zone which is characterized by a progressive increase in cell size which contributes extensively to longitudinal growth of the bone and a lower hypertrophic zone where the matrix mineralizes in preparation for eventual vascular invasion of the hypertrophic cell lacunae. This *lower* layer has been referred to by some as part of the zone of provisional calcification. Metaphyseal bone is formed in association with the advancing front of vascularization. (Reprinted with permission from Gerstenfeld and Shapiro, Expression of bone-specific genes by hypertrophic chondrocytes. J Cell Biochem. 1996;62:1–9. Copyright 1996 John Wiley and Sons). **c** Morphological characteristics at the growth plate cartilage–metaphyseal bone interface are shown in figure **ci–vii**. Diagrammatic illustration and surrounding high power photomicrographs are shown. Figure **ci** A diagrammatic outline of the major morphological and cellular events at the hypertrophic chondrocyte–metaphyseal interface is presented: *RBC*, red blood cell; *OB*, osteoblast; *OC*, osteocyte; *OCL*, osteoclast; *V*, vessel. The major morphological landmarks (Areas I–V) are depicted in the adjacent micrographs. Area I: is figure **cii**. Photomicrograph illustrates a portion of an undecalcified growth plate–metaphyseal junction from a 2-week-old rabbit metatarsal. The hypertrophic cells are seen above. Note the dark staining mineral in the longitudinal cartilage septae with very little or no mineral in the transverse septae. Vascular invasion of the hypertrophic cell lacunae has occurred on one side of a mineralized cartilage trabeculum, while on the opposite side there are newly differentiating mesenchymal cells designed to become osteoblasts and synthesize osteoid on the calcified cartilage core. The dots represent tritiated proline in the autoradiograph with sacrifice performed 20 min after injection. Area II: is figure **ciii**. High power photomicrograph shows the lower regions of the hypertrophic zone at *top* and the vascular and mesenchymal cell invasion from *below*. This histologic section and those depicting areas III, IV, and V are all demineralized preparations. The hypertrophic cells from the lowest layers of the hypertrophic zone are seen. Red blood cells from the metaphysis are seen adjacent to the last persisting hypertrophic cell lacunae. A multinucleated osteoclast is seen, as are undifferentiated mesenchymal cells which will shortly begin to synthesize an osteoid matrix on the persisting cores of calcified matrix. (Proximal tibial growth plate–metaphyseal junction in 1-month-old rabbit; plastic embedded JB4 section stained with 1 % toluidine *blue*.) Area III: is figure **civ**. Photomicrograph of metaphyseal tissue immediately adjacent to the hypertrophic zone of the growth plate from a 1-month-old rabbit proximal tibial metaphysis. The persisting cartilage cores are black. Newly synthesized bone can be seen adjacent to them. Osteoblasts (*arrow*) line the surface of the newly synthesized bone. Osteocytes are within. We refer to these as mixed trabeculae encompassing both bone and cartilage tissue. A vessel (*curved arrow*) is also seen. A multinucleated osteoclast is seen centrally where it is resorbing both cartilage and bone (*black arrow*). Area IV: is figure **cv**. Photomicrograph of tissue deeper within the metaphyseal region. There are areas of persisting cartilage (*black*) but much more newly synthesized light staining bone. Surface osteoblasts are seen as are osteocytes and osteoclasts. Area V: is figure **cvi**. A high power view of metaphyseal bone and cartilage trabeculae is seen. Osteoclasts can be seen resorbing both bone and cartilage. Figure **cvii**. Histologic section in color prepared with ruthenium hexammine trichloride shows maintenance of intact hypertrophic chondrocytes even at lowermost regions of hypertrophic zone immediately adjacent to site of vascular invasion **d** Mineralized sections of a rabbit metatarsal epiphysis and adjacent metaphysis are shown in sections *i–iv*. Figure **di** shows mineralized longitudinal cartilage septae passing up into the lower reaches of the hypertrophic zone. At far right the mineralized cortex is also seen. A higher power view of a part of the physeal–metaphyseal junction is shown in **dii**. It is the longitudinal septae that remain mineralized with the transverse septae for the most part free of mineral. In figures **diii**, **iv** a tritiated proline autoradiograph of the mineralized physeal-metaphyseal junction is shown. Centrally in iii one can note the red blood cells passing into the hypertrophic cell lacunae following disruption of the transverse and oblique septae. Section *iv* adjacent to the region of section *iii* shows at the *left side* of the central cartilage septum the proline labeled osteoblasts which are lying on the calcified cartilage core and will shortly begin synthesis of osteoid. **e** Photomicrograph from the metaphyseal region of a developing calf long bone. A central cartilage core is seen surrounded by newly formed bone. Young osteocytes are present within the bone matrix. Osteoblasts line the surface of the bone. Immediately adjacent to the osteoblasts one can see a multinucleated osteoclast resorbing bone and ultimately cartilage. The marrow contains two cell lines; one serves as a hematopoietic precursor including monocytes which fuse to form osteoclasts and the other cells called stromal precursors can differentiate into pre-osteoblasts and osteoblasts. **f** Formation and mechanism of action of an osteoclast are outlined

careful microscopy was raising the question not only of the function of the hypertrophic cell, but also of its persistence, much as did the work of Retterer and the many authors he referred to in the late nineteenth century. Holtrop also reported on transplantation experiments of 4-week-old mice rib growth plates into leg muscles [125]. These experiments were designed to assess the potency of the physeal tissue itself in relation to its presumed passive role at the terminal end of the endochondral sequence where it was resorbed. In the discussion she repeated her previous contention that "hypertrophic cartilage cells are able to transform into osteoblasts and osteocytes." She suggested that the development of endochondral ossification in cartilage transplants in the hypertrophic zone implied a more active role for the hypertrophic cells. A second study demonstrated that the function of the physeal transplant was independent of the host since younger transplants elongated more than older transplants using the same technique. The ultrastructure of the growth plate was described in detail in two subsequent articles [107, 108].

Hunziker and Schenk further clarified the functions of the specific cell regions of the growth plate [111, 112, 126]. The growth plate is structurally characterized by the resting or reserve zone, proliferation and hypertrophy of chondrocytes, calcification, and vascular invasion. Cells within the resting zone immediately adjacent to the epiphyseal bone occur singly or in groups of two, are distributed randomly within the matrix, and lack a columnar arrangement. Kember has shown these cells to have stem cell function and to undergo division only rarely. Cells adjacent to the tip of the columns below are considered as stem cells which feed daughter cells into the proliferating pool. The proliferating zone itself has a clear-cut columnar arrangement. Parallel to the long axis of the bone, chondrocytes divide in a transverse direction with daughter cells situated initially side by side. They then switch into a columnar transverse relationship at which time matrix synthesis occurs. Chondrocyte enlargement marks the border between proliferating and hypertrophic zones. Distinction is made between the upper hypertrophic zone where cell enlargement begins and the lower hypertrophic zone where most chondrocytes have attained final size. The hypertrophic chondrocytes are no longer considered to be degenerate cells [105]. Based on more exacting preparation techniques, they maintain a rough endoplasm reticulum and are felt to function even to the lowest margins of the zone. Mineralization of the matrix in the lower part of the hypertrophic zone is restricted to the longitudinal septae which is sometimes referred to as the "inter-territorial matrix." The territorial matrix involves collagen fibrils which run transversely around each chondrocyte. The region beyond the territorial matrix is thus in the longitudinal septae. The bulk of the transverse septae remains unmineralized.

The fact that the growth plate maintains its same height during most of its growth phase indicates excellent synchronization between vascular invasion and resorption from below and addition by cell proliferation and matrix production in the upper part of the cartilage. Approximately one-third of the proliferating zone is occupied by cells and two-thirds by matrix, a ratio which is reversed in the hypertrophic zone by the tremendous enlargement of chondrocytes. The marked size change during hypertrophy is an almost tenfold increase in volume. The orientation and shape of the cell also changes from the proliferative zone where the cell is ellipsoid and transversely oriented to the hypertrophic zone where it is cylindrical with its long axis oriented in the longitudinal direction. Cell hypertrophy causes primarily a stretching of the cell columns in their axial direction which thus contributes substantially to longitudinal growth. The hypertrophic cells expand by the act of transport of water and electrolytes through their cell walls. The cells continue to produce matrix. The rough endoplasmic reticulum at first glance appears scanty and dispersed, but considering the ten-fold increase in cellular volume, detailed studies actually show the organelles to be increased in extent. Longitudinal growth rate is thus a function of modulation in cell turnover, fluctuations in cell hypertrophy, and changes in matrix production.

Hunziker and Schenk sought to determine which of the many variables contributed most to longitudinal growth [112]. They reviewed the fact that changes in cell proliferation rate, height, volume, and matrix production had each been generally implicated in the process. They concluded on the basis of detailed histologic and histomorphometric studies of the rat physis that "growth acceleration is achieved almost exclusively by cell shape modeling, namely increase in final cell height and a decrease in lateral diameter." They felt that the cell proliferation rate in the longitudinal direction and net matrix production per cell remained unchanged such that the cartilage matrix itself appeared to play a subordinate role in regulating longitudinal bone growth rate. Growth can thus be most acutely regulated by factors acting on cell shape modeling. They noted the frequent observation that the cytoskeleton of the chondrocyte was relatively minimal compared to other cells which again indicated a diminished role for this organelle in controlling cell shape and size. Their morphologic studies of chondrocytes supported a high degree of coordination between matrix remodeling and chondrocyte shape change. Changes in the shape of the hypertrophic cell can occur much more rapidly than those which require changes in the cell turnover rate. Thus during both acceleration and deceleration of linear growth changes in hypertrophic cell activities appear to play an important regulatory role rather than the previously assumed fact that linear growth was modulated principally

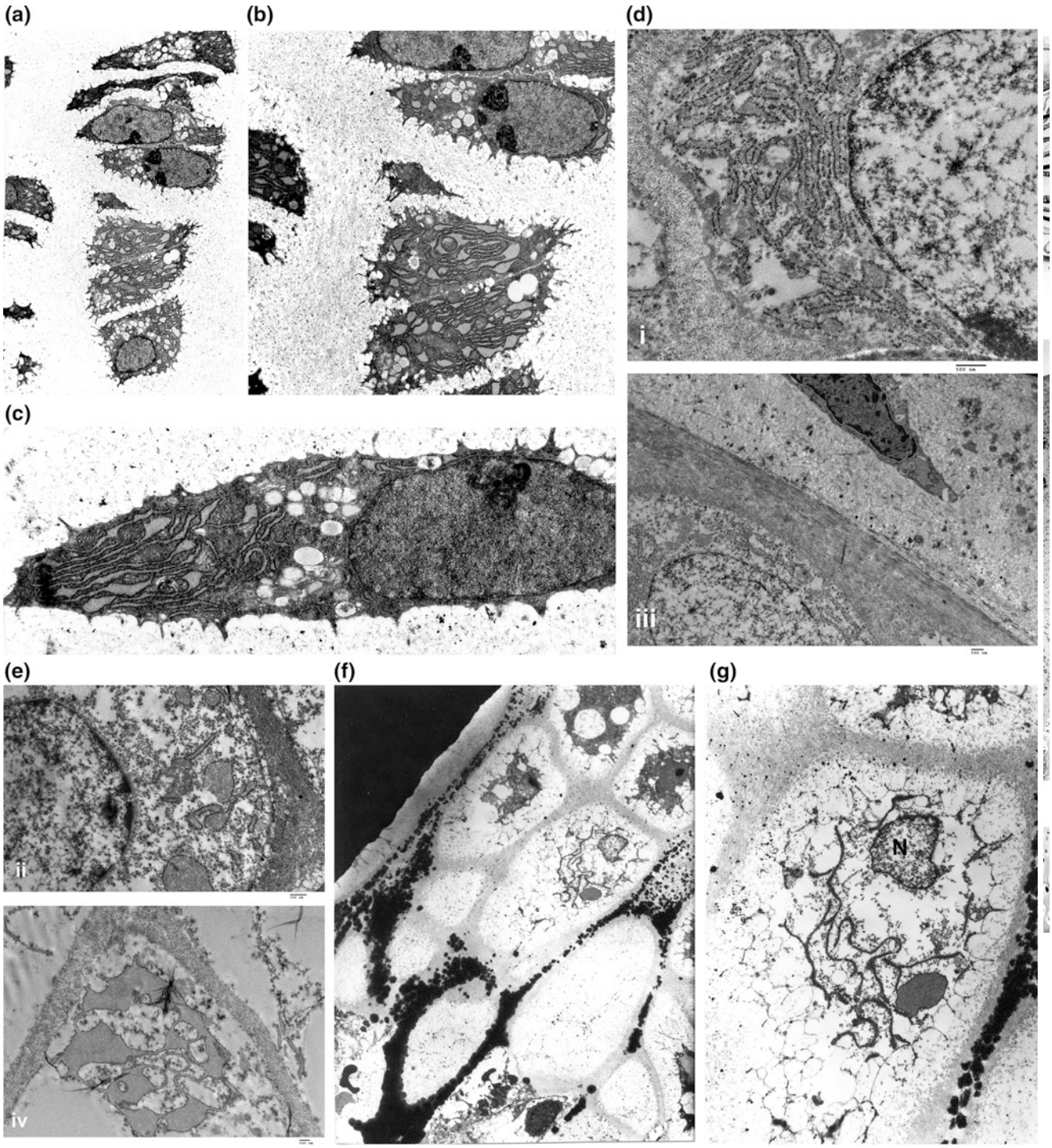
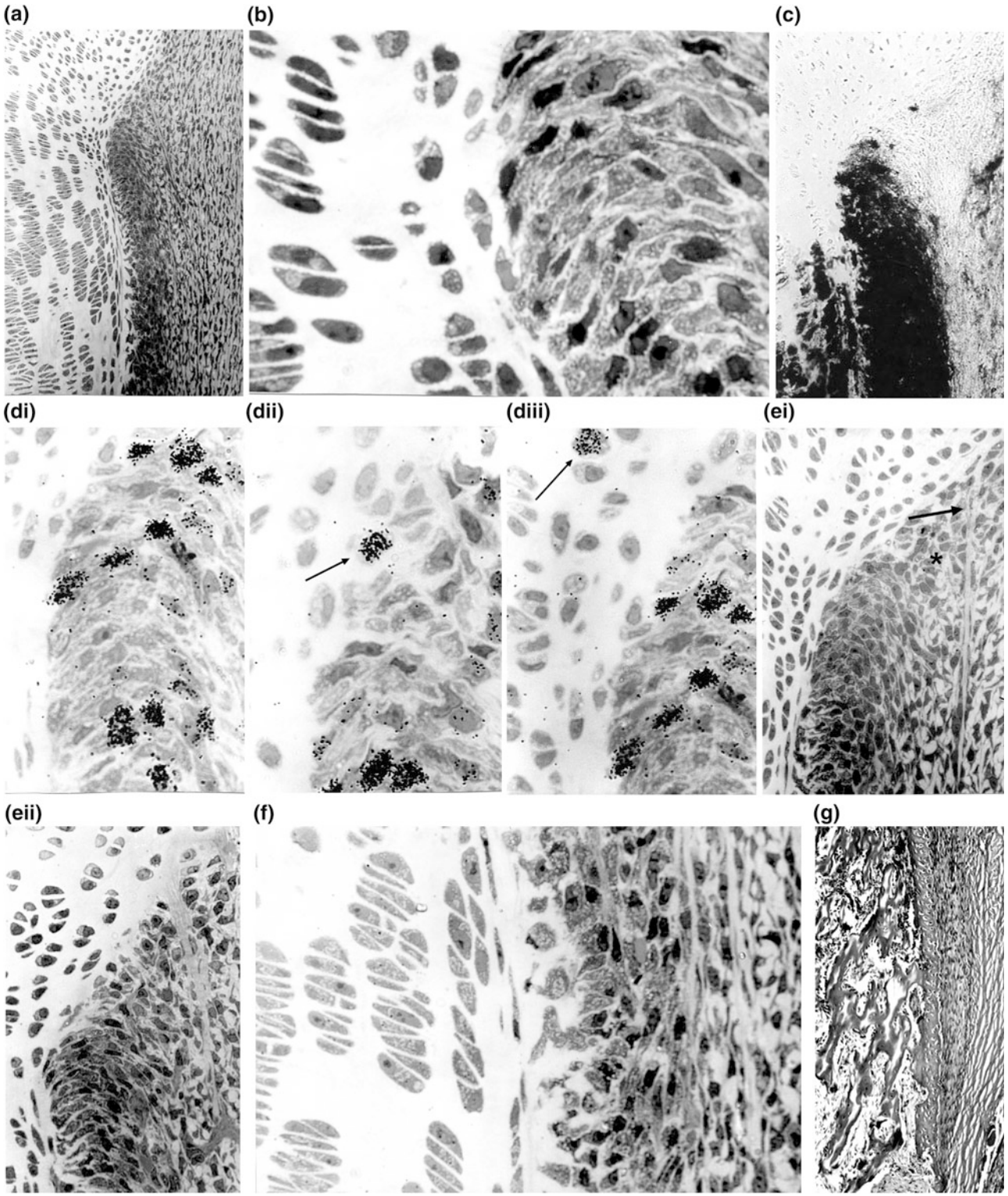


Fig. 1.11 Electron micrographs of the physeal region of the developing mouse are shown. **a** Electron micrograph from proliferating zone region of newborn mouse physis. The flattened cells are seen above. The rough endoplasmic reticulum is highly active and dilated indicating synthesis of protein. The Golgi apparatus in each cell can also be seen. **b** Higher power photomicrograph from a portion of figure **a** shows the proliferating zone. Note the extensive endoplasmic reticulum and Golgi apparatuses. **c** Flattened chondrocyte of the proliferating zone is seen. Note the prominent organelles for protein synthesis. **d** *Top (i).* Chondrocyte from the *upper* hypertrophic zone continues to show well developed active organelles. *Bottom (iii).* Hypertrophic chondrocyte (*lower left*) against periosteal osteoblast (upper right). **e** *Top (ii).* Cell further *down* the zone of hypertrophy shows areas of markedly distended rough endoplasmic reticulum, flattened ER, and increasing areas devoid of organellar definition. *Bottom (iv).* Further down the hypertrophic zone (toward the metaphysis) the chondrocytes are further swollen but organellar presence and function persist with dilated rough endoplasmic reticulum filled with mildly electron-dense homogeneous material. **f** Electron micrograph from the hypertrophic region shows mineralization primarily of the longitudinal septae with little to no mineralization of the immediately adjacent transverse septae. The cell lacunae show remnants of hypertrophic cell organelles. The space is considered to be filled with water which is responsible for the hypertrophic cell size increase and its contribution to longitudinal bone growth. **g** Mineralization of the longitudinal septum is shown as is the distinct absence of mineral from the transverse septum. The hypertrophic chondrocyte in the lowermost region of the physis shows a remnant of the nucleus (N), a dilated fragment of the rough endoplasmic reticulum and flattened segments of rough endoplasmic reticulum


(a)
(b)
(c)
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(g)

by changes in chondrocyte proliferation activity. In a careful quantitative analysis of physeal cell features they concluded that a proliferating chondrocyte needed approximately 54 h to duplicate its own volume, whereas during hypertrophy a corresponding volume increase would be achieved in a period as short as 5 h. Hypertrophy thus appeared to be a more proficient mechanism for bringing about columnar linear growth than would cell proliferation. They also concluded that it was a hypertrophic cell change in shape and volume itself which modulated growth since they could demonstrate that by the end of its life cycle the hypertrophic chondrocyte produced neither an increase or a decrease of its associated matrix volume. They felt that the matrix had its primary function as a space filling role between cells to compensate the changes in height, diameter, and volume and thus helped maintain columnar tissue organization during linear growth. The matrix was also crucial for maintenance of the biomechanical properties of growth plate cartilage [109, 111, 112]. The duration of the hypertrophic phase at approximately 48 h also remained remarkably constant irrespective of animal age or growth rate. Hunziker et al. also pointed out that individual physeal chondrocytes actually remained in a fixed location throughout their life during which their function and shape changed [111]. The two most prominent stages were those of cellular proliferation and hypertrophy. By the late hypertrophic stage, fourfold and tenfold increases in the mean cellular height and volume, respectively, and a threefold increase in the mean volume of the matrix synthesized per cell had been achieved. The continuing high metabolic activity of hypertrophic cells was also demonstrated on the basis of a twofold to fivefold increase in the mean cellular surface area of the rough endoplasmic reticulum, the Golgi membranes and the mean cellular mitochondrial volume. They also concluded that the hypertrophic chondrocytes had increased their volume by active transportation of fluid (water and electrolytes) across the plasma membrane into the cell itself.

Wilsman, Farnum, and colleagues have also shown the importance of structural changes in relation to growth plate cartilage function [127–129]. Their work also supports the concept that hypertrophic chondrocytes are fully viable cells that play a major role in endochondral ossification. It has not been determined whether or not all hypertrophic chondrocytes die or if some may survive and modulate to bone forming cells in the metaphyseal regions. It is now almost universally accepted that the large majority of hypertrophic cells are viable and functioning in terms of continuing matrix synthesis with some molecules such as type X collagen synthesized primarily in the hypertrophic cells and being involved directly or indirectly in the mineralization process. Terminal hypertrophic chondrocytes can be found in three morphologically distinct forms: (a) fully hydrated cells with

◀ **Fig. 1.12** The cell and matrix characteristics of the perichondrial ossification groove of Ranvier are illustrated. **a** A light micrograph from the developing groove of the distal femur of the rabbit is shown. The physeal cartilage is shown at *left*. Three cell populations within the groove are the region of densely packed cells at the depth of the groove, the region of less densely packed cells just above it, and the outer layer of fibrous cells. The region of densely packed cells is the terminal extension of the inner osteogenic layer of the periosteum. It secretes an osteoid matrix which ensheathes the physis and shortly begins to synthesize the intramembranous bone referred to as the bony ring or bony bark of the ossification groove. The fibrous layer is the continuation of the outer fibrous layer of the periosteum. (Reprinted with permission from Shapiro et al. Organization and cellular biology of the perichondrial ossification groove of Ranvier. J Bone Joint Surg Am. 1977;59A:703–723). **b** The beginning of the region of densely packed cells within the depth of the groove is shown. Note the curvilinear orientation of the cells. There is virtually no matrix seen between them. These cells do not add cartilage to the transverse diameter of the epiphyseal or physeal cartilage, but serve rather as bone forming cells. **c** The fact that the densely packed cells have differentiated along a bone forming line is shown by this alkaline phosphatase histochemical stain. The adjacent physis is seen at *left*. The region of densely packed cells is well outlined by the dark staining alkaline phosphatase at *right*. **d** Tritiated thymidine autoradiography outlines the high cell turnover activity in the region of densely packed cells. In figure **di** uptake initially is concentrated in the *upper* end and also along the outer margins which correspond to the presence of the rapidly dividing non-differentiated cells. The physeal cartilage is at left. In figure **dii** a labeled cell (*arrow*) in the region of less densely packed cells appears to be adding width to the physeal cartilage. In figure **diii** a labeled cell (*arrow*) is within the peripheral epiphyseal cartilage, suggestive of interstitial cartilage expansion. In summary, these tritiated thymidine autoradiographs show extensive uptake in the region of densely packed cells. There is uptake in the germinal zone of the physis figure **diii** which would serve to add more columns at the periphery and allow for interstitial widening of the physis and also a cell *right* at the point of juncture of the epiphyseal cartilage and the region of less densely packed cells (**dii**) indicating that this region contributes to transverse growth of the epiphyseal cartilage and ultimately of the physis by adding chondrocytes from the region of less densely packed cells. **e** Passage of the outer-fibrous layer into the epiphyseal cartilage (*arrow*) beyond the physeal cartilage is shown (**ei**). This is where the periosteum is firmly attached to the developing bone. The region of less densely packed cells (asterisk) is seen between the densely packed cells below and the outer fibrous layer above. At higher power magnification, (**eii**) the fibrous tissue layer inserts into the epiphyseal cartilage beyond the groove. **f** The groove components closer toward the metaphysis show increasing osteoid synthesis by osteoblasts. These cells synthesize the bony ring. The outer fibrous layer is at *right*. **g** The bony ring of the groove (*central part of image*) is shown adjacent to the metaphysis at *left*. It is an example of direct intramembranous bone synthesis. The outer-fibrous layer of the periosteum is shown at far *right*. At the metaphyseal region at *bottom of image*, there is discontinuity between the bone ring of the ossification groove and the cortex of the metaphyseal–diaphyseal area due to resorption by multinucleated osteoclasts

direct circumferential attachments of the plasma membrane to the peri-cellular matrix identical to that of the more proximal hypertrophic chondrocytes; (b) fully hydrated cells with asymmetric attachment to the last transverse septum; and (c) a condensed cell with the same asymmetrical attachment to the last transverse septum. They hypothesize that "the initial attachment of the chondrocyte plasma membrane to the last transverse septum represents the first of a series of rapid terminal morphologic changes that represent chondrocytic death. They feel that it is only the terminal chondrocyte that undergoes changes in which there is withdrawal of the plasma membrane from its attachments to the pericellular matrix, cellular condensation, and cellular vacuolization. They indicate that "cellular disintegration is complete before the opening of the chondrocytic lacunae." Hunziker has also suggested that only the terminal chondrocyte in each cell column dies and that it does so in fashion consistent with programmed cell death. There has been a persisting, if small, group of individuals studying growth plate function who have hypothesized "that terminal hypertrophic chondrocytes modulate in phenotype and change not only their chemical phenotypical expression but also their ultimate biological role." The terminal chondrocytes are viable and metabolically active. This group does not go so far, however, to indicate that they then switch to a bone phenotype within the metaphyseal area.

Breur et al. demonstrated that chondrocyte enlargement began immediately following cell division in the proliferative zone and that it consisted of two morphologically distinct phases [128]. The transition point between the first and second phases of chondrocytic enlargement corresponds with the junction between proliferative and maturation zones. The controlling features in longitudinal growth are the rates of new cell production in the proliferative zone and the role of chondrocyte hypertrophy. Their study suggested that "in growth plates, chondrocytic enlargement plays a major role in the determination of longitudinal bone growth". Chondrocyte enlargement is characterized by an increase in cell volume and a modulation of cell shape. In the proliferative zone, the cells are flattened ellipsoids while in the hypertrophic zone, they are more rounded and spheroid in a longitudinal plane. The increase in cell volume is mainly the result of cellular swelling by absorption of water with only some increase in cell organelles. Chondrocyte proliferation is felt to take place only in the proximal ends of the proliferative zone and the function of chondrocytes in the proliferative zone distal to the actively proliferating cells involves actual enlargement and hypertrophy. Each region thus merges with the next rather than being strictly separate as is sometimes indicated. In a study of rat growth plate structure, Breuer and colleagues demonstrated that (1) cell volume increase started immediately following cell division in the proximal portion of the proliferative zone, (2) the process of chondrocytic enlargement as it relates to longitudinal bone growth consists of two morphologically distinguishable phases, (3) the rate of cell volume increase and the rate of cell shape modulation are significantly higher during the second than during the first phase, and (4) cell volume increase during the first phase results mainly in an increase in vertical chondrocyte diameter while cell volume increase during the second phase results in a large increase of the vertical chondrocyte diameter and a smaller but significant increase of horizontal chondrocytic diameters. The cell volume increase starts immediately following cell division in the proximal portion of the proliferative zone and chondrocytic enlargement consists of a phase of slow and then rapid cellular enlargement.

The complex functions of the hypertrophic chondrocyte during endochondral bone development have recently been stressed in a work which combines consideration of molecular data with the histologic characteristics of the physeal–metaphyseal junction [85]. Endochondral bone formation is one of the most extensively examined developmental sequences within vertebrates. The major cellular events of this process include the recruitment and induction of both osseous and vascular tissues. Presumptive osteoblasts are recruited and line the trabeculae of mineralized cartilage to synthesize osteoid. The term mixed trabeculum refers to the presence of mineralized cartilage cores surrounded by newly synthesized bone. Vascular elements invade and line the empty lacunae of the lowermost hypertrophic chondrocytes which have undergone cell death. Pertinent questions relative to the osseous and vascular induction within these zones include the nature of the functional coupling among cartilage, bone, and vascular tissues. Signals elaborated by the endochondral cells are targeted to the subsequent development of the chondrocytic components of the growth plate (autocrine regulation) and toward the osteogenic and vascular elements (paracine regulators). Extracellular matrix components of the mineralized growth plate may elaborate signals or be a permissive substrate for osseous and vascular induction. The surrounding and resorption of the mixed trabeculae by osteoclastic cells is the terminal event in the remodeling process of the endochondral tissue. Signals elaborated from the mineralized cartilage/bone trabeculae, as well as the cells lining this trabeculae, are involved in this recruitment process. This process involves the coordinated temporal/spatial differentiation of three separate tissues (cartilage, bone, and the vasculature) into a variety of complex structures. The differentiation of chondrocytes during this process is characterized by a progressive morphological change associated with the eventual hypertrophy of these cells. These cellular morphological changes are coordinated with proliferation, a columnar orientation of the cells, and the expression of unique phenotypic properties including type X collagen, high levels of bone, liver, and kidney alkaline phosphatase, and

mineralization of the cartilage matrix. Several studies indicate that hypertrophic chondrocytes also express osteocalcin, osteopontin, and bone sialoprotein, three proteins which until very recently were widely believed to be restricted in their expression to osteoblasts. Recent studies suggest that the hypertrophic chondrocytes are regulated by the calcitropic hormones, morphogenic steroids, and local tissue factors. The considerations are based on the regulation by 1,25 (OH) 2D3 and the retinoids of the cartilage-specific genes as well as osteopontin and osteocalcin expression in hypertrophic chondrocytes. Studies further suggest that specific transcription factors mediate exogenous regulatory signals in a coordinated manner with the development of bone.

While it has been demonstrated to the satisfaction of some that the majority of hypertrophic chondrocytes undergo apoptosis during terminal stages of the developmental sequence, their response to specific exogenous regulatory signals and their expression of bone-specific proteins give rise to questions about whether all growth chondrocytes have the same developmental fates and identical functions. Aizawa et al. demonstrated apoptosis in hypertrophic growth plate chondrocytes in the rabbit using specific antibody staining techniques for TUNEL (terminal deoxynucleotidyl transferase (TdT)-mediated deoxyuridine triphosphate (dUTP)-biotin nick end labeling) [130]. Gibson reviewed the active role of chondrocyte apoptosis in endochondral ossification [131]. The physiological form of cell death appears not to be just a passive removal of unwanted cells but rather an event that plays an active role in initiating processes that follow cell death. The possible pivotal role of chondrocyte apoptosis is discussed for each calcification of the growth plate longitudinal septae, cartilage resorption, growth factor release, maintenance of growth plate height, and activation of vascular invasion and bone formation at the lower part of the endochondral sequence. Specific questions arise as to whether there are similar mechanisms or regulation for commonly expressed genes found in both cartilage and bone or whether these genes have unique regulatory mechanisms in these different tissues. These recent findings suggest that hypertrophic chondrocytes are functionally coupled during endochondral bone formation to the recruitment of osteoblasts, vascular cells, and osteoclasts.

Over 100 years ago some observers using light microscopy continued to maintain that at least some hypertrophic chondrocytes survived and differentiated to bone forming cells in the metaphysis (see Sect. 1.4 above). At present the ability of hypertrophic chondrocytes to synthesize specific matrix molecules is well accepted as is the fact that many or most of the hypertrophic chondrocytes subsequently undergo apoptosis. The question of whether some hypertrophic chondrocytes differentiate to an osteogenic line is still supported by some, based now on molecular studies. Roach et al. in a study in vitro of embryonic chick bones noted asymmetric cell division in hypertrophic chondrocytes with diverging fates of two daughter cells, one undergoing death by apoptosis and the other surviving, dividing, and generating osteogenic cells. Their work also referred to differing views on the matter published over the previous three decades. The crucial event in differentiation to a bone line was the asymmetric division noted. This division resulted in one viable and one apoptotic cell, following which the viable cell re-entered the cell cycle and gradually differentiated to the bone forming line.

Shapiro et al. [132] have studied hypertrophic and immediately adjacent pre-hypertrophic chondrocytes at the same stage of histologic development in 7-day-old post-natal Balb/C mouse physes and epiphyses. Laser capture microdissection (LCM) and GeneChip microarray analysis compared the molecular composition of the two hypertrophic chondrocyte regions. Molecules upregulated in dramatically higher levels in the epiphysis were gremlin (58-fold), epidermal growth factor-containing fibulin-like extracellular matrix protein 1 (25-fold), and frizzled related protein (6.4-fold and 5.7-fold). Molecules upregulated in higher levels in the physis were proline–arginine-rich end leucine-rich repeat protein (PRELP) (15.6-fold), pyrophosphatase (inorganic) 1 (tenfold), and hedgehog-interacting protein (7.3-fold). Immunocytochemistry for gremlin confirmed specific localization patterns. This study indicates a critical site-specific role for hypertrophic chondrocytes with different synthesis patterns in separate regions, even though they appear structurally the same and are at the same stage of development.

1.7.2 Perichondrial Ossification Groove of Ranvier

The endochondral and intramembranous bone formation systems always merge at the periphery of a developing bone in a specific series of tissue conformations referred to as the perichondrial groove of Ranvier [1, 2, 73, 133–135]. As we noted previously, the developmental sequence of the periosteal sleeve is always spatially and temporally slightly in advance of that of the contained endochondral sequence. This relationship persists even when the epiphyseal growth plate has established its definitive relative position at either end of the bone. The epiphyseal growth plate is thus surrounded by periosteal tissues which serve as a structurally supportive mechanism. Three cell populations have been defined in the depths of the groove [1]. The groove refers to the circumferential depression in the periphery of the epiphyseal growth plate which has its deepest extent opposite the resting or germinal cell layer and the adjacent epiphyseal cartilage. The outer fibrous layer of the periosteum continues surrounding the epiphyseal growth plate and inserting above the deepest part of the groove of

Ranvier into the cartilage of the epiphysis. The inner osteogenic cell layer of the periosteum is also continuous serving to surround the epiphyseal growth plate and commencing as an accumulation of densely packed cells in the depth of the groove adjacent to the germinal and proliferating cell layers of the physis. At their deepest part, these cells are undifferentiated mesenchymal cells which quickly differentiate to pre-osteoblasts and synthesize a characteristic osteoid matrix which shortly is mineralized forming actual intramembranous bone. These spicules of intramembranous bone surround the epiphyseal growth plate well into the level of the proliferating zone. Although they are not sufficiently wide to be seen radiographically, they are clearly present at a histologic level. The bone ring is sometimes referred to as the perichondrial bony bark or bony ring of Lacroix. The third region of cells specific to the groove of Ranvier are undifferentiated cells which are more loosely packed and which lie between the outer fibrous layer and the region of densely packed cells which are osteoblast precursors. These cells appear to add to the periphery of the epiphyseal cartilage and serve therefore as chondrocyte progenitors. The cells are considered to be responsible for the increase in width of the epiphysis [1, 133, 136–138]. Once deposited in the epiphyseal cartilage with growth, they are encompassed within the epiphyseal growth plate and then pass through the developmental stages from germinal to proliferating to hypertrophic cells. The increase in the transverse diameter of the physis is also achieved by interstitial growth in the resting cell layer [1, 139–141].

An integral part of development of the periphyseal region is the cutback zone which is responsible for the shaping of the metaphysis, a process sometimes referred to as funnelization. As this region is narrower than that immediately above it, it is evident that osteoclastic resorption must have occurred to remove the excess tissue. Histologic slides reveal abundant amounts of these osteoclasts which are responsible for the funnelization and shaping of the developing bone in the metaphyseal regions. In the large majority of instances, the bone bark is resorbed at the metaphyseal level along with adjacent metaphyseal endochondral bone serving to leave the circumferential bone ring as a structure anatomically separate from the cortex of the metaphyseal and diaphyseal regions. The outer fibrous layer of the periosteum, however, always remains intact.

Burkus and Ogden described the perichondrial ossification groove region of the human distal femur from the fetal time period to skeletal maturation at 16 years [142]. The cell regional structure including the bony ring was most evident in the young fetus. They felt that appositional chondrocyte growth was most evident during the first 5 months of gestation after which its activity diminished.

The structural characteristics of the perichondrial groove region are illustrated in Figs. 1.12a–g, 1.13a–c, and 1.14a–b.

1.7.3 Periosteum and its Relationship to the Epiphyses, Metaphyses, and Diaphyses

The periosteum is widely recognized to play a major role in cortical bone formation by the intramembranous mechanism. It is composed of an outer fibrous layer and an inner osteogenic or cambial layer. Less widely appreciated, however, is the fact that the periosteum also has a major support role in relation to stability at the physeal–metaphyseal junction as well as a role in applying appropriate tensile forces to the physis during the growing years. The outer fibrous layer of the periosteum passes beyond the physis and attaches into the epiphyseal cartilage. It serves as a continuous layer from the epiphyseal cartilage of the proximal end of a long bone to the epiphyseal cartilage of the distal end of that bone.

The periosteum is quite loosely attached to the underlying cortical bone in the developing child. The reasons for this relate to the differing growth rates within the bone itself and within the periosteum. The bone grows by apposition of tissue at either end but the periosteum has been shown to grow uniformly throughout its length by interstitial cell mechanisms [143]. In addition, one end of any long bone grows more rapidly than the opposite end. The loose attachment of the periosteum to the underlying bone enables the differential growth mechanisms to occur simultaneously without difficulty. The interstitial growth of the periosteum also serves to maintain the relationship of the muscle attachments to the periosteum, an occurrence which would be much more difficult if the periosteum itself grew only at its proximal and distal ends. The outer fibrous layer of the periosteum is continuous from epiphyseal cartilage to epiphyseal cartilage, whereas the inner osteogenic layer is often discontinuous at the region of the metaphyseal cutback zone in particular where this zone is quite angled. The periosteum is firmly adherent to the growing bone at either epiphyseal end. Lacroix indicates that the only area between these regions where periosteal elongation and bone elongation are the same is at the so-called “null point” of periosteal growth which is furthest away from the most active growth plate and nearest the least active growth plate [133]. This would occur, for example, in the tibia at about 35 % of the tibial length above the growth plate since only 35 % of tibial growth occurs at the distal end of bone.

The extrinsic support that the periosteum provides for the growth plate at the periphery of the groove of Ranvier region is considerable. John Poland, in his classic treatise on epiphyseal growth plate fractures, reports an experiment by

John Wilson in the 1820s in which weights were applied to anatomic specimens of children's distal femurs [144]. When the circumferential periosteal tissues were removed from the growth plate region the amount of weight required to dislodge the epiphysis from the metaphysis was only one-fifth as great as when the tissues were intact. Considerable structural support is provided by the periosteal and perichondrial tissues. Amamilo and associates also showed that a consistently higher force was needed in rats to produce epiphyseal displacement with the periosteum intact [145].

Cadet et al. have shown how metaphyseal cortical bone is formed by the coalescence of peripheral endochondral trabecular bone from the physis with intramembranous bone from the inner osteogenic (cambial) layer of the periosteum [146]. The greater the metaphyseal cutback zone, the greater the relative contribution of the endochondral trabecular bone. This is illustrated in Fig. 1.14c.

The muscles and tendons are attached directly to periosteum in the growing child rather than to the underlying cortical bone. There is a distinct change in adults, however, in whom the periosteum is much thinner, is firmly adherent to the underlying cortex, and demonstrates muscle and tendon fibrils which pass through it to gain direct attachment to the underlying cortex by Sharpey's fibers.

It has been postulated that there is a strong fibro-elastic periosteal sleeve effect on the physis which not only applies a certain degree of tension across it but may serve as a check to unconstrained longitudinal growth. Circumferential division of the periosteal sleeve especially if it is performed close to the metaphyseal–epiphyseal regions will allow for increased longitudinal growth of those bones [147–149]. What is unclear is whether the increased growth is due to the diminution of mechanical constraint during the time that the periosteal sleeve is discontinuous or to an increase in vascularity in the peri-epiphyseal region which occurs consequent to injury and during the repair phase. The absence of overgrowth when longitudinal cuts were made in the periosteum though supports the mechanical affects [148]. A medial hemi-circumferential division of the proximal tibial periosteum leads to medial overgrowth and valgus deformation [150]. When periosteal removal was done circumferentially in 4 mm wide strips, in the mid-diaphyseal region of 4-week-old rats, overgrowth was seen but was minimal being only 1.5 % greater than the opposite side [151]. Haasbeek et al. have shown that when periosteum is thickened adjacent to a physis, it serves as a tether to cause angular deformity [152]. They demonstrated the phenomenon in two clinical cases and experimentally. In summary, the periosteum is shown to affect growth of the physes mechanically since it unsheathes the physes and inserts beyond them into the epiphyseal cartilage. When periosteal tension is reduced, the longitudinal bone growth is increased and when the tension is increased, growth slows slightly.

1.7.4 Cortical (Diaphyseal) Bone Formation

The histologic appearance of cortical (diaphyseal) bone is well understood. The book "Osteologia Nova or Some New Observations of the Bones" by Clopton Havers published in London in 1691 in which he described longitudinal pores passing from one end of the bone to the other is widely considered to represent the initial scientific description of bone [153]. These longitudinal passages have come to be referred to as Haversian canals, even though Havers did not describe blood vessels within them. He also described transverse canals and clearly noted the internal structure of bone to be lamellar.

1.7.4.1 Woven Bone and Lamellar Bone

Bone formation is initiated with matrix deposition in a randomly oriented pattern referred to as woven- or coarse-fibered bone followed by its replacement with bone with a definitive lamellar structure. There are several patterns of lamellar bone deposition in vertebrates described by Foote as: (i) uniform lamellae encircling the entire diameter of the bone, (ii) a more complex pattern characterized by laminae separated from adjacent structures by vascular canals, or (iii) multiple Haversian systems or osteones such as occur in higher mammals including humans [154]. An ***Haversian system*** or ***osteon*** in cortical bone refers to a central canal containing longitudinally oriented vessels and associated osteoprogenitor cells surrounded by concentric lamellae of bone matrix. Many Haversian systems are present in a cross-section of cortical bone. Longitudinally oriented lacunae containing osteocytes are embedded in the lamellae and link both adjacent cells and osteoblasts accompanying the blood vessels. Canaliculi containing the osteocyte cell processes extend to and from the lacunae. Many Haversian sytems are present in a cross-section of bone.

The formation, structure, and continuous remodeling of the bone matrices have been the subject of detailed investigation with various works defining: coarse-fibered primary bone and fine-fibered lamellar bone [155]; woven-fibered bone, parallel-fibered bone, and lamellar bone (Weidenreich) [156]; and woven-fibered bone, primary osteones, secondary osteones, surface bone, and interstitial bone (Smith) [157, 158]. The mechanisms by which regions of woven bone are subsequently found to be composed of dense lamellar bone are of considerable biological and clinical importance.

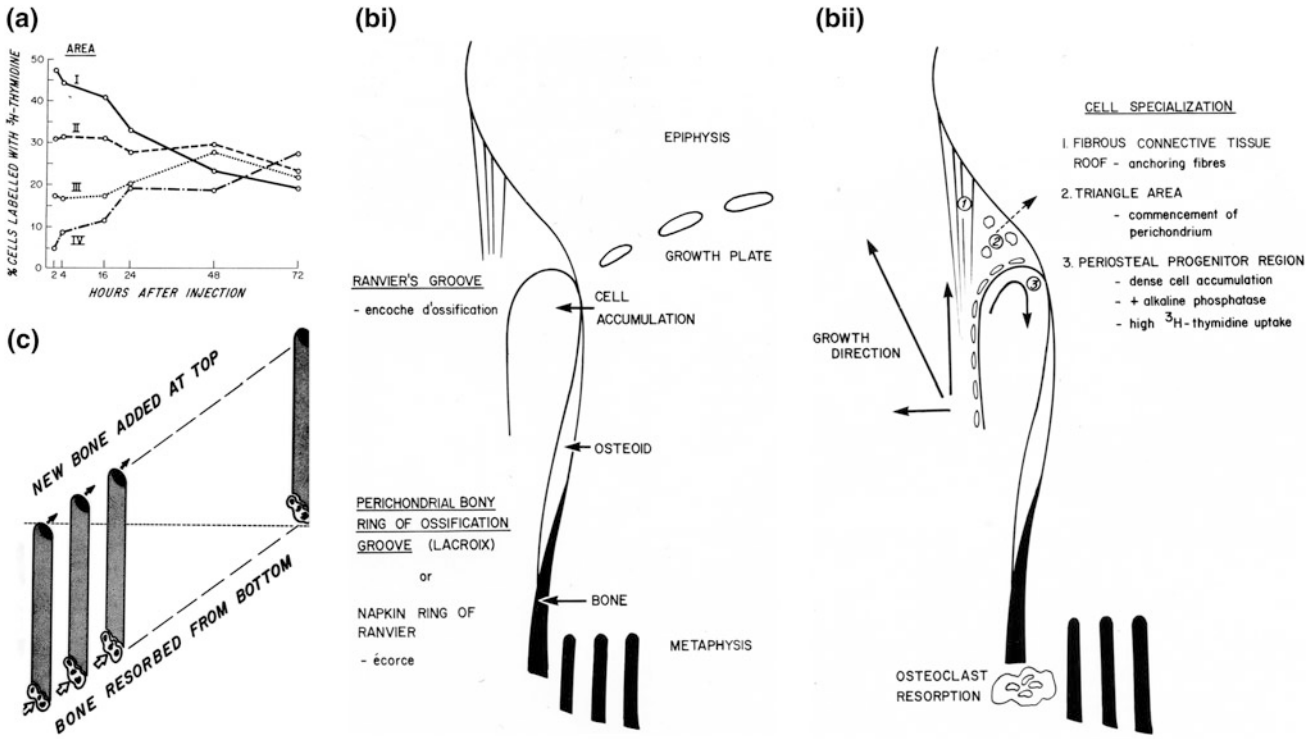


Fig. 1.13 **a** Tritiated thymidine labeling of progenitor cells in the region of densely packed cells is illustrated. The study assessed the number of labeled cells and their presence from 2 to 72 h after injection. Four comparably sized regions of the densely packed cells were measured with area 1 being at the upper most part and area 4 along the metaphyseal region. At 2–4 h, most of the cells are concentrated in area 1 and they progressively appear in area 4 with time as a reflection of their presence within the groove which itself is growing upwards and outwards. (Reprinted with permission from Shapiro et al. Organization and cellular biology of the perichondrial ossification groove of Ranvier. J Bone Joint Surg Am. 1977;59A:703–723). **b** The contributions of the various cell populations to growth at the peripheral regions of the physis are shown in Figures **bi**, **ii**. (Reprinted with permission from Shapiro F, Structural abnormalities of epiphyses in skeletal dysplasias in Buckwalter JA et al. (eds): *Skeletal Growth and Development.* Rosemont, IL. American Academy of Orthopaedic Surgeons, 1998, pp 471–489). **c** Illustration showing the relative changes of position of the perichondrial ossification groove and in particular the bone ring bark with growth. The bone ring tends to be positioned in an outward and upward direction with growth. New bone is added at the top and bone is resorbed from the bottom at the metaphyseal cutback zone. The physis would be to the *left*

Woven bone in the human is seen characteristically in association with bone formation: (i) in the fetus and newborn, (ii) in initial early repair following fractures and osteotomies, and (iii) in pathologic states as diverse as osteogenesis imperfecta and osteopetrosis.

Woven bone is synthesized by differentiating mesenchymal cells, which we refer to as mesenchymal osteoblasts (MOBL), which have just differentiated along a pre-osteoblast to osteoblast line in a localized region where no bone is present. It has a matrix with randomly oriented collagen and is relatively hypercellular with round to oval cells linked by cell processes in canaliculi which are also randomly oriented. It is weak structurally and is synthesized primarily to serve as a scaffold upon which the better oriented and mechanically stronger lamellar bone is deposited. Once a sufficient amount of woven bone has been deposited to serve as a scaffold, osteoblasts, which we refer to as surface osteoblasts (SOBL), align in single array along the woven bone surface and deposit new matrix in a linear or lamellar orientation [3].

Lamellar bone is less cellular than woven bone, its osteocytes are flattened and aligned along the long axis of the respective lamellae in the matrix, and the canaliculi are more regularly patterned parallel and perpendicular to the osteocytes and adjacent blood vessels. The lamellae in secondary (remodeled) bone align in multilayered cylindrical osteons around a central blood vessel.

The distinction between woven and lamellar bone can usually be made by unmodified light microscopy especially when the two types are closely apposed. Definitive

distinction is made however by ***polarized light microscopy*** using two polarizing lenses inserted between the light source and the histology slide on a rotating stage (Modis) [159]. A polarizing lens allows passage of light in only one plane. Woven bone does not allow light to pass throughout a complete 360° rotation of the specimen since there is always a random organization of the collagen fibrils regardless of the rotation of the specimen. The woven bone is said to be ***isotropic*** owing to the random orientation of the collagen which does not influence the polarization of light. The parallel alignment of collagen fibrils in lamellar bone allows the bone to transmit polarized light at certain degrees of rotation of the two polarizers. When the polarizers are in the same plane as the lamellae, which occurs at certain degrees of rotation, bright light is transmitted. Lamellar bone is said to be ***anisotropic*** because the properties of the oriented collagen fibrils are different in different directions which allow transmission of light through the oriented polarizers in one plane and no transmission at right angles to it.

The lamellae of cortical bone are not all in the same plane however. The early works of Gebhardt [160] and Petersen [161] demonstrated well the structural organization of the collagen fibers in mature bone. Thin and thick lamellae alternate and adjacent sheets are positioned at oblique angles to one another in what is referred to as a "***twisted plywood*** ***orientation*** (Giraud-Guille) [162] for structural support. The angles between adjacent arrays in lamellar bone have been studied (Weidenreich) [156] and it was shown that most angles were 30° with a subset at 70° (Weiner et al.) [163]. They proposed a structural model for collagen organization with an individual lamellar unit (thick and thin lamellae) composed of five arrays of parallel fibrils each offset by 30°. The spiral twisting of fiber orientation in bone lamellae has been assessed by others as well (Wagermaier et al.) [164], Weidenreich [156]. Another feature of collagen fibril orientation in lamellae is that it is a ***self-assembly process*** in the organic extracellular matrix determined to a large extent by local stress–strain conditions and by the intrinsic chemical properties of the collagen molecules rather than being specifically cell-directed (Bouligand et al. [165], Cisneros et al. [166], and Kadler et al. [167]).

Beginning with the primary center of ossification, and its increased development during the fetal time, woven bone is synthesized initially by the inner cambial layer of the periosteum. Very shortly once an appropriate amount of scaffolding has been synthesized new bone formation is lamellar in nature. The lamellar bone is deposited on the woven bone cores. With increasing development the lamellae become more compacted and by the late fetal period Haversian systems have clearly formed. This development continues throughout the post-natal period to skeletal maturation. With the increasing length and diameter of the long bone there is synthesis on the outer layer of the cortex and resorption internally as the marrow cavity forms and widens. The term woven bone refers to the randomly oriented positioning of the collagen fibrils in the newly synthesized matrix. Any time there is rapid synthesis of new bone in a spatial area where bone did not previously exist, the osteoblasts secrete the collagenous fibrils in all directions and themselves become enmeshed among the fibrillar mass. The newly formed collagen prior to mineralization is referred to as osteoid. Histologic characteristics of woven bone involve relatively large and numerous cells in relation to the amount of matrix present. We refer to the osteoblasts of woven bone as mesenchymal osteoblasts since they are newly formed along the undifferentiated cell line to pre-osteoblasts and then to osteoblasts. The term lamellar bone refers to bone tissue in which the collagen fibrils are well oriented in parallel array. The sheets of fibrils form lamellae which also relate to the term lamellar bone. Adjacent lamellae are at right angles to one another although both are in parallel array. This is sometimes referred to as an orthogonal arrangement. Lamellar bone is synthesized on preexisting cores of tissue which in cortical bone formation is primarily the initially synthesized woven bone. A structural characteristic of lamellar bone formation is that the osteoblasts responsible for it are present on the surface and they basically secrete the fibrils not only in parallel array but in a directional sense only along the adjacent surface of the underlying bone. This is in counter distinction to the mesenchymal osteoblasts which form woven bone in a 360° spatial pattern around the cell.

Lamellar bone tissue is synthesized in intimate relationship to the associated vessels. In a general sense, the vessels of bone run in parallel position along the longitudinal axis of the developing cortex. The vessels are associated with mesenchymal cells of the osteoblast line, the cells referred to in lamellar bone formation as surface osteoblasts. Bone tends to form circumferentially around the individual vessels, forming circumferential lamellae and synthesizing tissue internally until only the vessel and a small number of adjacent cells are present. This leads to what is referred to as compaction of bone which is evident radiographically as bone of increased density. The term Haversian system refers to the central vessel surrounded by the lamellae of bone which derives its nutrition from that vessel. This is the functional unit of bone and is also referred to as an osteon. The osteons and the central Haversian canal vessels tend to run along the long axis of the bone although few are strictly parallel to it. Vessels that connect adjacent Haversian systems in a plane transverse to the long axis of the bone are present in Volkmann's canals. They are typically illustrated as being along the transverse axis of the cortex and at right angles to adjacent Haversian systems although in fact they tend to be somewhat oblique in orientation.

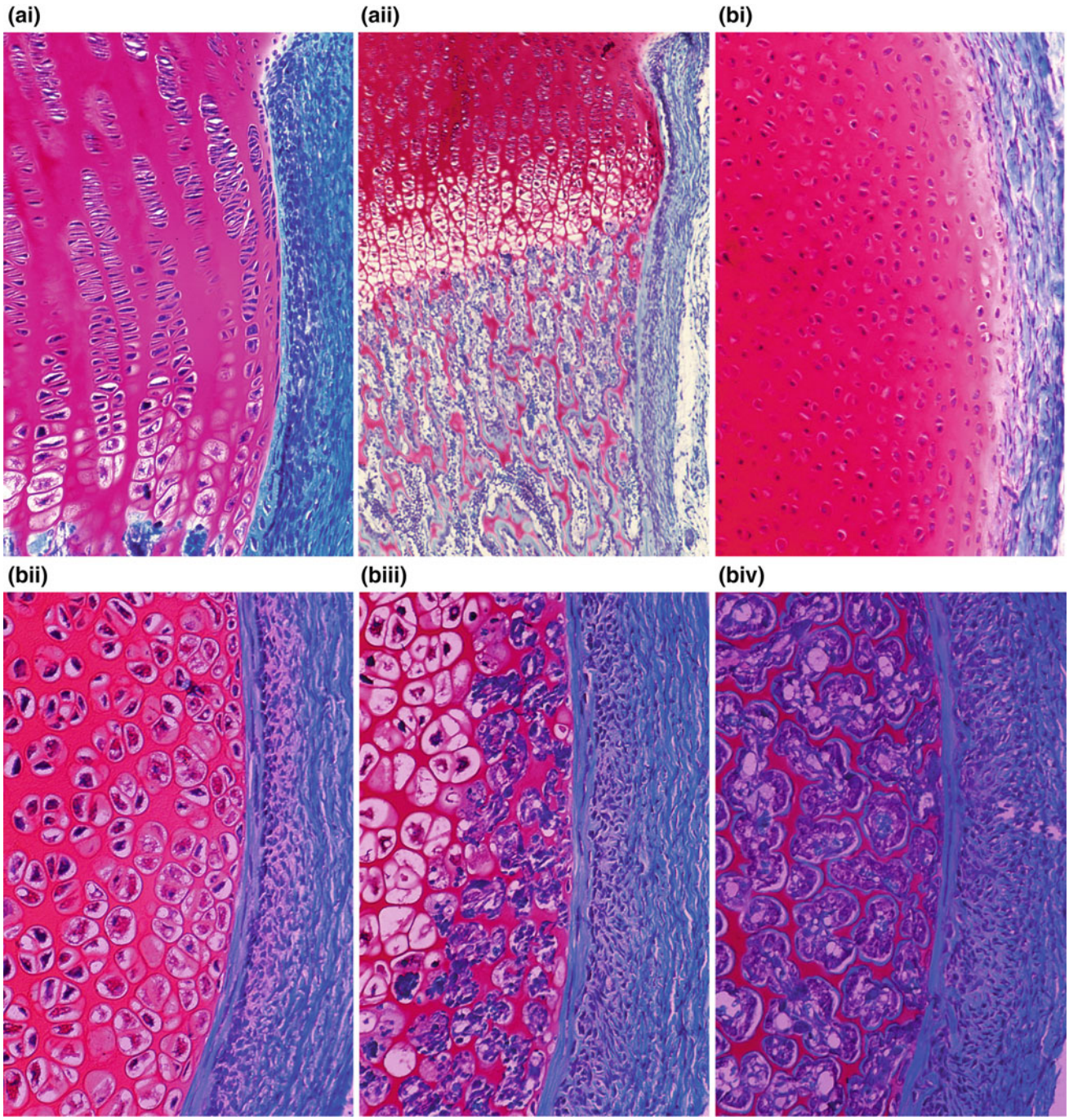


Fig. 1.14 (continued)

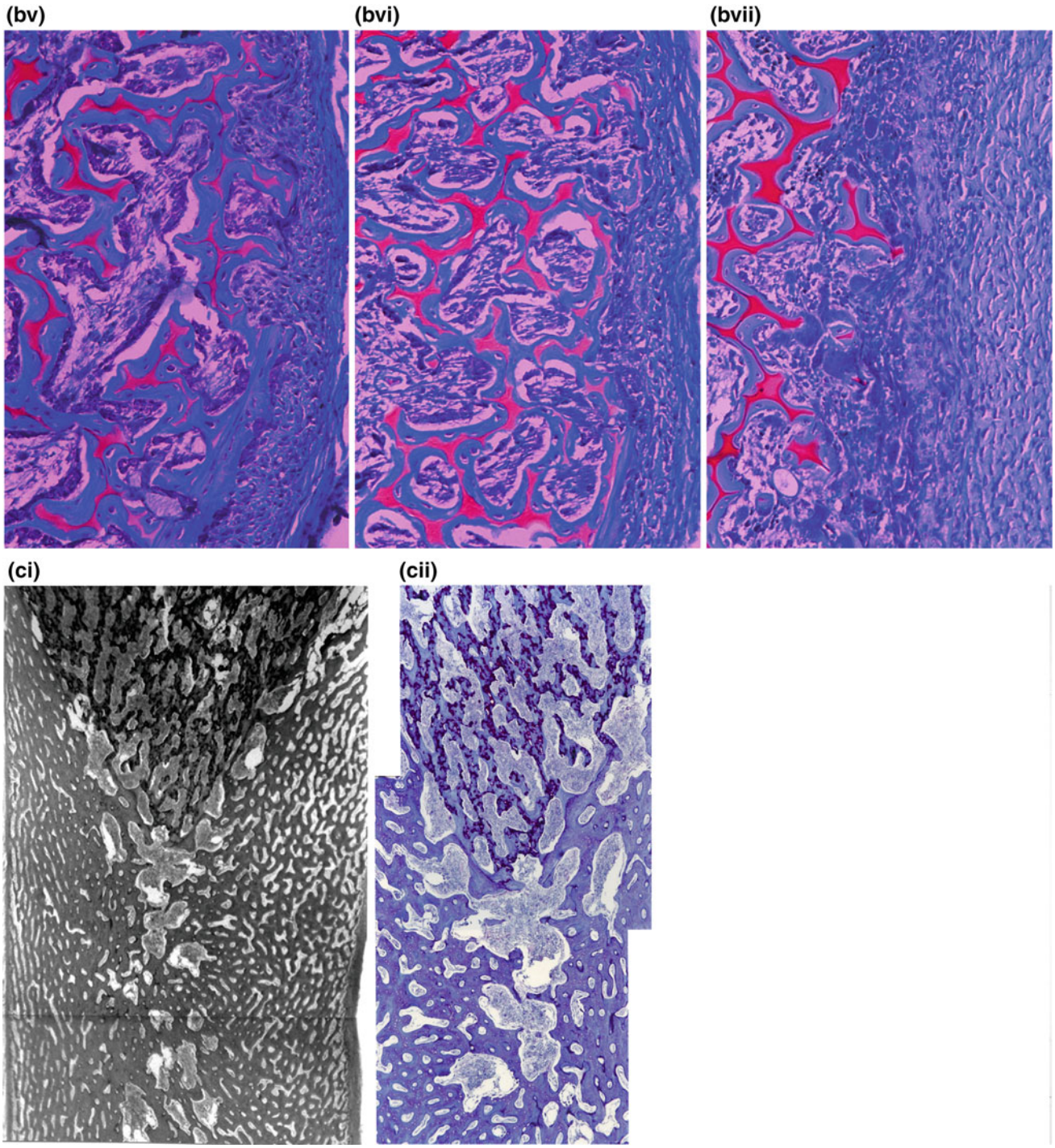


Fig. 1.14 (continued)

The osteocytes are present in lacunae and the osteocyte cell processes which link adjacent osteocytes are present in canaliculi. The lacunae and canaliculi in woven bone have no specific orientation consistent with the relationship of the various mesenchymal osteoblasts and young osteocytes. In lamellar bone the orientation of the cells and cell processes becomes more structured and the lacunae are oval structures flattened along the long axis of the lamella and the canaliculi also tend to pass either parallel to the lamellae or at right angles to them.

Two additional terms referring to the structure of bone can be introduced here. Bone is referred to as being either dense-compact or cancellous. Cancellous bone refers to spatial regions of the bone in which there is relatively more

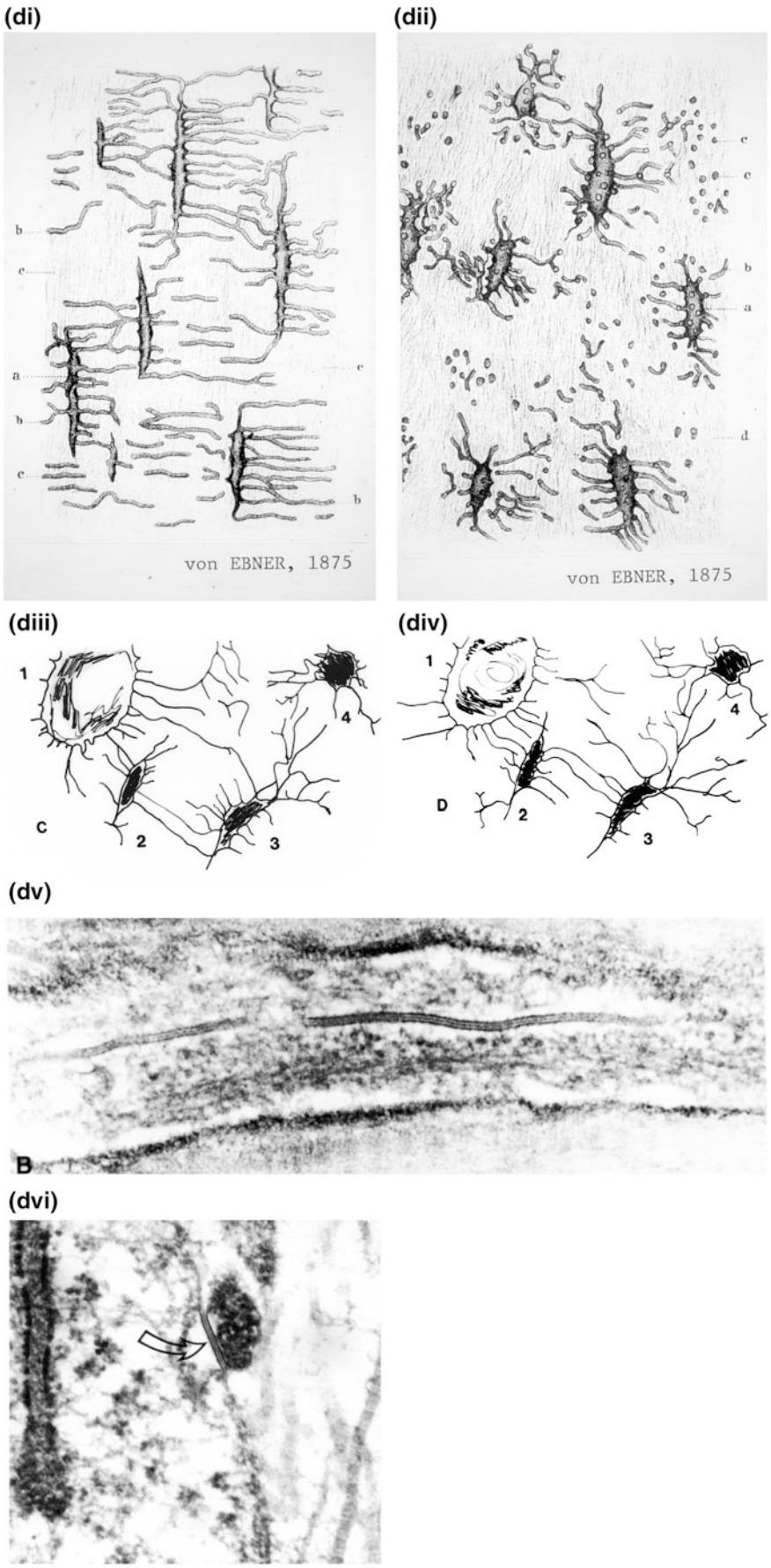


Fig. 1.14 (continued)

space filled with cells and vessels than there is mineralized bone tissue. Fine cancellous bone refers to this situation at a light microscopic level of resolution and it is commonly seen in the developing cortices of the fetus. Gross examination shows what would appear to be uniformly structured cortex but microscopic examination shows woven and early lamellar bone to be associated with relatively large spaces between the bone tissue filled with cells and vessels leading to the cancellous description. Coarse cancellous bone refers to appearances evident to gross examination in which there is relatively more space than bone tissue. The term is applied to the non-cortical metaphyseal and mature bone epiphyseal regions where the trabeculae of bone are surrounded by relatively large marrow spaces filled with cells and vessels.

1.7.5 The Lacunar–Canalicular System

The canalicular framework in woven and lamellar bone shows the changes in orientation and extensiveness during both development (Burger and Klein-Nuland) [12] and repair (Kusuzaki et al. [168]; Shapiro [16]) (Fig. 1.14d). The data on normal cortical osteocytes show excellent uniformity in terms of cellular shape, position, length, and width, and frequency of canalicular offshoots. Lamellar osteocytes are elongated and elliptical in shape, and lie parallel to the long axis of the lamellae. The data in our study [16] show the ratio of length to width in control osteocyte to be 3.5 to 1. The number of canaliculi emanating from a lacuna has been expressed as a perimeter-to-canalicular ratio, with the value obtained representing the average distance, in micrometers, between each canaliculus. This value is uniform in the normal mature cortical osteocyte, being 1.9 μm (standard deviation, 0.2) over the cell surface. The repair data show the woven bone osteocytes that have just differentiated from mesenchymal cells to have a length-to-width ratio of 1.8 to 1, consistent with their round-to-oval appearance. The repair lamellar osteocytes progressively take on the shape of mature osteocytes, and at 4 weeks the average ratio of length to width has reached 2.4 to one. The data on repair also demonstrate the development of uniformity in the number of caniculi that pass out from each lacuna. The value in repair lamellar bone osteocytes is comparable with that in mature cortical lamellar bone in the 2–4 week time frame, a value of 2.4 μm for the perimeter-to-canalicular ratio having been documented. Woven bone osteocytes show fewer canalicular offshoots by light microscopy, having a perimeter-to-canalicular ratio of 5.6 at 2 and 3 weeks, but this may be due partially to an inability to demonstrate them, since they take tortuous routes through the woven matrix. Development of the cell processes occurs during the first several days of repair, since transmission electron micrographs at 1 week show mesenchymal cells in the central parts of the defect to be without processes, whereas processes are clearly evident in woven and lamellar osteoblasts and osteocytes some days later. Scanning electron microscopic studies show extensive cell processes of osteoblasts during development.

The lacunar–canalicular system plays a dual role in the repair and maintenance of bone (Fig. 1.14di–iv). By linking osteoblasts, osteocytes, and blood vessels, it allows the

◀ **Fig. 1.14** Photomicrographs illustrate the cell and matrix contributions to the physis, the surrounding ossification groove, and the periosteum forming the cortex. **ai** A portion of the physis and metaphysis including the perichondrial ossification groove and bone ring from a rabbit metatarsal is shown. Note the hypertrophic cell invasion by the red blood cells below and immediately to the *right* the bony ring of the ossification groove extending well beyond the level of endochondral bone formation. (**ai**, **ii**) a larger part of the metaphysis is shown. The safranin O stains cartilage red and fast green counterstains bone and fibrous tissue green. (Reprinted with permission from Shapiro et al. Organization and cellular biology of the perichondrial ossification groove of Ranvier. J Bone Joint Surg Am. 1977;59A:703–723). **b** A series of transverse sections from **bi**–**vii** are shown indicating the changing cell and matrix relationships. The perichondrium, groove tissues, and periosteum and intramembranous bone are at right of each image while epiphyseal and physeal cartilage and metaphyseal bone are at left. **i** transverse cut through the epiphyseal cartilage; **ii** transverse cut through the proliferating and hypertrophic cell region of the physis; **iii** section through the hypertrophic zone at far *left* and outer reaches of the metaphysis centrally; **iv** section through the upper reaches of the metaphysis (bone ring intact); **v** section through the metaphysis at the cutback zone with part of bone ring resorbed; **vi** bone ring almost completely resorbed and **viii** bone ring completely resorbed by many osteoclasts. The outer fibrous layer remains intact in each of these images. Multinucleated resorptive osteoclasts are seen. The outer fibrous layer of the groove persists throughout all sections but the inner osteogenic layer and the bone bark become circumferentially incomplete and are eventually completely resorbed. Multinucleated resorptive osteoclasts are prominent. The cortex will be re-established at the metaphyseal–diaphyseal junction as intramembranous bone from the periosteum is again synthesized. **c** Longitudinal sections just beyond the midline in a piglet embryo femur show how the inner metaphysis (*triangular shape*) above merges with and is surrounded by the outer periosteum synthesizing cortical bone. **ci** shows a lower power view (*metaphyseal bone at top*) while **cii** is a color photomicrograph (*toluidine blue stain*) showing the inter-relationship of the inner endochondral and outer intramembranous bone. **di** Osteocytes in lacunae and canalicular connections in lamellar bone as illustrated by von Ebner in 1875 (Sitzungsb Akad Wissensch 71–22:49–138,1875) **d ii** Lacunae and canaliculi are pictured in slightly less organized bone. **diii**, **iv** Tracings of osteocyte lacunae linked by canaliculi in woven bone. Osteocytes in lacunae send out and are linked by cell processes in canaliculi via gap junctions. **dv**, **vi** Gap junctions linking two osteocyte cell processes in a canaliculus in young rabbit bone (**dv**) and linking osteoblast processes in osteoid (**dvi**) are seen in electron micrographs

extracellular fluid to relate to the matrix and the vascular system, providing nutrition to the bone cells and allowing deposition and removal of mineral. Extracellular fluids pass through the intracanalicular system but whether the preferred pathway is via an extracellular, extra-process position, being outside the actual cells and cell processes, is unclear. The changing topography of the lacunar–canalicular system and the presence ultrastructurally of intermediate filaments [17] and intercellular gap junctions [11] imply an active cell–cell communication role for the system, mediated in an intracanalicular intracellular fashion. Transmission electron micrographs demonstrate intracellular intermediate filaments, approximately 11 nm in diameter, within the mesenchymal cells and osteoblasts and within the osteoblast and osteocyte cell processes as well as 7 nm thick actin filaments in longitudinal array. The large number of canaliculi implies a major functional role for the cell processes and their filaments. Transmission electron microscopic studies document intercellular gap junctions between surface osteoblasts, between osteoblasts and osteocyte processes in the bone, between adjacent osteocytes (via cell processes), between endosteal cortical bone-lining cells, and between osteocytes and intracortical blood vessels (Fig. 1.14dv, vi). The length of the gap junctions is frequently quite extensive especially along the long axis of cell processes. The surface area of the gap junctions is frequently increased by curvilinear, stacked linear, or annular shapes [11].

1.8 Development of Joints—General Description

Development occurs by a series of cellular changes which are regional in scope. A group of undifferentiated cells forms initially which then undergo tissue differentiation and pattern formation from the very general to the specific. Joint development was described initially by von Baer (1837) [41] who observed that each element of the appendicular skeleton was originally laid down as a separate cartilage and that it was the unchondrified tissue between these more differentiated elements that eventually formed the joints. Appendicular development moves in a wave-like fashion from the proximal part of the extremity toward the distal part and development in the upper limb precedes that in the lower limb by several hours to a few days. The various bones are formed by initial centers of chondrification at the central region of the developing bone followed by progressive chondrification to each end in a well-patterned fashion. The joints form relatively late in development after the patterns of the two adjacent bones including their epiphyseal regions and articular cartilages have been established.

Development of the joints in the human extends from the first appearance of the joint rudiments at 11 mm CR length to the appearance of the cavities at 30–34 mm [19, 22, 24]. The skeletal development of the shoulder and pelvic girdles and larger bones continues as centers of chondrification in the interior of the blastema with one for each element at 11 mm. Muscle condensation slightly precedes chondrification. As chondrification expands toward the presumptive ends of each bone, the unchondrified mesenchymal tissues remaining between the cartilages gradually become thinned to form a series of cellular collections referred to as the interzones and it is these regions that form the first morphological indication of the joints. The cavities of the larger joints appear at or soon after the onset of periosteal ossification in the long bones. Joint development can thus be followed through clear stages of (i) homogeneous interzone, (ii) 3-layered interzone, (iii) the stage of early liquefaction, and (iv) the stage of full separation (Fig. 1.15). The 3-layered structure was described by Bernays [169], Schulin [170], and Kazzander [171] and best illustrated by Hesser [172] (152). Retterer ([173–175]) described the histologic aspects of joint formation in detail. Haines observed that the intermediate layer of the interzone is always liquefied soon after the synovial mesenchyme differentiates so that separation of two adjacent cartilage surfaces is complete by the 34 mm stage at the shoulder and radial–humeral joints, by 44 mm at the knee and probably at the hip, by 45 mm at the metacarpophalangeal joints and ankle joints while the wrist and carpal joints separate only after 50 mm [176].

It is only later that the joint cavities spread peripherally to develop the complex recesses they subsequently show. Hesser has indicated that the articular surfaces are shaped at a stage when their interzones are still homogeneous such that little or no movement of adjacent developing cartilage surfaces could occur. The synovial cavities are formed initially partly in the tissues of the interzone and partly in the synovial mesenchyme so that the articular surfaces are composed centrally of chondrogenous layers of the interzones and peripherally of tissues of similar constitution which originally are part of the intracapsular perichondrium. Near the margins of the articular surfaces there is a zone of transition between those articular surfaces and the perichondrium. With full chondrification of the articular surfaces the remains of the liquefied tissues of the interzone or synovial mesenchyme come to form a thin layer overlying the cartilage containing flattened cells some of them necrotic. Eventually these cells disappear. It is felt that the capsules and the region adjacent to the joints are new formations. Joint development is outlined by photomicrographs of histologic sections in Fig. 1.15a–d.

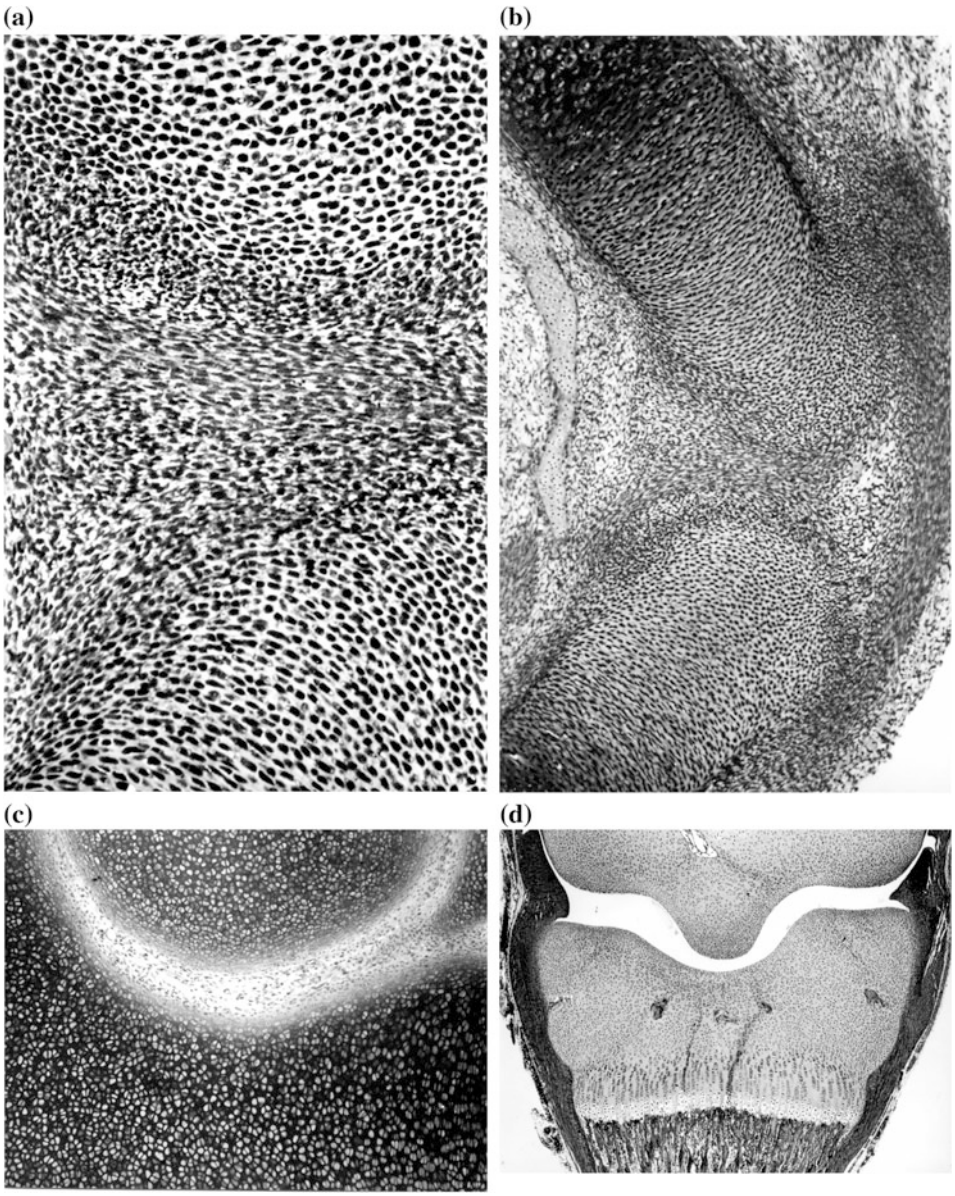


Fig. 1.15 A series of photomicrographs shows the stages of joint development in the rabbit embryo. **a** In stage one there is a homogeneous interzone with undifferentiated cells filling the space between the developing cartilage model of two adjacent long bones. **b** A 3-layered interzone is formed with relatively more dense accumulations of tissue outlining the articular regions of the adjacent epiphyses and slightly less dense but still homogeneous cell accumulations filling what will eventually become the joint space. **c** The stage of early liquefaction is shown here in the developing elbow joint. While there are still cells in the interzone region their density is diminished and areas of acellularity are seen. **d** The fourth stage of joint development represents the stage of full separation with a clear synovial cavity seen

1.8.1 Detailed Description of Joint Development

Joints are first defined in the interzone regions at 11 mm and the synovial cavities of the larger joints appear at 34 mm. The joints first appear as interzones which are formed from the remains of the skeletal blastema between the cartilages. The interzones form the more central parts of the articular cartilages and synovial cavities. Each interzone passes from a homogeneous stage, to a 3-layered stage with chondrogenous layers and an intermediate loose layer, and the stage where the interzone layer breaks down and the chondrogenous layers become fully chondrified. The fibrous capsule near the joints cuts the mesenchyme into two regions, one of which forms the synovial mesenchyme and the other the perichondrium which can be intracapsular. The intracapsular perichondrium is partly transformed into the more peripheral parts of the articular cartilage while the remainder persists throughout life. The synovial mesenchyme forms the more central part of the synovial cavities, synovial and sub-synovial tissues, and all intracapsular structures including ligaments, tendons, and fibrous cartilages. The interzones of the larger joints appear at 11–12 mm, the fibrous capsule at 16 mm, the interzones become 3 layered at 21–26 mm, liquefaction of the synovial mesenchyme begins at 30–34 mm, and the separation of the articular cartilages is complete by 40 mm. Eventually when the synovial cavities are formed the remnants of the liquefying tissue are totally destroyed. By 12 mm, the cartilages at the shoulder and elbow have adopted their characteristic shapes and the interzones are relatively thick but quite distinct with

each formed by a mass of undifferentiated blastemal tissue between the cartilage. At the knee the interzone at first stage is indistinct since chondrification of the distal femur and proximal tibia has not progressed as far relatively speaking as of those of the upper extremity at the elbow. At the hip the pelvis is still represented by dense blastemal tissue continuous without form with the upper end of the femur with the interzone not yet in evidence. By 13 mm at the shoulder, hip, and knee each interzone is now formed by a distinct plate of condensed tissue whose cells pass without interruption into the cartilages on either side. Peripherally the interzone is continuous with the perichondrium of the skeletal elements. At the hip the interzones, perichondrial tissues, and condensed tissues are in unbroken continuity. There is virtually no differentiation within the interzone area during the time in which considerable differentiation of peri-articular tissues is occurring. The interzone shows little sign of the shape of any future articular surfaces. At the hip and knee in particular the interzones are flat with the eventual shape not yet distinguishable. By 14 mm the ends of the cartilages have assumed their characteristic shapes. By 16 mm the interzones of the larger joints are still homogeneous and continuous with the perichondrium surrounding the cartilages. Differentiation of fibrous capsule and ligaments is beginning to be seen and the interzone region is continuous at its periphery with the intracapsular perichondrium which in turn is continuous with the extracapsular perichondrium. The early synovium forms between the capsule and extracapsular perichondrium in its own less condensed tissue. This will eventually differentiate into the synovial and sub-synovial tissues and such intercapsular structures as are formed. The early derivatives of the blastema including the cartilages, perichondrial tissues, and interzones are free of blood vessels at this stage. Vessels ramify over the outer surfaces of the perichondrial tissues. Vessels do not enter the perichondrium until this layer alters in structure in preparation for the formation of periosteal bone. Some vessels, however, appear in the fibrous capsules of the joints and are seen lying in the synovial mesenchyme. By 19 mm the pattern of the interzone, synovial mesenchyme, capsule, and perichondrium is more distinct. The interzones remain fully homogeneous dense structures composed of tightly packed cells at 18–20 mm, with the cells continuing to undergo frequent mitotic division. As development proceeds a characteristic 3-layered interzone is formed in particular in the intracapsular region. At 21 mm at the elbow both the humeral–radial and humeroulnar joints are clearly 3 layered with two dense cartilage layers which are destined to form the articular surfaces separated by an intermediate loose cell layer. At the periphery of the presumptive joint the intermediate layer of the interzone is continuous with the synovial mesenchyme but the interzone tissue is always avascular. Embryologists refer to the cartilage layer of the developing ends of the bones as true perichondria which are continuous with the extracapsular perichondrium. There are clear differences, however, from the perichondrial tissues which can be removed from underlying surfaces and which are well vascularized from those within the joint itself which never have a blood supply.

In the shoulder joint at 21 mm there is early loosening of the middle layer of the interzone with the capsule and the adjacent tendons differentiated from the dense mesenchyme. At the knee, dense interzonal tissue still intervenes between each femoral condyle and the articular surface of the tibia. By 23 mm the interzone of the shoulder has attained a typical 3-layered structure and a fibrocartilaginous labrum is seen. At 24 mm at the hip and knee the interzones are still dense and homogeneous. At 26 mm the interzones of the knee are in the early 3 layered. In the knee the interchondral interval is filled with an abundant vascular synovial mesenchyme from which the cruciate ligaments appear as well as the menisci. At 29 mm just before the joint cavities appear, the distinction of the layers of the interzone becomes sharper. In the intermediate layer the cells become flattened and lie with their surfaces parallel to the surfaces of the interzone. The matrix of this tissue becomes clearer in preparation for resorption. At the shoulder which is advanced in development from other joints, the synovial mesenchyme on either side of the joint is breaking down and small cavities are being formed. By 29 mm all the larger joints have reached the stage in which the interzone is 3 layered. The times at which this appearance is attained vary: shoulder 23 mm; elbow 21 mm; wrist and most of the carpal joints 25 mm; all of the interzones of the fingers 27 mm; hip 30 mm; knee 26 mm; ankle 27 mm, smaller intertarsal joints 32 mm; and toes 32 mm.

By 30 mm the middle layer of the interzone and the inner portion of the synovial mesenchyme are softening and begin to break down to form the first joint cavities. Between the cartilage surfaces there is a loose liquefying tissue. At 34 mm the cavity of the humeroradial joint is well formed but still contains a few cells in its interior. At the hip the cavity is spreading around the head of the femur and the ligamentum teres lies in this synovial mesenchyme accompanied by conspicuous blood vessels which will later supply the cartilage canals of part of the head of the femur. At the knee the menisci are sharply differentiated and joint cavities have developed between the anterior parts of the menisci and the femoral condyles.

1.9 The Blood Supply of Bone

1.9.1 Blood Supply of the Cortex

Bone is a well-vascularized tissue and organ. The ***periosteal circulation*** supplies the periosteum, the surrounding muscles, and the outer one-third of the underlying cortex. The bone marrow and inner two-thirds of the cortex are supplied

by the ***medullary circulation***, which originates from the nutrient arteries which enter the bone through specific nutrient foramina and then branch within the marrow cavity toward each end of the diaphyseal bone. There are considerable intracortical anastomoses between the inner medullary and outer periosteal vessels [101, 177]. In a study of the vascular supply of human fetal long bones (femur, humerus at 17–24 weeks) Skawina et al. [178] found that the medullary arteries entering via the nutrient foramina supplied both marrow and the bone cortex. There was no arterial supply to the shaft cortex from the periosteal side but numerous periosteal capillaries entered the cortex. The metaphyseal capillaries abruptly stopped at the lower physeal cartilage. The nutrient and periosteal vessels were interconnected by a network of intracortical capillaries and sinusoids and occasionally by larger arteries and veins traversing the cortex. Occasional metaphyseal arteries entered via the periosteum. Connections between nutrient vessels and bone marrow sinusoids were frequent.

1.9.2 Epiphyseal Blood Supply

The epiphyseal cartilage receives nutrition from vessels in the ***cartilage canals*** which also provide a source of osteoprogenitor cells for the secondary ossification centers (Haines [179]; Shapiro [180]). The articular cartilage is never vascularized, receiving nutrition by diffusion from the synovial fluid, and the physes are also avascular except for the presence of transphyseal vessels in the fetal period and early post-natal months. The physis has a dual blood supply although the vessel systems are totally separate from one another. The resting, proliferating, and upper hypertrophic layers are supplied by diffusion via ***epiphyseal vessels [E-vessels]*** above while the ***metaphyseal vessels [M-vessels]*** below enter the lower hypertrophic region only and provide osteoprogenitor cells to synthesize bone on the calcified cartilage cores (Dale and Harris [181]). The metaphyseal vessels are the terminal ramifications of the medullary circulation within the marrow.

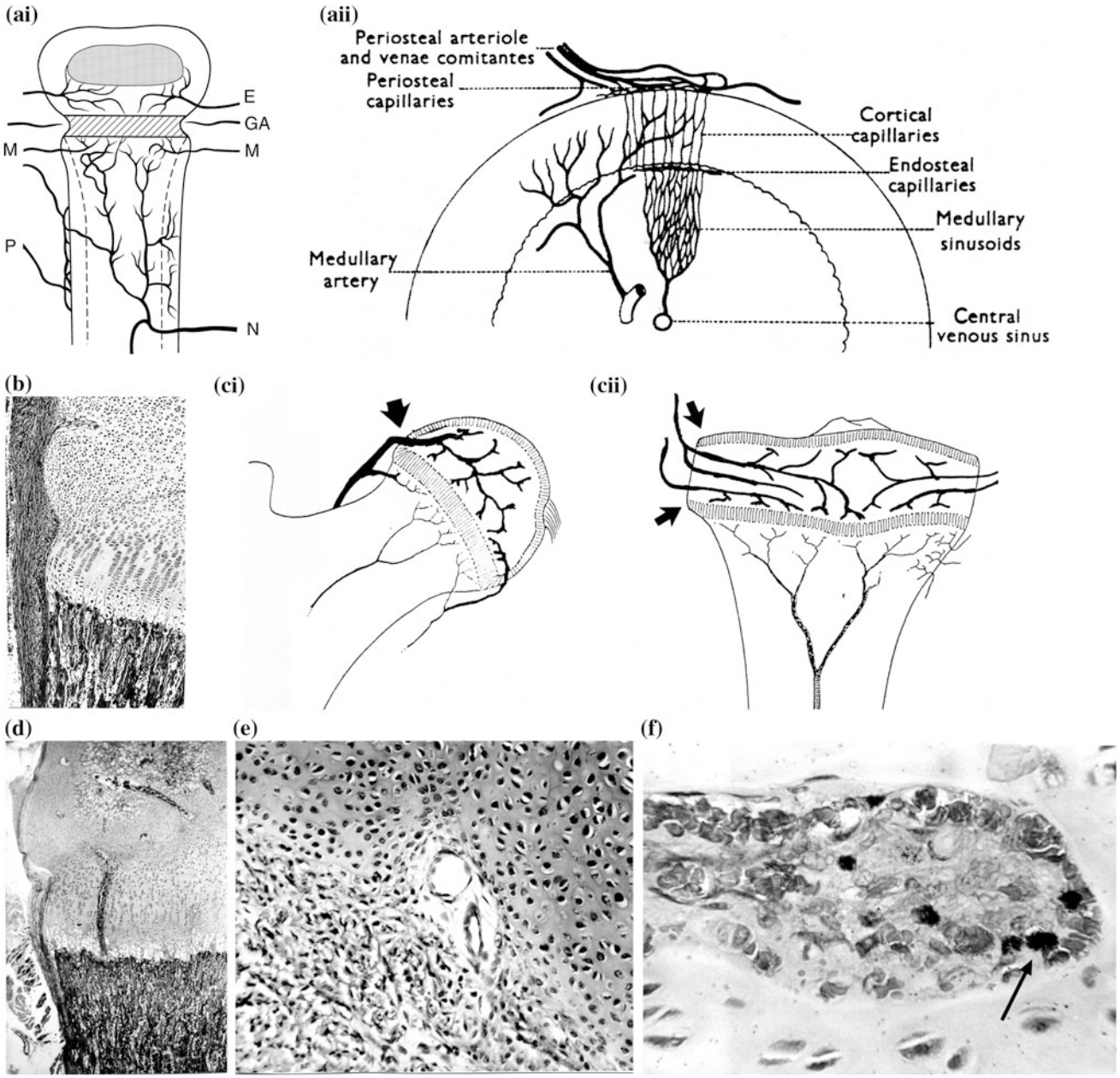
1.9.2.1 General Description. Dual Physeal Blood Supply from Epiphyseal and Metaphyseal Vessels

The blood supply of developing and mature bones has been well described and is illustrated in Fig. 1.16ai, ii [101, 181–186]. The growth plate itself is avascular but has a dual blood supply receiving its nutrition from two separate sources—the epiphyseal vessels that supply the germinal, proliferating (columnar), and upper hypertrophic cell layers by diffusion and the metaphyseal vessels that supply the zone of calcification beginning in the lower hypertrophic cell layers by passing only two–three cells deep into the hypertrophic cell lacunae. The epiphyseal vessels are thus responsible for permitting longitudinal growth to occur, whereas the metaphyseal vessels, accompanied by the osteoprogenitor cells, are responsible for laying down bone on the calcified cartilage matrix cores.

The specific roles of the epiphyseal vessels and of the metaphyseal vessels have been studied for some time with the works of Haas (1917) [187, 188], Trueta and Amato (1960) [185], and Brashear (1963) [189] being most helpful. Each of these works has documented the fact that the proliferation of epiphyseal cartilage cells to enhance longitudinal growth depends on the epiphyseal circulation (Fig. 1.16b) and that damage to this blood supply causes not only necrosis of the secondary ossification center but marked changes in the epiphyseal plate and longitudinal growth. The diffusion of nutrients encompasses much of thickness of the plate including into the hypertrophic zone. The rich blood supply on the metaphyseal side of the physis plays no role in the growth process but has as its main role the calcification of the matrix in the lowermost part of the hypertrophic zone, the invasion of the hypertrophic cell lacunae, and the transport of associated osteoprogenitor cells which synthesize bone on the calcified cartilage cores. The experimental evidence points to the fact that blood carried by the metaphyseal side vessels is of no nutritional importance to the hypertrophic cells. Indeed, when the metaphyseal circulation is markedly ablated, the hypertrophic zone not only persists but increases in size owing to the continuation of diffusion from the epiphyseal vessels above.

Harris demonstrated the separation of epiphyseal and metaphyseal vessels using vascular injection in the physiological range in an early (1929) study [190]. No anastomoses were seen to penetrate the growth cartilage in the proximal femur of a young dog and the distal femur of a stillborn child. Irving found that no vessels passed through the growth cartilage in the rat (up to 8 weeks of age) with the cartilage forming a complete barrier between the separate epiphyseal and metaphyseal vessels [186].

The dual vascular supply to the physeal regions has been demonstrated by Trueta and Morgan using vascular perfusion studies [101]. The epiphyseal vessels pass through the bone plate of the well-developed secondary ossification center and then ramify over the surface of the germinal zone of cartilage of the physis without passing into the physeal cartilage itself. The epiphyseal arteries cross through canals in the bone plate and expand into terminal spurs before turning back as large veins, although not always through the same canal. Each terminal expansion covers the space corresponding to from 4 to 10 physeal cell columns although the vessels themselves do not penetrate into the physeal cartilage. Transverse histologic sections immediately under the bone plate and thus on the surface of the germinal zone of physeal cartilage show a very rich vascularity with the


(ai)
E
GA
M
M
P
N
(aii)
Periosteal arteriole and venae comitantes
Periosteal capillaries
Cortical capillaries
Endosteal capillaries
Medullary sinusoids
Medullary artery
Central venous sinus
(b)
(ci)
(cii)
(d)
(e)
(f)

whole of the vascular expansions forming a ceiling over the physeal cartilage. The second set of vessels for the dual blood supply represents those from the metaphyseal side with approximately 4/5th of the vessels reaching the growth plate from the metaphyseal side consisting of the last ramifications of the nutrient artery distributed over the most central parts of the growth plate with the outer fringe of the lower plate supplied from the system of large perforating metaphyseal arteries from the adjacent periosteum. These two metaphyseal side systems merge, however, such that there is no detectable distinction between the end vessels of the two sources.

Morgan (1959) [191] and Irving (1964) [186] have further refined the blood supply of the growth plate into three sources: epiphyseal, metaphyseal, and a circumferential vascular ring around the plate. (This description still leaves intact the concept of the dual blood supply of the growth plate.) The circumferential blood supply is a small artery which runs around the periphery of the plate. It is formed by fine branches from the superficial anastomosis of the periosteal arteries connected to both the epiphyseal and metaphyseal sides. The circular series of vessels at either end of a long bone were originally described by Hunter in 1743 [192]. One set (smaller) surrounds the growth plate and the other (larger) is opposite the joint line. Small branches from the peri-physeal region form the principal supply to the circumferential artery of the plate. The epiphyseal side of the plate is supplied primarily by the epiphyseal vessels which penetrate the bone plate and ramify along the surface of the resting zone of chondrocytes. It is also supplied at its periphery from vessels from the circumferential ring. The metaphyseal side of the plate is supplied by the terminal extensions of the nutrient artery, which pass into the lower regions of the hypertrophic chondrocyte layer and terminate as dilated sinusoids shaped like an inverted "U". The more peripheral regions of the metaphyseal side of the plate (hypertrophic zone) receive vessels passing inwards from the metaphyseal periosteal vessels.

1.9.2.2 Extrinsic Blood Supply

There are two basic extrinsic patterns of blood supply to the epiphyses [181]. In the large majority of epiphyses, vessels pass through the perichondrium of the side walls into the epiphyseal cartilage throughout the circumference of the epiphysis from the level of the articular cartilage to that of the physeal cartilage (Fig. 1.16b). In epiphyses that are covered almost entirely by articular cartilage, namely those of the proximal femur and the proximal radius, the blood supply is more tenuous and vessels enter the epiphyseal cartilage in a small region between the articular cartilage and the growth plate cartilage. In the former instance the physeal regions are extracapsular in position and in the latter they are intracapsular (Fig. 1.16c).

The vessels entering the hypertrophic zone are terminations of both the nutrient and metaphyseal arteries. Arsenault and Hunter also studied the microvascular organization of the epiphyseal–metaphyseal junction in rats by light microscopy, serial section reconstructions, and scanning electron microscopy [193, 194]. The metaphyseal and nutrient arteries undergo extensive arborization and anastomosis near their terminal ends. The microvascular system that projects into the hypertrophic cell region consists of saccular and bulbous terminal arteriole extensions. It is not formed of capillary loops returning arteriole blood to formed venules;

◀ **Fig. 1.16** The blood supply of a developing bone is illustrated. **ai** The epiphyseal vessels (*E*) are responsible for supplying the epiphyseal cartilage, the secondary ossification center, and also the growth plate, by diffusion from *above*. The *lower part* of the growth plate is supplied by the metaphyseal vessels coming in from the periphery and by the terminal ramifications of the nutrient (*N*) artery. The periosteal (*P*) vessels supply the outer one-third of cortical bone while the nutrient artery supplies the inner two-thirds. There is, however, a rich anastomosis within the cortex. The tissues of the groove are supplied by the perichondrial groove artery (*GA*). **aii** A cross-section illustration of blood supply to cortex and marrow from mid-diaphyseal region. **b** A light power photomicrograph shows a perichondrial vessel (*upper left*) passing into the epiphyseal cartilage above the physis and well before the formation of the secondary ossification center. **c** In those epiphyses which are fully intracapsular (**ci**, proximal femur), the epiphyseal region is covered almost completely by articular cartilage and the articular cartilage and the physeal cartilage are quite close (*arrow*). The vessels must enter in a restricted circumferential region through a narrow area between the articular and physeal cartilages. This pattern is seen at the proximal femoral and proximal radial epiphyses. The vessels are vulnerable to any shift of the epiphysis by acute trauma. This type of blood supply is referred to as type A by Dale and Harris [181]. The more common type of blood supply to the epiphyseal regions is shown at *right* (**cii**) referred to as type B by Dale and Harris. The vessels enter circumferentially through the side walls of the epiphysis in a broad region between the articular cartilage (*arrow*) and the physeal cartilage (*arrow*). These epiphyses are extracapsular in position. (Reprinted with permission from Shapiro F, Epiphyseal growth plate fracture-separations: a pathophysiologic approach. Orthopedics. 1982;5:720–736). Reprinted with permission from SLACK Incorporated. **d** A transphyseal vessel is seen from proximal humeral epiphysis of rabbit. **e** Perichondrial vessels at the periphery of epiphyseal cartilage mass are illustrated from a 1-week-old distal femur (rabbit). Vessels are present in the indentation at cartilage periphery. The perichondrium and fibrous tissue are at *lower left*. The vessels in the indented areas are generally associated with a cellular connective tissue front. **f** Tritiated thymidine autoradiography demonstrates the high degree of cell proliferation (*arrow*) in the vessels and connective tissue cells of the epiphyseal cartilage canals continuous with the perichondrial vessels in the distal femur at 1 week. This cartilage canal was continuous with a perichondrial vessel.

venous return occurs below the hypertrophic zone of the epiphysis within anastomosing blood vessels which drain into large blood sinuses.

1.9.2.3 Intrinsic Blood Supply of Epiphyseal Cartilage. Cartilage Canals

Each of the major epiphyseal cartilages in the human is vascularized beginning from the third to the seventh fetal month, which represents a long period of time in each epiphysis prior to formation of the secondary ossification center [142, 182]. The primary function of the canals is nutrition and only later and secondarily do they participate in forming the secondary ossification centers. The vessels within the epiphyseal cartilage are present in cartilage canals in which a central artery or arteriole, capillaries, and a plexus of veins are enclosed in a connective tissue matrix [58, 65, 179, 180, 182, 195–219] (Fig. 1.16d–f). In small canals there is only a capillary plexus. The vessels within the canals do not, therefore, directly contact the cartilage matrix nor do the arteries and veins run separately from each other. The canals and their contents appear to derive from and be continuous with the perichondrium, although Delgado-Baeza et al. (76) commented that vessels, perivascular cells, or perichondrium were not necessary for canal morphogenesis and that based on structural cell differences the canals were not a continuation of the perichondrium. Two mechanisms for formation of cartilage canals have been proposed with support still expressed for both. One mode of origin of the cartilage canals is referred to as the theory of inclusion whereby the vessels are considered to be present within the cartilage in a passive sense; as the cartilage matrix grows outwards by perichondrial cells becoming chondrocytes it incorporates the perichondrial vessels which continue to function. A more widely supported origin for the canals, the theory of invasion, involves an active invasive or chondrolysis component to the cartilage canals as they position themselves into relatively large areas in need of nutrition not satisfied by passive diffusion. We have recently assessed cartilage canals by tritiated thymidine autoradiography and concluded that active vessel invasion and proliferation occurred [180]. Tritiated thymidine labeling studies to assess cell proliferation activity were done in newborn and 3-, 4-, and 7-day-old New Zealand white rabbits. Proximal humeral, distal femoral, and 3rd metatarsal epiphyses were assessed by histology and serial section autoradiography. Cartilage canals were seen in each epiphysis. Transphyseal vessels were seen in each epiphysis continuous from the epiphysis to the metaphysis or present within the physis traversing the proliferating and hypertrophic cell zones (Fig. 1.16d). Histologic sections showed vessels from the perichondrium continuous from those of the epiphyseal cartilage canals at proximal humeral, distal femoral, and metatarsal epiphyses. Serial sections showed vascular buds and connective tissue cells lying in indentations at the periphery of and present within the epiphyseal cartilage (Fig. 1.16e). Autoradiographic studies showed extensive labeling of vessel wall cells and surrounding connective tissue cells of the cartilage canals (a) within the epiphyseal cartilage, (b) traversing the physis, and (c) within the epiphyseal cartilage but continuous with the perichondrial vessels (Fig. 1.16f). The labeling was always far more extensive than in the surrounding chondrocytes and was always present throughout the entire extent of the canals. The cell labeling activity strongly supports an active dynamic phenomenon underlying the vascularization of epiphyseal and physeal cartilage.

Kugler et al. studied cartilage canals in the rat as they related to formation of the secondary ossification center observing that cartilage canals advanced within the cartilage matrix by chondroblastic absorption [209]. One autoradiograph showed thymidine labeling of cartilage canal connective tissue and blood vessel cells. Although some cells similar to chondroclasts can be seen within cartilage canals our observations indicate that the large majority of canals are not associated with such cells. Fibroblast-like cells and uninuclear macrophages appear responsible for the chondrolysis [197, 198]. Cole and Wezeman [198] noted chondroclasts in mouse epiphyseal cartilage canals but felt they were related to calcified matrix resorption specifically rather than to the invasive stage of canal positioning. Chondrolytic aspects of cartilage cell positioning do not appear to be mediated exclusively or even predominantly by chondroclasts.

According to Haines and others there are no anastomoses between separate canals within the cartilage and the vessels function as end vessels [198]. Haines defines the patterns of cartilage canals as (i) simple branched or unbranched canals, which project into the cartilage and end blindly; (ii) double or multiple rooted canals which take their origin by two or more separate roots from the perichondrium, but join within the cartilage and then act as simple canals; (iii) tunnel canals which traverse peripheral tongue-like projections of cartilage from edge to edge; (iv) dividing and reuniting canals which end as simple canals; (v) transphyseal communicating canals which originate from the perichondrium and end in the bone marrow of the shaft. After the ossification center has formed there are then (vi) nutrient canals which supply the bony center from the perichondrium and (vii) centrifugal canals which arise from the bony center but behave as simple canals. Hurrell has noted that the vascular pattern of the cartilage canals is always different even in corresponding epiphyses in different fetuses [207]. Cartilage canals are present in the human and vertebrates such as pig, lamb, calf, and rabbit. They are not present in the mouse [220] and rat [221] where vascular invasion of the epiphysis from the perichondrium occurs only at the time of secondary

ossification center formation. The primary function of the canals is to provide nutrition to the epiphyseal cartilage. Only weeks to months later do they provide vascularization for endochondral bone formation of the secondary ossification centers. Many have noted cartilage canal presence from the third fetal month.

1.9.2.4 Transphyseal Communicating Cartilage Canals

While the separation of epiphyseal and metaphyseal vessels is well established and accurate, in the human in the fetal period there are occasional occurrences of epiphyseal cartilage canals, which originate from the perichondrium, passing through the physeal cartilage and communicating with the metaphyseal marrow. The large majority of these are obliterated either before birth or soon after a secondary center is ossified. Such communicating canals are more prominent in other species such as the lamb where several such canals can often be seen in one section across the width of a physis. They are noted histologically to contain red blood cells, indicating participation in blood flow, but the extent of their participation is not quantified. Many observers have noted transphyseal vessel communication in the human including Hurrell [207], Hintsche [205], Haines [179], Bidder [65], Bardeen [222], Brookes [182], Trueta and Morgan [101], Watermann [215–217], Levene [210], Wang [214], Chappard et al. [197, 198], Gray and Gardner [25], Gardner and Gray [24], and Tilling [223]. Brookes [182] studied human fetal lower extremity bone by barium sulfate microvascular injection techniques. Vascular cartilage canals were detected in epiphyses in rudimentary form of 16 cm as early as 20 weeks but they were well developed in both ends of femur and tibia by 22 cm CR length. Transphyseal connections were seen from 22 cm CR length onwards and were more numerous in older fetuses. They were seen at both upper and lower femoral ends. Transphyseal vessels are also present in other species. Levene [210] showed transphyseal vessels in lamb, cat (partial), rabbit, goat, and human; Parsons [224] in the young deer; and Hayashi [204] in the fetal rabbit proximal femur. Lutfi [211] and Hunt et al. [206] showed vessels in the proliferating and hypertrophic layers of the chicken. They are noted histologically to contain red blood cells, indicating participation in blood flow, but the extent of their participation is not quantified. We described transphyseal vessels in the New Zealand white rabbit, in newborn and 3-, 4-, and 7-day-old proximal humeral, distal femoral, and metatarsal bones [180] (Fig. 1.16d).

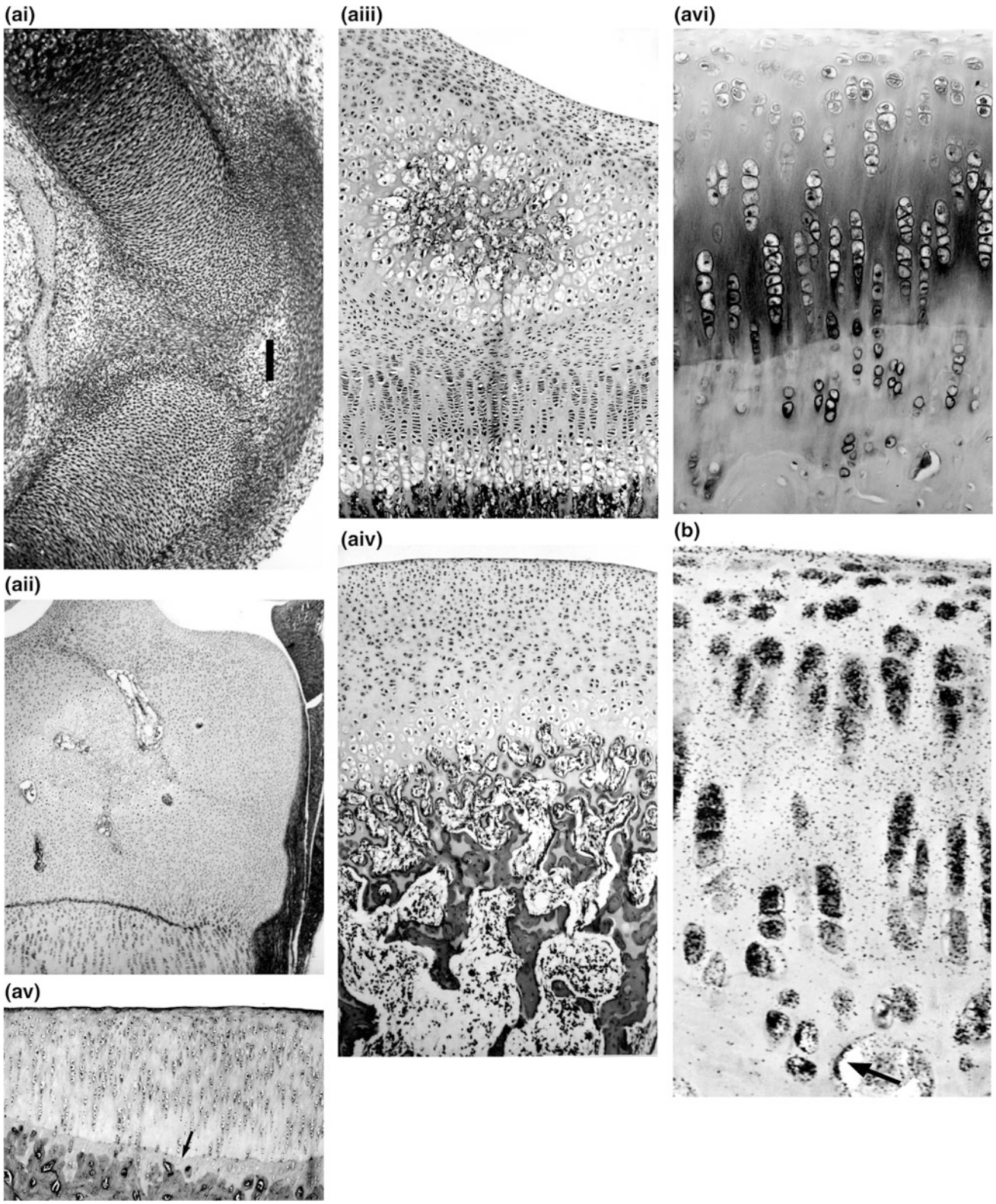
Brookes [182] has shown that the lower end of the femur is vascularized by four groups of canals entering at the intercondylar notch, the suprapatellar surface, and the collateral aspects of the condyle. Multiple sections allow for demonstration of a vascular cartilage canal from the epiphyseal cartilage passing through the physeal cartilage into the metaphyseal area. The upper end of the tibia is canalized by vessels penetrating the intercondylar eminence and the whole circumference of the superior tibial perichondrial cartilage region. The vascular pattern shows a convergence toward the center of the epiphysis. The distal tibial epiphysis also shows arteries entering from all aspects circumferentially with some entering the medial surface of the malleolus as a separate group. At the proximal femur the vessels enter the femoral neck and head region circumferentially early on at 22 cm CR length. Later a superior and an inferior group are distinguished.

Hurrell [207] felt, unlike others, that transphyseal communication was passive with epiphyseal vessels persisting with growth and being encompassed by the physeal cartilage and then metaphyseal marrow. The connection was thus felt to be "accidental and functionless". No vascular canal grew actively from the diaphyseal–metaphyseal shaft into the epiphysis. He noted vessels communicating at birth in upper humerus and upper tibia. Haines noted perforating transphyseal canals in several mammals at certain stages of their development. He also felt that the development of such canals was passive. Obliteration of the canals was a constant phenomenon at a slightly later stage of growth. Haines noted them to be "very conspicuous" in the early stages of ossification. The articular cartilage was always avascular.

Smaller mammals such as the mouse and rat have no cartilage canals and develop their secondary centers by direct communication from perichondrial vessels at the time of bone formation.

1.9.2.5 Cartilage Canals and Secondary Ossification Center Formation

Hurrell [207] and Retterer [58] have provided detailed reviews of the many descriptions of cartilage canals in the nineteenth century. The cartilage canals tend to become obliterated with time but many persist to supply the secondary ossification centers. Haines [179] believed from his serial reconstructions that the ossification center always appears centrally in an avascular zone between sets of cartilage canals. The canals are present in relatively large epiphyses and serve as sources of nutrition where diffusion from the periphery alone would be ineffective. Once an area that is not served by cartilage canals reaches a certain stage the chondrocytes hypertrophy and degenerate, the cartilage matrix calcifies and invasion by vessels from the cartilage canals follows bringing in osteoprogenitor cells to form the secondary center of ossification. Bone is then synthesized on calcified cartilage cores. According to Haines "there can be no possibility of the osteoblasts of the epiphysis being derived from periosteal buds growing up from the bone marrow of the shaft, for at the time of ossification all communications between the shaft and the epiphysis have disappeared. It is highly likely that they are derived from the


(ai)
(aii)
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(aiii)
(aiv)
(avi)
(b)

connective tissue of the cartilage canals …. The connective tissues of the cartilage canals and the perichondrium are exactly similar and are continuous with one another." The cartilage canals (i) determine by their distribution the position of a clear space or avascular lamina which is where the ossification center forms and (ii) they give origin to the osteoblasts and marrow of the center. Hintsche [205], using serial section reconstructions, noted a uniform cartilage canal vascularity in epiphyseal cartilage and no relation of vessel pattern to site of secondary center formation or of center formation to avascular regions. More recently Wilsman and van Sickle [219] noted a direct relation of cartilage canal glomerular ends to foci of calcified cartilage such that the endochondral sequence of the secondary center was the same as that at the under surface of the physis. They also found cartilage canals to be very evenly spaced.

1.10 Development of the Articular Cartilage

1.10.1 Stages in Articular Cartilage Development

The articular cartilage is being shaped initially during the times of epiphyseal and interzone formation. Once resorption of the interzone region has occurred, however, the smooth, free surface of the articular cartilage is evident. Four stages in the development of the articular cartilage can be defined (Fig. 1.17a). In the second stage the articular cartilage merges imperceptibly at a histologic level of resolution with the underlying epiphyseal cartilage. Other than the fact that the superficial one to two cell layers of the articular cartilage tend to be somewhat flattened parallel to the surface, the underlying articular chondrocytes are randomly dispersed and demonstrate no different pattern or orientation from the chondrocytes of the epiphysis. Mankin has demonstrated differing cell proliferation zones, however, using tritiated thymidine autoradiography [225, 226]. Thymidine localization in the cartilaginous epiphysis occurs in two distinct layers indicative of regions of high cell proliferation. One zone was sub-adjacent to the articular surface where it contributed to growth of the articular surface and the other zone was just peripheral to the secondary ossification center contributing to the epiphyseal expansion and laying the groundwork for enlargement of the ossific nucleus. The third stage of development occurs once the secondary ossification center has been formed and has reached its greatest relative extent referable to replacing the epiphyseal cartilage. At this time the undersurface of the articular cartilage merges with the physis of the secondary ossification center, which is referred to by some as the mini-plate. The physis of the secondary ossification center or the mini-plate represents the mechanism by which the epiphyseal region of the bone continues to grow on one hand and to transform to secondary ossification center bone on the other. Strictly speaking the mini-plate is part of the epiphyseal cartilage rather than being an integral part of the articular cartilage, although there is no line of demarcation at a structural level between the lowermost portions of the articular cartilage and the outermost portions of the epiphyseal cartilage. The final stage in the development of the articular cartilage occurs at skeletal maturation at the same time that the physis closes. Both the physeal and mini-plate sequences lose their proliferative capacity. The physeal cartilage is resorbed allowing for bony continuity between the marrow of the secondary ossification center and that of the metaphysis. At this time, the innermost layer of the articular cartilage calcifies, forming the calcified layer of the articular cartilage which persists throughout life. The articular cartilage has now reached its final development and is structurally composed of four layers which cover the subchondral bone plate.

1.10.2 Layers Within Articular Cartilage

The outermost layer of the articular cartilage is the tangential zone in which 2–3 cell thicknesses of chondrocytes are flattened with their long axes parallel to the surface of the cartilage. This region is characterized by a relatively high

◀ **Fig. 1.17** Articular cartilage development in the rabbit along with the tissue of the epiphysis immediately adjacent to it is shown in photomicrographs at progressively older time periods. **ai** The interzone region (*I*) of the embryonic rabbit knee is shown with femur above and tibia *below*. The presumptive joint remains filled with cells. The area destined to become articular cartilage of proximal tibia shows cells packed slightly more densely. **aii** The articular cartilage merges imperceptibly with the epiphyseal cartilage. The secondary ossification center at this stage is just beginning to form with hypertrophic cells seen. **aiii** The secondary ossification center has formed but is still relatively far from the articular cartilage. The articular and epiphyseal cartilages still merge. **aiv** Most of the epiphyseal cartilage has been converted to secondary ossification center bone. Some still remains. The undersurface of the articular cartilage appears to be continuous over a short distance with the endochondral sequence at the periphery of the enlarged secondary ossification center. The latter region can be referred to as the mini-plate at this stage. **av** The articular cartilage at skeletal maturity has its lowermost zone calcified separating it from the subchondral bone of the mature epiphyseal region. The tidemark (*arrow*) separates the radial zone of the articular cartilage from the calcified zone of the cartilage. **avi** Higher power view of the articular cartilage at skeletal maturity. **b** Tritiated proline autoradiograph shows nutritive pathway of immature articular cartilage. The proline (an indicator of collagen synthesis) was dropped onto the surface of the rabbit distal femur cartilage at open operation. Uptake (*black dots*) 2 h post-injection is concentrated over the articular chondrocytes but much label is seen in matrix. Note that osteoblasts of underlying bone have also taken up label and synthesized collagen with dense label indicative of new osteoid on subchondral bone surfaces (*arrows*). The proline is incorporated into newly synthesized collagen. At skeletal maturity the label does not pass the tidemark indicating no nutrition of subchondral bone from synovial fluid after skeletal maturity

concentration of type 1 collagen such that it will invariably stain green with Safranin O, fast green owing to the relatively diminished amount of proteoglycan. The zone beneath this is called the second or transitional zone referring to the orientation of the collagen fibers as they pass from the superficial tangential zone where they are virtually parallel to the surface to the third or radial zone where they run perpendicular to the surface of the articular cartilage. Between the radial zone and the fourth or calcified zone is a thin dense staining line referred to as the tidemark [227]. The chondrocytes remaining within the calcified layer are viable based on autoradiographic studies although their activity level is extremely low and perhaps non-existent. Below the calcified zone of articular cartilage lies the subchondral bone plate. This is composed of lamellar bone and is much more dense than the marrow trabeculae of the mature epiphysis. Polarizing microscopy studies have helped to define the general orientation of the collagen fibrils of articular cartilage [228, 229]. Benninghoff (1925) described their orientation as a series of arcades with the fibers of the radial zone perpendicular to the surface, anchored at the base, oblique in the transitional zone, and often parallel to the surface in the tangential zone [228]. Subsequent high power studies at the ultrastructural level failed to reveal this degree of collagen fibrillar orientation but more recent studies have confirmed their general accuracy. The fibrils, however, do not form continuous sheaths such as can be seen in the outer fibrous layer of the periosteum. As shown at the ultrastructural level, the fibrils are short and discontinuous but their cumulative orientation is consistent with the arcade pattern.

1.10.3 Nutrition of Articular Cartilage

The articular cartilage is always avascular throughout the entire period of its development and in adult life. In the human and in the other relatively large species in which cartilage canals form they are never present within the articular cartilage regions. They are not seen in random or serial histologic sections or by angiographic studies. Articular cartilage thus receives its nutrition by diffusion from the synovial fluid at all ages. In the time period prior to skeletal maturity the cartilage of the lowermost part of the articular cartilage and the outermost part of the epiphyseal cartilage forms a mini-plate which undergoes the endochondral sequence. This mini-plate or physis of the secondary ossification center as we prefer to call it allows for outward growth of the articular and epiphyseal cartilage and for enlargement of the secondary ossification center. Labeling studies in the immature animal clearly demonstrate that articular cartilage chondrocytes and chondrocytes of this endochondral sequence including bone and marrow cells at the outermost reaches of the secondary ossification center can receive nutrition by diffusion from the articular surface (Fig. 1.17b). The bone and marrow of the secondary center also receive nutrition from the epiphyseal blood supply to that region [230]. McKibbin and associates have also shown that in the immature rabbit, fluid (and by inference nutrition) from the epiphyseal secondary ossification center blood supply can pass freely into joint cartilage [231]. In the skeletally mature adult, however, transfer from bone to articular cartilage could not be demonstrated across the lowermost calcified cartilage layer [231]. At skeletal maturity the inner layer of the articular cartilage calcifies and remains calcified through life as noted above. At this stage, synovial nutrients cannot pass through the calcified zone into underlying bone, and there is no vascular flow and thus no possibility of nutrition passing from epiphyseal bone through the calcified zone of articular cartilage to the upper three zones of cartilage. In the adult, articular cartilage receives nutrition only by diffusion from the synovial fluid and the subchondral or epiphyseal bone receives nutrition only from the blood supply to the bone.

1.10.4 Bone and Articular Cartilage Formation in Metacarpals, Metatarsals, and Phalanges Where Only One End Has a Physis

In several vertebrates including mouse, rat, rabbit, and human, the metacarpal, metatarsal, and phalangeal bones develop with only one end of each bone having a physis. This physis is proximal in the first metacarpal and metatarsal, distal in all other metacarpals and metatarsals, and proximal in all phalanges [232]. Development of the cartilage model in the embryo begins in normal fashion with the primary center of ossification forming with chondrocyte hypertrophy in the central shaft region. As development proceeds toward either end, that end where a physis will form develops in the regular way. A physis forms, the epiphyseal cartilage is present, and at the appropriate time a secondary ossification center forms. At the opposite end, the developing marrow continues to form progressing toward the articular cartilage. At the undersurface of the developing articular cartilage some additional cartilage persists with evidence of a tendency to form some hypertrophic chondrocytes but no structural physis. No secondary ossification center forms at this end. The articular and adjacent cartilage helps to shape the joint surface and widen the end appropriately but virtually all growth in length appears to occur at the physeal end. At skeletal maturity the articular cartilage at each end appears the same.

1.11 Summary of Coordinated Contributions of Cell and Tissue Regions to Bone Growth and Shaping

Considerable coordinated contributions of cell and tissue regions are needed to allow a bone to grow from the fetal period to skeletal maturity while retaining its shape and proportionality. The epiphyses are responsible for transverse and spherical growth of the ends of the bone, the shaping of the articular surfaces, and the longitudinal growth of the metaphyses and diaphysis (the latter via the physes or growth plates). Epiphyseal growth also includes a small amount of longitudinal growth at the undersurface of the articular cartilage. The growth plate is uniquely structured to allow for longitudinal bone growth via chondrocyte proliferation, matrix synthesis, and hypertrophy, replenishing itself through the reserve/germial zone and being replaced by bone at the physeal–metaphyseal junction. This allows the length of the entire bone to increase, keeping the growth plate the same thickness while the physis at either end is displaced progressively away from the center of the bone (and from each other). Increase in the transverse diameter of the physis is achieved by (i) interstitial growth in the resting/germinal cell layer setting up new columns of chondrocytes for the physis and (ii) by appositional growth from the region of loosely packed cells (perichondrium) of the groove.

The diaphyseal cortex is widened by additional bone synthesis from the inner cambial layer of the periosteum. The metaphysis and its thinner cortex are widened by bone from physeal growth just beyond it and by apposition of periosteal bone on its outer surface (where physeal and metaphyseal widths are essentially the same) or by bone from physeal growth just beyond it, by apposition of intramembranous (endosteal) bone on its inner surface with shaping by outer surface resportion (where funnelization narrows the metaphysis in relation to physeal width). The marrow cavity and inner cortices increase their relative widths by osteoclastic resportion. These mechanisms are illustrated in Fig. 1.17.

1.12 Models and Patterns of Limb and Bone Development

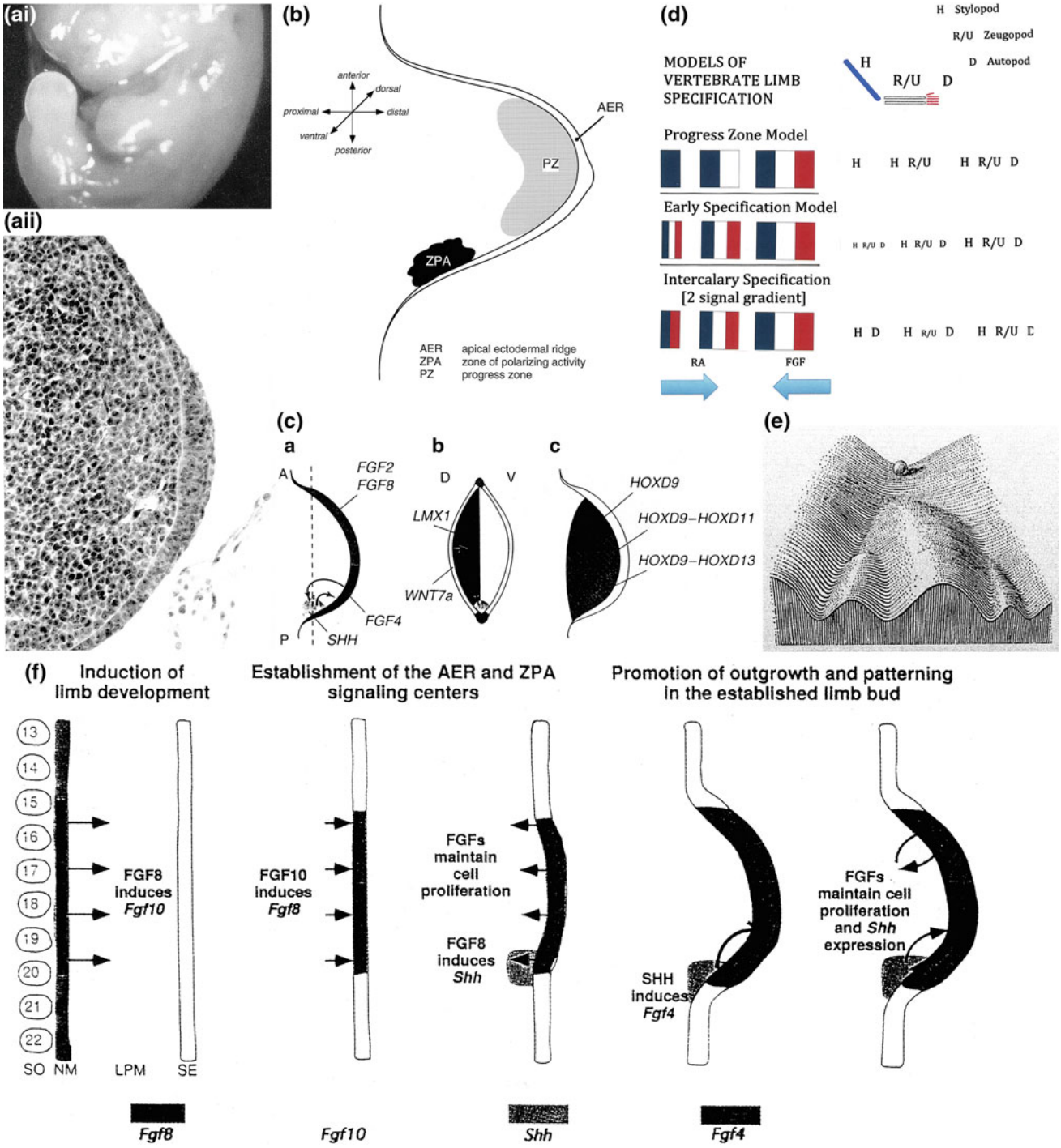
The limb bud in the human forms as a cellular outpouching from the body wall during week 4 of gestation and by week 8 the buds have differentiated and expanded to contain all the mature limb skeletal structures as cartilage models including the digits as well as muscle, innervation, and vasculature. The limb bud is initially composed of cells within the lateral plate mesoderm located in specific positions in the side of the embryo. The upper extremity limb bud appears on day 27 and the lower extremity on day 28. Once the limb bud forms (Fig. 1.18a) there are three axes along which differentiation occurs. Limb bud cells are initially undifferentiated but with development along the three axes asymmetric structures form (Fig. 1.18a–c). These involve (i) the proximal–distal P/D longitudinal axis with those regions closer to the shoulder and hip developing in advance of those more distal; (ii) the antero-posterior axis A/P which defines 1st digit side to 5th digit side structures; and (iii) the dorso-ventral D/V axis which defines the differentiation of extensor compartment from flexor compartment structures. The apical ectodermal ridge (AER) at the distal tip of the limb bud directs proximo-distal growth, the zone of polarizing activity (ZPA), a small region of mesenchyme at the posterior margin, directs antero-posterior patterning, and the dorsal non-ridge ectoderm directs dorso-ventral growth. Another unique and essential feature of development is left/right specification which leads to tissue-specific laterality where the gene Nodal plays a major role.

The proximal, middle, and distal parts of each limb develop in sequential fashion, proximal to distal, and are referred to in the embyologic developmental sequence as follows: *stylopod*-most proximal region (arm-humerus and thigh-femur, one bone), *zeugopod*-middle region of limb (forearm-radius, ulna and leg-tibia, fibula, 1 bones), and *autopod*-most distal region (carpals and hand and ankle and foot, variable number up to 5 digits) (Fig. 1.18d).

A series of classical experiments began to outline the principles of limb development before molecular identification was possible. Surgical extirpation experiments on the chick embryo limb bud showed that removal of the apical ectodermal ridge (AER) results in failure of formation of distal structures [233]. Also, the removal of the AER at different stages of wing development causes truncations progressively more distally restricted, the later the operation is performed. For example when the AER was removed early, zeugopod and autopod were absent but when it was removed later only autopod was absent showing clearly that AER was essential for skeletal development.

1.12.1 Epigenesis, Epigenetics, and Development

Development of a fully formed individual from a fertilized egg (zygote) has long fascinated the biologic community. Extensive study in the 1800s increasingly discounted the concept of preformationism and recognized the sequential development of morphological complexity, epipgenesis, as the primary series of events (see also Sect. 1.3.1). In the first half of the twentieth century, before the recognition and description of DNA and the whole array of genes and molecules, developmental biologists developed cohesive theories


(ai)
(aii)
(b)
anterior
dorsal
proximal
distal
ventral
posterior
AER
PZ
ZPA
AER apical ectodermal ridge
ZPA zone of polarizing activity
PZ progress zone
(d)
MODELS OF VERTEBRATE LIMB SPECIFICATION
H Stylopod
R/U Zeugopod
D Autopod
Progress Zone Model
Early Specification Model
Intercalary Specification [2 signal gradient]
RA
FGF
(c)
a
A
P
FGF2
FGF8
FGF4
SHH
b
D
V
LMX1
WNT7a
c
HOXD9
HOXD9–HOXD11
HOXD9–HOXD13
(e)
(f)
Induction of limb development
Establishment of the AER and ZPA signaling centers
Promotion of outgrowth and patterning in the established limb bud
13
14
15
16
17
18
19
20
21
22
SO NM
LPM
SE
FGF8 induces Fgf10
FGF10 induces Fgf8
FGFs maintain cell proliferation
FGF8 induces Shh
SHH induces Fgf4
FGFs maintain cell proliferation and Shh expression
Fgf8
Fgf10
Shh
Fgf4

to explain developmental phenomena. A leading biologist of this era was CH Waddington who defined the term ***epigenetics*** and studied its role in developmental biology. The term was more specific than in the 1800s when the concept of epigenesis essentially referred to embryological differentiation and growth. A prominent theory of development in the 1800s was referred to as recapitulation wherein the embryonic development of an individual was considered to pass through each of the various developmental stages of lesser species as it reached its final stage of maturation. This included even adult stages in Meckel's version but only embryonic stages in von Baer's. This theory was often encapsulated by the phrase "ontogeny recapitulates phylogeny". This portion of biologic history has been well summarized by Russell in "Form and Function" [40] and more recently by Gould in "Ontogeny and Phylogeny" [234]. Waddington defined epigenetics as the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being [235–237]. He linked epigenesis to genetics (both obviously necessary) to establish epigenetics as a developmental principle and discipline. In one of his earliest papers in 1942 he developed the concepts of canalization of development and the inheritance of acquired characters [238] and then in 1957, produced a description (and illustration) of the *epigenetic landscape* [236, 239] (Fig. 1.18e) which remains highly instructive. Waddington's epigenetic landscape highlights both the limits of cell developmental variability but also differing outcomes possible based on pathways (canals) traveled in response to (sometimes subtle) environmental stimuli. The diagram of the epigenetic landscape with its branching hills and valleys shows how an undifferentiated cell (at top of the illustration) can take any of several permitted trajectories (differentiation patterns) as it traverses the landscape leading to different outcomes or cell fates [236] (Fig. 1.18e). The differentiation pathways are induced by environmental, not genetic, differences. This approach also explains how acquired characters can be inherited. Waddington refers to this canalization as a buffering of the genotype, a not-too radical change since it is constrained at any point in one of the two directions. Development is canalized in the naturally selected animal especially where environment is favorable. Once a favorable developmental response to an environmental stimulus is canalized, it tends to become repetitive by the internal mechanism of a genetic factor. The same considerations which render the canalization advantageous will favor the genetic stimulus over the environmental one. Siegel and Bergman have applied consideration of how transcriptional regulators constrain the genetic system to produce canalization [240].

Current definition and status of epigenesis. With the onset of the genetic/molecular era, epigenetics has itself evolved into a much more clearly defined discipline. Epigenetics has

◀ **Fig. 1.18** Early limb bud characteristics are outlined. **ai** Rabbit embryo with head at top, upper limb bud (*center*), and lower limb bud (*at left*). **aii** Histologic section of a limb bud of a rabbit in which the mesenchymal cells are uniform in appearance and densely packed. The apical ectodermal ridge is shown at *right*. **b** The developing axes and signaling regions of the early limb bud are illustrated. The zone of polarizing activity and the progress zone cannot be differentiated by light microscopy but require immunocytochemistry and in situ hybridization demonstration of specific molecules concentrated there. **c** Main molecular signaling components of regions of limb bud are outlined. In (*a*) *A* anterior and *P* posterior. In (*b*) *D* dorsal and *V* ventral. (Reprinted with permission from Cohn and Tickle, Limbs: a model for pattern formation within the vertebrate body plan. Trends Genet. 1996; 12:253–257. Copyright 1996 Elsevier). **d** Three models to explain and help investigate vertebrate embryonic limb development are shown. In these models development proceeds from early (*at left*) to later stages (*at right*). (i) The Progress Zone Model (or Progressive Specification Model) defines proximal-to-distal limb formation or patterning as occurring sequentially, beginning (in the upper extremity) with proximal shoulder/humerus (*H*) morphogenesis as represented by the blue box. Once this is established, formation of the next more distal region of the foream (radius/ulna, *R*/*U*; white box.) is allowed. This region then induces or permits formation of the most distal region of wrist, metacarpals, and digits (*D* digits; *red box*) leading to the complete blue-white-red sequence. (ii) The Early Specification Model evolved a few decades later to account for experimental observations not completely consistent with the Progress Zone Model. In this model all regional position values are specified very early with the entire limb (*blue–white–red*) outlined and then enlarging and further differentiating with time. Thus, the *blue–white–red* segments are represented by progressively enlarging boxes. (iii) The Intercalary Specification Model defines two molecular gradients working at differing regions of the early limb bud. Retinoic acid (*RA*) in the developing trunk helps establish the limb field proximally (*blue*) while fibroblast growth factor (*FGF*) defines development from more distal positioning (*red*). *FGF* induces formation of the apical ectodermal ridge (AER) at the advancing tip of the limb bud. An intermediate region (*white*) is positioned or intercalated between the two and enlarges/further differentiates with time leading in this way to the full *blue–white–red* pattern. At upper right, in the forming upper limb: the proximal region is depicted by *H* (*blue*, humerus) (corresponding in the lower extremity to the femur); the next region by R/U (white; radius and ulna) (corresponding in the lower extremity to the tibia and fibula); and the most distal region by D (*red* wrist, metacarpals, and phalanges of the fingers) (corresponding in the lower extremity to the ankle, metatarsals, and phalanges of the toes). In embryologic literature, the proximal region of a developing limb is referred to as the stylopod, the middle region as the zeugopod, and the distal region as the autopod. To the *right* of each model the descriptive letters are arranged to help express the developmental sequences. **e** Waddington's epigenetic landscape is illustrated. He used this to help explain the process of cellular decision-making during development. The cell is represented by the ball at the *top* of the illustration. As it rolls downwards, the cell is directed or randomly takes one or other of the pathways in its course which then further defines its functional development. All events for a cell or a group of cells are not rigidly pre-determined but, as the landscape illustration/concept indicates, there is a causal interaction between the cell (the cell's genes) and its products or between genes and their spatial environment which then brings the phenotype into being. (Reprinted with permission from Goldberg et al. Epigenetics: A landscape takes shape. Cell. 2007;128:635–638. Copyright 2007 Elsevier). **f** Inter-relationship of various fibroblast growth factors with the apical ectodermal ridge (*AER*) and other factors such as sonic hedgehog (*shh*) in establishing early limb bud differentiation. The sequence of images shows the major roles played by *FGF* 8, *FGF* 10, and *FGF* 4, as well as Shh in early limb differentiation

evolved into a molecular field of study but still in reference to Waddington's concept of the "epigenetic landscape". Even though virtually all cells in a multicellular organism share an identical genotype, development generates a diversity of cell types with disparate yet stable profiles of gene expression and distinct cellular functions [237]. This cellular differentiation is an epigenetic phenomenon largely governed by changes in the epigenetic landscape rather than by alterations in genetic inheritance. Epigenetics may be defined as the study of any potentially stable and ideally heritable change in gene expression or cellular phenotype that occurs without changes in Watson–Crick base-pairing of DNA [236]. Other brief descriptive phrases of epigenetics as reviewed by Shi include the concept of heritable changes not involving genetic alterations or changes in phenotype that are heritable but do not involve DNA mutation [241]. At a molecular level epigenetics is the sum of alterations of the chromatin template that establish and propagate different patterns of gene expression (transcriptor) and silencing from the same genome. Another definition of epigenetics defines it as all meiotically and mitotically heritable changes in gene expression that are not coded in the DNA sequence itself.

Epigenetic research focuses on the study of modifications of DNA and histone proteins and how these modifications influence overall chromatin structure. Chromatin, the complex of DNA and its intimately associated histore proteins, plays the central role in shaping the cell's epigenetic landscape. The modifications tend to a heritable silencing of genes without a change in their coding sequence.

The epigenetic changes or alterations of the chromatic template (DNA and histone proteins) are brought about by three mechanisms: DNA methylation, covalent and noncovalent modifications to histone proteins, and production of noncoding RNAs to silence genes and DNA sequences [236, 241–243]. These pathways interact with one another. *(i) DNA methylation.* DNA methylation is the best-characterized chemical modification of chromatin. Nearly all DNA methylation occurs on cytosine residues of CpG dinucleotides by a number of DNA methyltransferases. *(ii) Covalent and noncovalent mechanisms of chromatin variation.* Covalent histone modifications are now connected to epigenetic phenomena. Modifications by acetylation and phosphorylation can directly alter the physical properties of the chromatin fiber. These are post-translational modifications of histones of conserved lysine residues at the amino-terminal ends. Other modifications occur by methylation, ubiquitination, and proline isomerization. Noncovalent mechanisms such as chromatin remodeling and incorporation of histone variants also occur. *(iii) RNA silencing*. RNA in the form of antisense transcripts, noncoding RNAs, or RNA interference (RNAi) can also lead to mitotically heritable transcriptional silencing by forming heterochromatin. The noncoding RNA, in particular silence both genes and repetitive DNA sequence and the long-term silencing effects, can be inherited through cell division.

1.12.2 Signaling Regions Which Affect the Patterns of Bone Development

Hox genes in the intermediate mesoderm specify where the limbs grow by initiating limb bud formation. Limb buds form from the lateral plate mesoderm. Three major signaling regions have been identified in developing limbs which control patterning and morphogenesis [244] (Fig. 1.18b). (i) A continuous ridge of elevated epithelial cells called the apical ectodermal ridge (AER) forms running anterior to posterior along the distal outer tip and distal inner borders of each developing limb bud. At the tip of the limb bud this ridge is markedly thickened due to an increased number of closely packed epithelial cells induced by the underlying mesenchyme. This structure stimulates growth and differentiation of the immediately proximal mesenchymal limb bud cells by inductive means. It outlines limb development along the proximal/distal axis. Ridge formation depends on signals from the mesenchyme but, once established, there are reciprocal ridge–mesenchyme (or epithelial/mesenchymal) interactions as development proceeds. Surgical removal of the ridge in experimental investigations leads to decreased cell proliferation in the underlying mesenchyme and proximal–distal growth alteration such that the more proximal humeral and femoral segments appear normal (since they had already been patterned) while the more distal segments are missing. (ii) The AER mediates growth at the distal tip of the limb bud immediately adjacent to it from a zone of undifferentiated cells called the progress zone (PZ). As development proceeds proximal to distal damage to or removal of the AER immediately halts development. Early removal leads to proximal truncations and later removal leads to more distal truncations. The types of structures formed however are governed by the mesenchymal cells themselves. (iii) Development along the antero-posterior axis is mediated from an area in the posterior mesenchyme referred to as the zone of polarizing activity (ZPA) which is not distinctive histologically but was defined on the basis of chick embryo transplantation experiments in which damage to the posterior caudal area induced changes in wing digit development. (iv) Development along the dorso-ventral axis is mediated by dorsal non-ridge ectoderm. Each of the controlling regions AER, PZ, ZPA and dorsal non-ridge ectoderm appear to be interdependent. The AER and the ZPA were defined initially by transplant experiments but subsequently by molecular localization. The main molecular signaling components of regions of the limb bud are shown in Fig. 1.18b.

1.12.3 Models of Tissue Patterning

Johnson and Tabin have reviewed the mechanisms of 3-dimensional pattern formation of organisms [245]. The general features of the body are initially produced along the rostral–caudal axis and during subsequent development more specific regional differentiation occurs in semi-autonomous fashion in areas referred to as secondary fields. Pattern formation in secondary fields such as a developing limb then occurs in four basic stages: (1) cells that make up the field are defined; (2) specific signaling centers are established within the field to provide positional information; (3) the positional information is recorded on a cell-by-cell basis; (4) cells differentiate in response to additional cues according to the encoded positional information.

Several theories of pattern formation have been devised over several decades with sophisticated systems defined well before gene and molecular information was available such as that of Waddington. These are increasingly amenable to experimental verification by gene and molecular studies. A monograph by Held [246], "Models for Embryonic Periodicity", summarizes the many theories of pattern formation into three conceptual classes: position dependent, rearrangement, and cell lineage. The concept of pattern formation is crucial to understanding both normal skeletal development and abnormal development in a wide array of disorders. Development proceeds from the limb bud stage, in which histological sections show only a uniform mass of undifferentiated mesenchymal cells, to full limb development by a combination of mechanisms of differentiation wherein one cell type generates many different types of cells and structures. Mathematical models have been generated to help understand patterning mechanisms. These can be reduced to the three classes referred to above based on commitment of embryonic cells to different pathways of development long before they show any tissue differentiation. The cells are described as determined for different fates and possessing distinct states of determination. This commitment has allowed them to be determined for synthesizing different tissues and programmed in regard to their position in the limb. In the words of Held, "given the notion of states, the problem of pattern formation can be reduced to simple mathematical terms." Although the "causal relationships define distinct classes of mechanisms …. actual developmental pathways typically employ multiple strategies."

Many of these models are amenable to investigation by transplanting cells from one position to another. If a transplanted cell changes its fate by adopting a fate appropriate for its new position, then its position was causing its state. If the cell moves back to its original position following transplantation, then its state was causing its position. If the cell changes neither fate nor moves back, then the third type of mechanism would be indicated. When 'p' is used to designate the position of a cell and 's' is its state of determination or differentiation, then any pattern can be represented as a set of ordered pairs (p, s). The general problem thus becomes: "what causes the correlation of particular values of p and s?" Whenever two entities are correlated in nature, either one causes the other or both are caused by a third force. For p and s, there are three classes of possibilities: (1) p produces s: The position of a cell causes it to adopt a particular state (position-dependent class); (2) s produces p: The state of a cell causes it to adopt a particular position (rearrangement class); and (3) X produces p and s. Some third agent (X) causes the correlation of positions and states. An example of X is cell lineage since a mother cell can divide directionally (causing the p of each daughter) and bestow instructions (s) asymmetrically.

Held further defines the three classes of pattern formation models with additional subclasses. A. The position-dependent class (p producing s) involves (i) the positional information subclass as determined by gradient models, polar coordinate models, or the progress zone model; (ii) the pre-pattern subclass, for which there are physical force models, reaction–diffusion models, and induction models; (iii) the determination wave subclass, for which there are chemical wave models (Belousov–Zhabotinsky reaction), sequential induction model, clock and wave-front model, and inhibitory field and competence wave models; and (iv) the Darwinian subclass with cell death and state-change models. B. The second class is the rearrangement class (s producing p) with adhesion, repulsion, interdigitation, and chemotaxis models. C. The final class is a cell-lineage class (x produces p, s) with quantal mitosis, stem cell, and cortical inheritance models.

In summary, cell differentiation to form specific structural patterns occurs either because a cell's position causes its state, its state causes its position, or both are caused by a third agent. In the position-dependent class, the position of each cell relative to field boundaries or neighboring cells-dictates its state of differentiation. In the rearrangement class, each cell adopts a state, perhaps randomly; the states then cause cells to move until they reach particular locations. In the cell-lineage class, the cells divide asymmetrically according to rigid pedigree rules placing each daughter into a definite position and assigning it a particular state. The various models and categories and their distinguishing features are summarized in Table 1.7.

1.12.4 Positional Information Mechanisms

Positional information models postulate a position-dependent assignment of differentiated states whereby cells are informed of their positions and this

information causes them to select particular states according to determined rules (Fig. 1.18d, f). Wolpert and colleagues have indicated that cells acquire a positional value with respect to boundaries and then interpret this in terms of a program determined by their genes and developmental history [247–250]. Cell-to-cell interactions can then specify position. Positioned fields are small, being <0.5 mm long with the times needed to specify position on the order of hours. The various models differ only in how they specify positional information. The mechanical gradient model is most common in this regard being mediated by long-range diffusible molecular signals. This has come to be referred to as the progress zone model in which the cells at a particular region of the limb bud acquire positional information via temporal information in which they can measure time and switch off their specific function when they exit a zone. Each cell records the concentration of a particular chemical which has an origin or source and a terminal point or sink. The polar coordinate model is also one defining positional information and assumes that cells assess their position by observing coordinates of their immediate neighbors, presumably by direct cell surface contact [250]. In this model, the position of limb cells is specified by one coordinate corresponding to the proximal–distal axis of the limb and another corresponding to position on one of a concentric series of circles at different proximal-distal levels. The molecular basis of this system is beginning to be outlined as genes that specify the circumferential coordinate have been found in Drosophila embryo with different genes expressed in varying local segments [250]. Other genes are expressed at varying proximal-distal regions.

Development based on positional information. Progress zone model. Polar coordinate model. Early specification model. The concept of positional information has been used to explain proximal-to-distal limb development. Each of the undifferentiated mesenchymal cells in the limb bud just proximal to the apicol ectodermal ridge at the tip of each limb bud in what is referred to as the progress zone is said to have positional information recognizing both where it is and the length of time it has been in that region. The proximal (shoulder–arm–humerus) area differentiates first under the influence of the AER. As cell proliferation and limb growth occur that region is relatively displaced from the AER at the tip and comes to rest out of the diffusion zone where it can be influenced by the AER. The cells in the progress zone then differentiate to the next distal region (elbow–forearm–radius/ulna) after which the most distal region develops (wrist–hand–metacarpals–phalanges). This form of development defined by Summerbell and Wolpert and associates has been referred to as the progress zone model. French et al. further refined this positional information concept of limb pattern development to also include specification in terms of polar coordinates in two dimensions. They proposed that cells within the progress zone region would develop according to two simple rules: The shortest intercalation rule and the complete circle rule. If regions of the developing embryo are excised in relation to these planes/segments, repair serves only to fill in the gaps with tissue resembling that removed since the borders persisting provide the positional information (directing the repair cells to only replicate the missing regions).

Early specification model. Continuing studies of limb development seemed more consistent to Sun et al. [251] and Dudley et al. [252] with early specification of each of the three limb regions (proximal, middle, distal) as distinct domains with subsequent development involving expansion of these progenitor populations before differentiation. The positional models are illustrated in Fig. 1.18d, f. These two revisionary concepts have been well discussed by Duboule [253] and Tabin and Wolpert [254].

1.12.5 Pre-pattern Mechanisms

Pre-pattern mechanisms define cell differentiation patterns on the basis of mechanical or chemical signals within cell layers. Identical signals will thus induce identical structures. Several models have also been defined within this subclass of developmental mechanisms. Physical force models postulate that the physical properties of cells and matrices can produce local deformations in response to internal or external forces and these distortions could promote the development of structure. A more accepted model today is the reaction–diffusion model defined by Alan Turing based on pattern differentiation between chemicals [255]. Chemically reactive molecules which diffuse at different rates cause the concentration of their product to peak at wavelength intervals which induce periodic or segmented structures. Many of these reaction-diffusion models are somewhat indeterminate in that the final configuration of the pattern cannot be exactly predicted from starting positions unlike positional information which are strictly deterministic by which is meant they yield identical patterns from case to case. Such patterns are defined as epigenetic in that they are not invariably the same but relate to a cascade of formative principles by which each region is specifically dependent on that which preceded it. Even the most subtle difference therefore can lead the developmental pattern into slightly different areas.

1.12.5.1 Turing. The Chemical Basis of Morphogenesis

Turing's classical article in 1952 defined the concept of the chemical basis of morphogenesis based on principles of theoretical biology and applied mathematics [255]. He suggested that "a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is

Table 1.7 Models of tissue patterning mechanisms

Model or category	Distinguishing features
A. Position-dependent ($p \rightarrow s$) class	The position of each cell (relative to field boundaries or neighboring cells) dictates its state of differentiation
I. Positional information subclass	Cells know where they are via coordinates which they 'interpret' as particular states of differentiation. The coordinate systems allow the patterns to 'regulate'
• Gradient model	The coordinate system is established (independently of growth) to be a scalar variable with fixed boundary values
• Polar coordinate model	A 'Shortest Route Rule' or 'Smoothing Rule' fills in missing coordinates by intercalary growth
• Progress zone model	Coordinates are assigned temporally as cells exit a growth zone
II. Prepattern subclass	Cells assume particular states of determination due to mechanical or chemical signals within the cell layer or by induction from an adjacent cell layer
	Identical signals are used for identical elements
	Patterns do not regulate (unless ad hoc assumptions are added)
• Physical force models	Deformation arises at periodic intervals within a tissue layer, causing cells to adopt particular states of determination about a certain threshold of stress or strain
• Reaction-diffusion models	Chemicals which have different diffusion rates react, causing an initially uniform chemical distribution to peak at 'wavelength' intervals
	Above a certain threshold concentration, cells adopt a particular state of determination
• Induction model	Periodically arranged cells in one layer induce states of determination int he cells of an apposed layer
III. Determination wave subclass	States of determination are specified within a zone that traverses an array of cells
• Chemical wave models	Traveling (or standing) waves in the concentration of a diffusible molecule (or precipitate) arise through chemical reactions
• Sequential induction model	Each cell induces a neighboring cell to adopt a particular state
• Clock and wave front model	Cells oscillate between two states and cease oscillating when a wave front reaches them
• Inhibitory field and Competence wave model	Cells are not 'competent' to differentiate before a wave front reaches them
	Cells that can adopt a 'preferred' state do so and inhibit neighboring cells from doing so
IV. Darwinian subclass	Each cell adopts a state (perhaps randomly) and then examines the states of its neighbors; if it matches a neighbor, then it takes action to correct this 'error'
• Cell death models	Homotypic matches are eliminated by having one of the matched cells die
• State-change models	Homotypic matches are eliminated by having one of the matched cells change its state
B. Rearrangement ($s \rightarrow p$) class	Each cell adopts a state (perhaps randomly); the states then cause cells to move until they reach particular locations
• Adhesion models	The final location of a cell is determined by its ability to adhere to a target cell(s)
• Repulsion models	Each cell moves as far as possible away from cells of its own kind
• Interdigitation models	Stripes of unlike cells interdigitate
• Chemotaxis models	Dispersed cells aggregate by mutual attraction
C. Cell-lineage ($x \rightarrow p, s$) class	Cells divide asymmetrically (according to rigid pedigree rules), placing each daughter in a definite position and assigning it a particular state
• Quantal mitosis model	All cells undergo an asymmetric and polarized 'quanta' mitosis, which assigns left daughters one state and right daughters another
• Stem cell model	A cell cyclically changes its state as it divides, causing the states of its daughters to alternate in space as it oscillates in time
• Cortical inheritance model	A periodic pattern of molecules is created in the cortical layer of a cell, and each daughter differentiates according to the molecules it inherits

Derived from Held (Ref. [246])

adequate to account for the main phenomena of morphogenesis. Such a system, although it may originally be quite homogenous, may later develop a pattern or structure due to an instability of the homogenous equilibrium, which is triggered off by random disturbances. Such reaction–diffusion systems are considered in some detail in the case of an isolated ring of cells, a mathematically convenient, although biologically unusual system. The investigation is chiefly

concerned with the onset of instability. It is found that there are six essentially different forms which this may take." [255]. He outlined "a possible mechanism by which the genes of a zygote may determine the anatomical structure of the resulting organism" and considered that "certain well-known physical laws are sufficient to account for many of the facts."

He defined two forms of a mathematical model. In one the cells are idealized into geometrical points and in the other the matter of the organism is imagined as continuously distributed. With either of the models the "state of the system" is defined. A key feature is then the determination of the state from the state at a moment very shortly before. With either model the state consists of two parts, the mechanical and the chemical. The mechanical part of the state describes the positions, masses, velocities, and elastic properties of the cells and the forces between them. In the continuous form of the theory the same information is given in the form of the stress, velocity, density, and elasticity of matter. The chemical part of the state (cell form) is given as the chemical composition of each separate cell including the diffusability of each substance between two adjacent cells. In the continuous form the concentrations and diffusibilities of each substance need to be given at each point. The substances acting chemically are called morphogens (form producers). The chemical substances diffuse through the tissues of a given geometrical form and react within it. Diffusion follows the ordinary laws of diffusion. Turing even models symmetry and left–right sideness. The pattern of morphogen concentrations was described in terms of "waves" and six types of possibilities arose.

Several decades later Turing's work is proving to be accurate and the principles he defined to be studied in relation to defining morphogenesis. Tompkins et al. showed that Turing's description that diffusion can interact with chemical reactions to generate up to six periodic spatiotemporal chemical structures remains for the most part accurate. They also demonstrated that reaction–diffusion processes lead to chemical differentiation which drives physical morphogenesis. Their work induced five of the six structures predicted by Turing along with a seventh structure which necessitated a modification of his theory to include heterogeneity [256].

Meinhardt has worked extensively studying the theoretical and applied aspects of morphogenesis. He established the concept that pattern formation is possible only if a self-enhancing reaction is coupled with an antagonistic process of longer range [257]. Adding this consideration allows Turing's principles to be further validated. He also shows how the morphogenetic theories are beginning to receive experimental validation in relation to functioning of *Wnt* molecules as well as *Nodal/Lefty2* interactions when autocatalytic activation and long-range inhibition reactions occur.

1.12.6 Determination Wave Mechanisms

From 1920 to 1954, the reigning paradigm in developmental biology was that of the determination wave mechanism in which a propagating signal or substance spread from an "organized center" to control the fate of cells in its domain. Subsequently, the pre-pattern (1954–1969) and positional information (1969-present) schools gained prominence. Many models of definition within this subclass were defined. The progress of morphogenesis sequentially and along varying axes led to the development of several wave mechanism theories. Among the theories used to support this mechanism were those of chemical waves. An example of this was the Belousov–Zhabotinsky reaction where the concentration of a chemical oscillates in time and space and produces patterns similar to those seen in structural organisms [258–261]. Intricate patterns can be defined by employing contact-mediated cellular communication instead of diffusible chemicals. The sequential induction model is an example where the notochord induces formation of the central nervous system. Variations on this theme include waves of developmental signals which induce adjacent groups of cells to oscillate between active and inhibited states. These biophysical mechanisms have not been applied extensively to skeletal development.

Even Darwinian models have been defined utilizing cell death and state-change models. The Darwinian concept implies that even within individual embryo selection among competing groups of cells leads to longevity of some and programmed cell death of others. There is currently great interest in the phenomenon of programmed cell death or apoptosis, which plays a major role in developmental states. A clear example of cell death in normal limb development relates to joint formation in which the interzone cells die after formation of the model of each developing bone to subsequently allow for joint cavitation. Some consider the death of terminal hypertrophic zone chondrocytes to represent another example of apoptosis in skeletal development. State-change models imply the ability of cells to react to changes in adjacent cells by subtle differentiation to help maintain or recreate their previous state.

1.12.6.1 Self-Organization in Cell Biology as a Formative Mechanism

The mechanisms forming structured objects on the basis of chemical and mechanical signals, as outlined in the previous two sections, have come to be known as examples of self-organization as a formative or morphological principle. Misteli has explained that two different mechanisms generate macromolecular structures: self-assembly and self-organization [262]. Self-assembly involves the physical association of molecules into an equilibrium structure; a set

of components assembles into a stable static structure that reaches a thermodynamic equilibrium. Self-organization involves the physical interaction of molecules in a steady-state structure; components assemble into a dynamic structure. Self-organization in cell biology is defined as the capacity of a macromolecular complex or organelle to determine its own structure based on the functional interaction of its components. The interactions of the molecular parts determine its architectural features. There are three requirements for self-organization of macroscopic cellular structures: the cellular structure must be dynamic, material must be continuously exchanged, and an overall stable configuration must be generated from the dynamic components. Misteli describes the self-organization involved with the cytoskeleton, the cell nucleus, and the Gogli complex.

Karsenti reviews the history of the self-organization principle in cell biology stressing its emergence from theoretical considerations, the chemical principles of the Belousov–Zhabhabotinsky reaction, and reaction-diffusion processes as defined in mathematical terms by Turing leading to steady-state spatial patterns [263]. Self-organization in physico-chemical systems came to be recognized as an explanation for subcellular and whole-cell morphogenesis.

1.12.7 Rearrangement Mechanisms

Rearrangement mechanisms refer to the concept of cell and tissue movements which characterize many early developmental states. Cell movement is particularly well defined in central nervous system development. A cell's state of determination or differentiation causes it to assume a specific position relative to other cells by propelling it in a particular direction. This developmental subclass makes use of the "self-assembly" concept, for example, in mediating the supra-cellular neuro-architecture where specific cell axons link only with specific neurons based on specific chemical reactions. Both adhesion and repulsion models have been used to account for cell movement within an embryonic region.

1.12.8 Cell Lineage Mechanisms

Cell Lineage Mechanisms were postulated for some time but have been almost completely supplanted by newer mechanisms. They implied that a cell's positions and states are assigned via strict pedigree rules with no involvement of intercellular communication. Cell lineage plays a major role in later tissue differentiation but little in embryonic morphogenetic patterning.

1.12.9 Overview of Developmental Biology

Early developmental biology was based on descriptive embryology and then on experimental embryology in which certain regions at certain stages were either removed from a developing embryo or transferred to atypical positions with development then followed carefully. Theoretical biology concepts evolved to explain the observed phenomena and serve as a point of reference for subsequent investigation. These approaches led to key concepts of developmental biology now being defined by gene and molecular mechanisms. One concept is that of induction, by which is meant the development of specific structure in a region based on the presence of an initiating group of cells. The initiating cells induce the latter region to differentiate along certain lines. The inducer is the tissue that produces the signal that changes the cellular behavior of the other tissue, the responder. Well-known examples of induction are cellular interations between sheets of epithelial cells (which can orignate from any germ layer) and mesenchymal cells (which originate from mesoderm and neural crest). The interactions are referred to as epithelial–mesenchymal interactions.

These interactions occur in two ways. Direct cell–cell contact allows cell membrane proteins on one surface to physically interact with receptor proteins on adjacent cell surfaces, referred to as juxtacrine interactions. A protein on one cell can bind to its receptor on another cell; a receptor on one cell can bind to its ligand on the extracellular matrix; or signal is transmitted from the cytoplasm of one cell through passages into the cytoplasm of an adjacent cell. In these instances the chemical does not diffuse from the producing cell. More commonly the cells are discrete and proteins synthesized by one cell diffuse over small distances in the intercellular fluid to induce changes in neighboring cells by a paracrine interaction. (Endocrine factors, hormones, exert their effects long distance via bloodstream transference.) Paracrine factors are thus defined as growth and differentiation factors and are grouped into four main families: fibroblast growth factor (FGF) family, hedgehog family, wingless (Wnt) family, and the transforming growth factor-beta (TGF-ß) superfamily. Other paracrine factors, not linked to other families, are epidermal growth factor and stem cell factors. With the recent increase of information concerning the molecules present within the developing systems and recognition of patterning genes, developmental studies have become much more specific. Gilbert has defined developmental biology as the science connecting genetics with anatomy to which we could easily add histology. In situ hybridization techniques and the generation of transgenic animals with specific molecules subtracted at the varying stages of development have allowed for more specific

analysis. Disorders of morphogenesis are now recognized on the basis of abnormalities within molecular families such as collagen or PAX genes. Increasingly however abnormal development was sought within more widely ranging developmental pathways. Examples might include series of signal-transduction pathways composed of ligands, receptors, enzymes, intracellular mediators, and transcription factors. That development is hierarchical is evident. What is unclear, however, is whether the pattern is totally deterministic which would allow understanding of development to be reduced to recognizing which molecules at each stage of development perform which activities such as synthesizing certain substances, acting as enzymes, regulating genes, etc. On the other hand, much of development is epigenetic in which only the early pre-patterns are rigidly determined after which each subsequent step is a combination of gene synthesis and automatic self-assembly based on the presence of certain molecules. These questions span the entire spectrum from gene to ultrastructure, genotype to phenotype, or linear DNA to 3-dimensional morphology. In the epigenetic approaches, there are no genes which directly specify the entire sequence of events but only those which give approximate direction. The rest of the formation is based on epigenetic or self-assembly mechanisms. It is thus the interactions among many genes that determine the outcome of any dynamic process. Many have suggested that the detailed structure of multicellular organisms occurs on the basis of many intermediate levels of interaction each with its own emergent properties such that the edifice is virtually entirely epigenetic. This idea was expressed by Driesch over a century ago in which he indicated that development started with a few ordered reactions but that each reaction created by interaction of new structures which then acted upon the original ones to provide new differences and so on. Opposed to this are the strictly deterministic approaches such as the homeobox gene synthesis patterns. The homeobox genes are ordered along their chromosomes and allow specific anatomic regions to appear. They not only have a spatial and regional preference, but also a temporal one.

As molecular information in relation to limb development continues to accumulate, it is increasingly found that many of the proposed models of limb development are not fully supported by the known gene activity. Tabin and Wolpert have reviewed two of the main positional information models outlining how proximo-distal axes form the progress zone model and the early specification model, and concluded that neither was completely satisfactory nor consistent with known facts [254]. They concluded that new frameworks of understanding could now be based "directly on the molecular data." They observe molecular domains along the proximo-distal axis and now refer to the progress zone as the undifferentiated zone with the proximal border of this region being the differentiation front.

1.13 Gene and Molecular Controls of Limb Development

Gene and molecular mechanisms associated specifically with the early stages of limb embryogenesis have been outlined [244, 264–279]. Specific genes and molecules controlling limb development and comprising the extracellular matrix are listed in Table 1.8. Four specific regions of the developing limb play major directing roles in morphogenesis. (See Fig. 1.18b, d, f, g). More recent comprehensive reviews are by Towers and Tickle [280] and Benazet and Zeller [281].

1.13.1 Limb Bud Outgrowth

Limb buds form from the proliferation of lateral plate mesoderm which is initiated by certain Wnt and FGF signals. In the upper extremity limb bud Wnt-2b and FGF-B induce FGF-10 in the lateral mesoderm with reciprocal ectoderm–mesoderm interactions. In the lower extremity bud Wnt-8c is exposed along with the two FGFs.

1.13.2 Apical Ectodermal Ridge

The apical ectodermal ridge (AER) is the thickened rim of epithelium present at the tip of each limb bud (Fig. 1.18a). The AER runs from anterior to posterior and forms the boundary between dorsal and ventral parts of the limb bud. It consists of pseudostratified elongated cells that are closely packed and linked by extensive gap junctions. AER maintains cell proliferation in the underlying mesenchyme progress zone and there are constant reciprocal interactions between ridge and mesenchymal tissues. The AER mediates proximo-distal (P/D) outgrowth of the limb bud, controls the deposition of undifferentiated cells just proximal to it in the progress zone, and outlines tissue formation from shoulder to digits and hip to digits. The boundary between dorsal and ventral parts of limb bud, FGF-8 is expressed throughout the AER early in limb development, while FGF-4 is detected later concentrated in the AER posteriorly. These are the two essential FGFs for AER functioning. FGF-4 is most prominently expressed in the AER and appears to play the major role in proximo-distal outgrowth and patterning.

1.13.3 Progress Zone

The progress zone is at the distal region of the limb bud where undifferentiated mesenchymal cells actively divide. The mesenchymal cells here are kept in a proliferating and undifferentiated state by the AER and act closely in relation

Table 1.8 Skeletal gene database

Gene	Protein	Cellular function	Disease
ADA	Adenosine deaminase	Involved in T cell and B cell immune function	Adenosine deaminase deficiency
ALPL	Alkaline phosphatase liver, bone, kidney type	Linked to the outer membrane, enzyme acts physiologically as a lipid-anchored phosphoethanolamine and pyridoxal 5′ phosphate ectophosphatase	Hypophosphatasia murine (Alp1-I-) seizures but normal skeletal development
ANXA5	Annexin A5; calcium- and phospholipid-binding protein, endonexin 2, placental protein 4, anchorin CII	Collagen receptor of chondrocytes predominantly expressed in chondrocytes of growth plate, downregulated in adult growth cartilage	
ARSE	Arylsulfatase E	Involved in bone and skeletal development	X-linked recessive chondrodysplasia punctata (brachytelephalangic type)
BMP1	Bone morphogenetic protein 1; also known as procollagen, C-proteinase	Induce formation of ectopic cartilage and bone in vivo	
BMP2	Bone morphogenetic protein 2, a member of transferring growth factor β superfamily	Induce formation of ectopic cartilage and bone in vivo	
BMP3	Bone morphogenetic protein 3, a member of transferring growth factor β superfamily	Induce formation of ectopic cartilage and bone in vivo	
BMP4	Bone morphogenetic protein 4	Involved in bone induction and tooth development	Fibrodysplasia ossificans progressiva
BMP5	Bone morphogenetic protein 5, a member of transferring growth factor β superfamily	Induce formation of ectopic cartilage and bone in vivo	Murine: mutations in short-car locus association with homozygous deletions of BMP5 coding regions result in viable and fertile short ear mice with specific skeletal defects
BMP6	Bone morphogenetic protein 6, a member of transferring growth factor β superfamily	Induce differentiation of osteoblast and chondroblast lineage cells from uncommitted mesenchymal precursors, BMP6 produced by osteoblasts is increased in the presence of estrogen and is thought to mediate the skeletal effects of estrogen	
BMP7	Bone morphogenetic protein 7, a member of transferring growth factor β superfamily osteogenic protein 1	Induce formation of ectopic cartilage and bone in vivo	
BMP8	Bone morphogenetic protein 8, osteogenic protein 2	Induce formation of ectopic cartilage and bone in vivo	
BMPR1A	Bone morphogenetic protein receptor, type 1A	Cell surface receptor with predicted serine/threonine kinase activity, may bind to ligands from the transforming growth factor β supergene family	
CA2	Carbonic anhydrase II	Involved in osteoclast function, bone remodeling and resorption	Osteopetrosis with renal tubular acidosis and cerebral calcification
CASR	Calcium-sensing receptor	Parathyroid hormone-sensitive involved in calcium homeostasis	Neonatal severe hyperparathyroidism
			Familial hypocalciuric hypercalcemia
			Autosomal dominant hypocalcemia
			Murine (Casr +*I*-) familial hypocalciuric hypercalcemia
			Murine (Casr +*I*-) neonatal severe hypercalcemia

(continued)

Table 1.8 (continued)

Gene	Protein	Cellular function	Disease
CBFA1	Core-binding factor α subunit 1	Osteoblast-specific transcription factor	Cleidocranial dysplasia
			Murine Cbfa +*I*-cleidocranial dysplasia
			Murine Cbfa +*I*- perinatal lethal with deficient ossification of skeleton
CBP1	Collagen-binding protein 1; collagen 1	Bind specifically to type I and type IV collagen and gelatin, may be involved as a chaperone in the biosynthetic pathway of collagen	
CBP2	Collagen-binding protein 2; collagen 2	Bind specifically to type I and type IV collagen and gelatin, may be involved as a chaperone in the biosynthetic pathway of collagen	
CD36	Type 1 collagen receptor, thrombospondin receptor; CD 36 antigen	Bind to collagen and thrombospondin involved in platelet collagen adhesion	Platelet glycoprotein IV deficiency
CD36L1	CD 36 antigen like 1; type 1 collagen receptor like 1; thrombospondin receptor like 1; scavenger receptor class B type 1 (SRB 1)	High density lipoprotein receptor	
CD36L2	CD 36 antigen like 2; type 2 collagen receptor like 1; thrombospondin receptor like 2	Lysosomal integral membrane protein II	
CDMP/GDF5	Cartilage-derived morphogenetic protein 1	Involved in skeletal morphogenesis, i.e., chondrocytic differentiation and growth of long bones	Greb chondrodysplasia
			Hunter–Thompson dysplasia
			Brachydactyly type C
			Murine brachypodism
CKTSF1B1	Cysteine knot superfamily 1; BMP antagonist 1; also known as gremlin	Block BMP signaling by binding to BMPs, preventing them from binding to their receptors	Murine: limb deformity mutation (ld) disrupts Shh/Fgf4 feedback loop. In mouse embryos mesenchymal expression of gremlin is lost in limb buds. Grafting gremlin expressing cells into ld mutant limb buds rescued Fgf4 expression and restored the Shh/Fgf4 feedback loop
COL1A1	Type I collagen α1 chain	Major collagen of skin, tendons, and bone	Osteogenesis imperfecta
			Type VIIA Ehlers–Danlos syndrome
			Osteoporosis
COL1A2	Type I collagen α2 chain	Major collagen of skin, tendons, and bone	Osteogenesis imperfecta
			Type VIIA Ehlers–Danlos syndrome
COL2A1	Type II collagen α1 chain	Collagen of cartilage and vitreous	Achondrogenesis type II
			Hypochondrogenesis
			Kniest dysplasia
			Spondyloepiphyseal dysplasia congenita.
			Wagner syndrome
			Spondyloepimetaphyseal dysplasia. Strudwick type and Namaqualand type spondyloepimetaphyseal dysplasia
			Osteoarthritis with mild chondrodystrophy
			Transgenic Col2a1-*I*-mice perinatal lethal with absent endochondral ossification

(continued)

Table 1.8 (continued)

Gene	Protein	Cellular function	Disease
COL3A1	Type III collagen α1 chain	Fetal collagen, expressed throughout embryogenesis essential for normal fibrillogenesis of collagen 1 in cardiovascular system and other organs	Ehlers–Danlos syndrome type III
			Ehlers–Danlos syndrome type IV
			Murine Col3a1-*I*- Ehlers–Danlos type IV
			Aortic aneurysm
COL4A1	Type IV collagen α1 chain	Collagen of basement membrane, associated with laminin, entactin, and heparan sulfate proteoglycans to form basement membranes that separate epithelium from connective tissue	
COL4A2	Type IV collagen α2 chain	Collagen of basement membrane, associated with laminin, entactin, and heparan sulfate proteoglycans to form basement membranes that separate epithelium from connective tissue	
COL4A3	Type IV collagen α3 chain	Associated with lamin, entactin, and heparan sulfate proteoglycans to form basement membrane separating epithelium from connective tissue	Autosomal recessive A1-port syndrome type I
			Murine knockout Col4a3 Al-port syndrome
			Induction of Goodpasture's syndrome
COL4A4	Type IV collagen α4 chain	Associated with lamin, entactin, and heparan sulfate proteoglycans to form basement membrane separating epithelium from connective tissue	Autosomal recessive A1-port syndrome type II
			Autosomal dominant benign familial hematuria-q37
COL4A5	Type IV collagen α5 chain	Collagen of basement membrane	X-linked recessive Al-port syndrome
			Canine X-linked hereditary nephropathy
COL4A6	Type IV collagen α6 chain	Collagen of basement membrane	X-linked Al-port syndrome with diffuse leiomyomatosis contiguous gene deletion syndrome
COL5A1	Type V collagen α1 chain	Minor collagen involved in regulation of fibrillogenesis of dermis rather than bone	Ehlers–Danlos syndrome type I
			Ehlers–Danlos syndrome type II
COL5A2	Type V collagen α2 chain	Minor collagen involved in regulation of type I and type II collagen fibrils, collagen of fetal membrane	Ehlers–Danlos syndrome type I
			Ehlers–Danlos syndrome type II
			Murine Col5a2-*I*-spinal deformities, skin and eye abnormalities
COL6A1	Type VI collagen α1 chain	Anchoring structural protein involved in maintaining the integrity of muscle fiber	Bethlem myopathy
			Murine Col 6a1-*I*-Bethlem myopathy
COL6A2	Type VI collagen α2 chain	Anchoring structural protein	Bethlem myopathy
COL6A3	Type VI collagen α3 chain	Acts as a cell-binding protein	Bethlem myopathy
COL7A1	Type VII collagen α1 chain	Main constituent to anchoring fibrils	Autosomal dominant dystrophic epidermolysis bullosa
			Autosomal recessive dystrophic epidermolysis bullosa
			Dystrophic epidermolysis bullosa Bart's syndrome type: transient bullous dermolysis of newborn
COL8A1	Type VIII collagen α1 chain	Endothelial cell collagen expressed in eye, skin, and calvarium major components of Descemet's membrane	

(continued)

Table 1.8 (continued)

Gene	Protein	Cellular function	Disease
COL8A2	Type VIII collagen α2 chain	Major component of Descemet's membrane	
COL9A2	Type IX collagen α2 chain	Cartilage-specific fibrillin-associated collagen	Multiple epiphyseal dysplasia type II intervertebral disk disease
COL9A3	Type IX collagen α3 chain	Fibrillin-associated collagen with interrupted triple helices expressed in cartilage	Multiple epiphyseal dysplasia multiple epiphyseal dysplasia with myopathy
COL10A1	Type X collagen α1 chain	Major collagen of cartilage	Schmid metaphyseal chondrodysplasia
COL11A1	Type XI collagen α1 chain	Major collagen of cartilage fibrillar collagen	Stickler syndrome
			Marshall syndrome
			Murine Col11a1-*I*-perinatal lethal with abnormalities in cartilage of limbs, ribs, mandible, & trachea
COL11A2	Type XI collagen α2 chain	Major collagen of cartilage fibrillar collagen	Otospondylomegaepiphyseal dysplasia (OSMED)
			Weissenbacher–Zweymuller syndrome
			Stickler syndrome without ocular anomaly
			Non-syndromic hearing loss
COL12A1	Type XII collagen α1 chain	Fibril-associated collagen with interrupted triple helices (FACIT)	
COL13A1	Type XIII collagen α1 chain	Short chain collagen with some features found in genes for fibrillar collagen and some unique features	
COL14A1	Type XIV collagen α1 chain	Fibril-associated collagen with interrupted triple helices (FACIT), extracellular matrix protein confined to dense and soft connective tissues associated with mature collagen fibrils	
COL15A1	Type XV collagen α1 chain	May be involved in the adherence of basement membrane to underlying connective tissue stroma	
COL16A1	Type XVI collagen α1 chain	Fibril-associated collagen with interrupted triple helices (FACIT), associated with type I and type II collagen fibrils and is involved in interaction of these fibrils with other matrix components	
COL17A1	Type XVII collagen α1 chain, bullous pemphigus antigen 2 (BPAG2 or BP 180)	Collagen found in stratified epithelium and maintains adhesion between epidermis and dermis	Generalized atrophic benign epidermolysis bullosa
			Nonlethal variant localisata of junctional epidermolysis bullosa
COL18A1	Type VIII collagen α1 chain, also contains endostatin	Extracellular matrix protein that has multiple triple helix domains and interruptions	
COL19A1	Type XIX collagen α1 chain	Fibril-associated collagen with interrupted triple helices, produces adhesion to fibrils and provides interaction with other matrix component, expressed in cartilage	

(continued)

Table 1.8 (continued)

Gene	Protein	Cellular function	Disease
COL1AR	Type I collagen, α1 receptor	Bind collagen	
COL4A3BP	Collagen type IV, α3 (Goodpasture antigen-binding protein)		
COL12A1L	Type XII collagen α1 like		
COLQ	Collagen-like tail subunit of end plate acetylcholinesterase	Anchor acetylcholinesterase to the underlying basal lamina, acetylcholinesterase-associated collagen	Congenital myasthenic syndrome with end plate acetylcholinesterase deficiency
COMP	Cartilage oligomeric matrix protein	Involved in calcium binding	Pseudoachondroplasia
			Multiple epiphyseal dysplasia (Fairbanks and Ribbing types)
CTSK	Cathepsin K	Expressed in osteoclasts involved in bone remodeling and resorption	Pycnodysostosis
			Knockout Cusk mice pycnodysostosis
DCN	Decorin	Small collagen-binding proteoglycan of the extracellular matrix affects the rate of fibril formation and binds to fibronectin and TGF-β when expressed ectopically, docorin suppresses tumor cell growth by activating the epidermal growth factor receptor	
DDR2	Discoidin domain receptor family member 2	Are tyrosine kinases activated by collagen	
DTDST/DTD	Diastrophic dysplasia sulfate transporter	Undersulfation of proteoglycan in cartilage matrix	Diastrophic dysplasia
			Achondrogenesis type IB
			Achondrogenesis type II
EBP	δ(8)–δ(7) sterol isomerase emopamil binding protein	Involved in cholesterol biosynthesis	X-linked dominant Conradi–Hünermann–Happle chondrodysplasia punctata
			Murine male tattered (Td) perinatal lethal
			Conradi–Hünermann–Happle syndrome
EOMES	Eomesodermin	Essential for mesoderm formation and trophoblast development	Murine targeted disruption of Eomes results in mice deficient in Eomes and arrest at the blastocyst stage
EXT1	Exostosin 1	Involved in alteration of synthesis and display of cell surface heparan sulfate glycosaminoglycan	Multiple exostoses type I
			Langer–Giedion micro-deletion syndrome
			Chondrosarcoma (loss of heterozygosity)
EXT2	Exostosin 2	Involved in regulation of bone growth	Multiple exostoses type II
			Chondrosarcoma (loss of heterozygosity)
EXT3	Gene not cloned yet		Multiple exostoses type III
FBN1	Fibrillin 1	Major constituent of extracellular microfibrils found in elastic and non-elastic connective tissue	Marfan syndrome
			Shprintzen–Goldberg craniosynostosis syndrome
FBN2	Fibrillin 2	Direct the assembly of elastic fibers during early embryogenesis	Congenital contractural arachnodactyly (Beal syndrome)

(continued)

Table 1.8 (continued)

Gene	Protein	Cellular function	Disease
FCN1	Ficolin 1	Containing collagen fibrinogen domain	
FCN2	Ficolin 2	Lactin-containing collagen/fibrinogen	
FCN3	Ficolin 3–Hakata antigen	Containing collagen/fibrinogen domain	
FGFR1	Fibroblast growth factor receptor 1	Involved in tyrosine kinase activation and signal transduction	Pfeiffer syndrome
FGFR2	Fibroblast growth factor receptor 2	Involved in tyrosine kinase activation and signal transduction	Pfeiffer syndrome
			Apert syndrome
			Crouzon syndrome
			Jackson–Weiss syndrome
			Beare–Stevenson cutis gyrata syndrome
			Saethre–Chotzen syndrome
FGFR3	Fibroblast growth factor receptor 3	Involved in tyrosine kinase activation and signal transduction, inhibits osteogenesis	Achondroplasia
			Murine Fgfr3-*I*-skeletal overgrowth
			Knock in murine Fgfr3 achondroplasia hypochondroplasia
			Thanatophoric dysplasia type I and type II
			Crouzon syndrome with acanthosis nigricans
			Muenke nonsyndromic coronal craniosynostosis
			Severe achondroplasia developmental delay, acanthosis nigricans syndrome
			Saethre–Chotzen syndrome
FN1	Fibronectin 1	Bind cell surfaces and collagen, fibrin, heparin DNA, and actin. Involved in cell adhesion, cell mtility, opsonization, wound healing, and maintenance of cell shape	Ehlers–Danlos type X may be associated with fibronectin deficiency
FMOD	Fibromodulin	Involvement in the assembly of extracellular matrix by virtue of ability to bind and to interact with type I and type II collagen fibrils	
FUCA1	α-L-fucosidase 1	Enzyme degrades fucosidase, the accumulation results in lysosomal storage	Fucosidosis (dysostosis multiplex)
GDF10	Growth differentiation factor 10, BMP 3b-precursor, bone inducing protein, member of transforming growth factor β superfamily	Induce enchondral bone formation	
GL3	Member of GLJ Knuppel family, a zinc finger transcription factor	Involved in vertebrate development of limbs and other tissues	Postaxial polydactyly type I1A
			Greig cephalopolysyndactyly
			Pallister–Hall syndrome
GM1/GLB1	βgalactosidase 1	Enzyme degrades mucopolysaccharides	GM1 gangliosidosis (dysostosis multiplex)
			Morquio type B syndrome (dysostosis multiplex)
GNAS1	Guanine nucleotide binding protein, α stimulating activity polypeptide 1	Involved in regulating activity of parathyroid hormone-sensitive adenylate cyclase	Pseudohypoparathyroidism
			McCune–Albright polyostotic fibrous dysplasia

(continued)

Table 1.8 (continued)

Gene	Protein	Cellular function	Disease
GNS	*N*-acetylglucosamine 6 sulfate sulfatase	Enzyme degrades heparan and keratan sulfate	Sanfilippo syndrome D or mucopolysaccharidosis type III (dysostosis multiplex)
GUSB	βglucuronidase	Enzyme degrades mucopolysaccharides	Sly syndrome or mucopolysaccharidosis type VII (dysostosis multiplex)
			Canine Gusb-*I*- Sly syndrome
HOXA1	Homeobox A1; member of a family of transcription factors	Determine embryonic cell fate	
HOXA2	Homeobox A2; member of a family of transcription factors	Determine embryonic cell fate	Murine Hoxa-*I*-embryonic mice show defective axonal path finding resulting in loss of cochlear nuclei and enlargement of lateral part of cerebellum
HOXA3	Homeobox A3; member of a family of transcription factors	Determine embryonic cell fate	Murine homozygous null Hoxa3-*I*- embryos show complete absence of thymus and alteration of hyoid cartilage. Complementation with hoxd3 protein restores thymus and corrects alteration of hyoid cartilage, suggesting that Hoxa3 and Hoxd3 can carry out identical biological functions
HOXA4	Homeobox A4; member of a family of transcription factors	Determine embryonic cell fate	
HOXA5	Homeobox A5; member of a family of transcription factors	Determine embryonic cell fate	
HOXA6	Homeobox A6; member of a family of transcription factors	Determine embryonic cell fate	
HOXA7	Homeobox A7; member of a family of transcription factors	Determine embryonic cell fate	Murine transgenic mice generated to ectopically expressed Hoxa7 died shortly after birth with multiple craniofacial anomalies such as cleft palate, open eyes at birth, non-fused pinna, phenotype seen in that of human retinoic acid embryopathy
HOXA9	Homeobox A9; member of a family of transcription factors	Determine embryonic cell fate	Several patients with myeloid leukemia were noted to have translocation t (7;11) resulting in genomic fusion of nucleoprotein gene NUP98 with Hoxa9, suggesting that NUP98 and Hoxa9 may be involved in myeloid differentiation
HOXA10	Homeobox A10; member of a family of transcription factors	Determine embryonic cell fate	Murine targeted disruption of Hoxa 10 results in homozygous Hoxa10-*I*-male and female mice with lumbar vertebral abnormalities and severe fertility defects
HOXA11	Homeobox A11; member of a family of transcription factors	Determine embryonic cell fate, pattern the posterior region of the vertebrate embryo and the appendicular skeleton	Murine targeted disruption of Hoxa11 & Hoxd11 results in double mutants with abnormal phenotype not apparent in mice homozygous for individual mutations. These double mutants have virtual absence of radius and ulna of the forelimbs, homeotic transformation of the axial skeleton, and kidney defects. These anomalies suggest that paralogous Hox genes function together to specify limb outgrowth and patterning along the proximo-distal axis

(continued)

Table 1.8 (continued)

Gene	Protein	Cellular function	Disease
HOXA13	Homeobox A13; member of a family of transcription factors	Determine embryonic cell fate	Murine of Hoxa13 results in the autosomal dominant hand–foot–uterus characterized by hand and foot dysplasia, partial duplication of the female genital tract
			Murine mutation of Hoxa13 results in hypodactyly due to arrest of digital arch formation
HOXB1	Homeobox B1	Determine embryonic cell fate	
HOXB2	Homeobox B2	Determine embryonic cell fate, have a determinant role in the body plan organization with Hoxa2, control dorso-ventral patterning of neuronal development in the rostral hindbrain	
HOXB3	Homeobox B3	Determine embryonic cell fate	
HOXB4	Homeobox B4	Determine embryonic cell fate	
HOXB5	Homeobox B5	Determine embryonic cell fate involved in the positioning of mouse upper limb bud	
HOXB6	Homeobox B6	Determine embryonic cell fate specify positional identity along the anterior–posterior axis	Transgenic mice generated with a gain-of-function mutation of Hoxb6 result in early post-natal lethality and craniofacial skeletal perturbations at birth including open eyes, micrognathia, microtia, skull bone deformities and structural and positional deformities, and structural and positional alterations in the vertebral columns. Complete or partial absence of the supraoccipital bone and malformation of the exo-occipital and basioccipital bones are also found
HOXB7	Homeobox B7	Determine embryonic cell fate	
HOXB8	Homeobox B8	Determine embryonic cell fate involved in establishing the antero-posterior polarity of anterior mouse limb, controlled SHH through a negative feedback loop	
HOXB9	Homeobox B9	Determine embryonic cell fate	
HOXB13	Homeobox B13	Determine embryonic cell fate maintain collinearity	
HOXC4	Homeobox C4	Determine embryonic cell fate involved in mouse anterior and posterior limb patterning	
HOXC5	Homeobox C5	Determine embryonic cell fate involved in patterning of mouse anterior limb, a target for regulation by retinoic acid and HOX hemeproteins	
HOXC6	Homeobox C6	Determine embryonic cell fate involved in mouse anterior and posterior limb patterning	
HOXC8	Homeobox C8	Determine embryonic cell fate involved in mouse anterior and posterior limb patterning and innervation of the limb may be involved in chondrocytic differentiation	Transgenic mice with overexpression of a Hoxc8 transgenic exhibit cartilage defects with accumulation of proliferating chondrocytes and reduced maturation

(continued)

Table 1.8 (continued)

Gene	Protein	Cellular function	Disease
HOXC9	Homeobox C9	Determine embryonic cell fate involved in mouse posterior limb patterning	
HOXC10	Homeobox C10	Determine embryonic cell fate involved in mouse posterior limb patterning	
HOXC11	Homeobox C11	Determine embryonic cell fate involved in mouse posterior limb patterning	
HOXC12	Homeobox C12	Determine embryonic cell fate	
HOXC13	Homeobox C13	Determine embryonic cell fate, may have a function common to hair, nail, and filiform papillae of tongue	Murine targeted disruption resulting in homozygous deficient Hoxc13-*I*-mice with defects in hair, nail, and tongue, the most striking effect being brittle hair resulting in alopecia
HOXD1	Homeobox D1	Determine embryonic cell fate	Heterozygous deletion of the Hoxd cluster (Hoxd3–Hoxd13) in two human patients results in developmental defects of A–P limb and genitalia with oligodactyly and penoscrotal hypoplasia
HOXD3	Homeobox D3	Determine embryonic cell fate involved in the regulation of cell adhesion processes required to set up physiological constriction along the previously un-subdivided gut mesoderm	Murine homozygous null Hoxa2-*I*-embryos show complete absence of thymus and alteration of hyoid cartilage. Complementation with Hoxd3 protein restores thymus and corrects alteration of hyoid cartilage suggesting that Hoxa3 and Hoxd3 can carry out identical biological functions
HOXD4	Homeobox D4	Determine embryonic cell fate, require to set up physiological constriction along the previously un-subdivided gut mesoderm	Murine construction of mini-complex with all Hoxd genes deleted except for Hoxd1 and Hodx3, the latter of which was functionally impaired results in mice homozygous for mini-complex with retarded development, death within 2 weeks, absence of ileocecal valve and aberrant pylorus of stomach. In the absence of Hoxd function, mice lack sphincters
HOXD8	Homeobox D8	Determine embryonic cell fate, express in genitourinary tract and may play a continuing role in adult genitourinary tract function, require to set up physiological constrictions along the previously un-subdivided gut mesoderm	Murine construction of mini-complex with all Hoxd genes deleted except for Hoxd1 and Hoxd3, the latter of which was functionally impaired results in mice homozygous for the mini-complex with retarded development, death within 2 weeks, absence of ileocecal valve and aberrant pylorus of stomach. In the absence of Hoxd function, mice lack sphincters
HOXD9	Homeobox D9	Determine embryonic cell fate, require to set up physiological constriction along the previously un-subdivided gut mesoderm	Murine construction of mini-complex with all Hoxd genes deleted except for Hoxd1 and Hoxd3, the latter of which was functionally impaired results in mice homozygous for the mini-complex with retarded development, death within 2 weeks, absence of ileocecal valve and aberrant pylorus of stomach. In the absence of Hoxd function, mice lack sphincters

(continued)

Table 1.8 (continued)

Gene	Protein	Cellular function	Disease
HOXD10	Homeobox D10	Determine embryonic cell fate, require to set up physiological constriction along the previously un-subdivided gut mesoderm	Murine construction of mini-complex with all Hoxd genes deleted except for Hoxd1 and Hoxd3, the latter of which was functionally impaired results in mice homozygous for the mini-complex with retarded development, death within 2 weeks, absence of ileocecal valve and aberrant pylorus of stomach. In the absence of Hoxd function, mice lack sphincters
HOXD11	Homeobox D11	Determine embryonic cell fate, require to set up physiological constriction along the previously un-subdivided gut mesoderm	Murine construction of mini-complex with all Hoxd genes deleted except for Hoxd1 and Hoxd3, the latter of which was functionally impaired results in mice homozygous for the mini-complex with retarded development, death within 2 weeks, absence of ileocecal valve and aberrant pylorus of stomach. In the absence of Hoxd function, mice lack sphincters
HOXD12	Homeobox D12	Determine embryonic cell fate, interacting with Hoxd13 during mouse limb development, require to set up physiological constriction along the previously un-subdivided gut mesoderm	Murine construction of mini-complex with all Hoxd genes deleted except for Hoxd1 and Hoxd3, the latter of which was functionally impaired results in mice homozygous for the mini-complex with retarded development, death within 2 weeks, absence of ileocecal valve and aberrant pylorus of stomach. In the absence of Hoxd function, mice lack sphincters
HOXD13	Homeobox D13	Involved in regulating patterning during limb development, may play a role in reproductive physiology, may be involved in sphincter formation	Syndpolydactyly
			Murine SPDH-*I*-severe synpolydactyly with formation of all 4 ft including polydactyly, syndactyly, and brachydactyly also lack preputial glands
HOX11	Homeobox 11, orphan homeobox gene located outside the HOX clusters, encodes a DNA-binding nuclear transcription factor	Photo-oncogene involved in tumorigenesis of T cell lymphoma leukemia, required for survival of spleen by maintaining splenic precursors during organogenesis	In human patients with T cell leukemia and chromosomal translocation involving 10q24, the proto-oncogene TCL3, also known as HOX11, becomes activated following the arrangement
			Murine by targeted disruption, homozygous HOX11 null embryos have spleen formation commencing normally up to a certain stage of embryogenesis and then undergo complete and rapid resorption
HOX1L1	Homeobox 11-like 1	Require for proper positional specification and differentiation of cell fate of enteric neurons	Murine ENX (HOX1111)-*I*-mice develop neuronal intestinal dysplasia and megacolon
HSPG2	Heparan sulfate proteoglycan 2, perlecan	Interact with extracellular matrix protein growth factors and receptors and influence cellular signaling. Essential for cartilage and cephalic development	Murine disruption of perlecan results in 40 % of HSPG2-*I*-mice that died in embryonic day 10.5 with defective cephalic development. Sixty percent died shortly after birth with skeletal dysplasia resembling thanatophoric dysplasia type I. Only 6 % HSPG2-*I*-mice had exencephaly and skeletal dysplasia

(continued)

Table 1.8 (continued)

Gene	Protein	Cellular function	Disease
IDA/IDUA	α-L-iduronidase	Enzyme degrades mucopolysaccharides	Hurler syndrome (dysostosis multiplex)
			Sclerie syndrome (dysostosis multiplex)
IDS	Iduronate 2 sulfatase	Enzyme degrades mucopolysaccharides	Hunter syndrome
IGF1	Insulin-like growth factor 1, somatomedin C	Prenatal and post-natal growth regulation	Growth retardation with sensorineural deafness and mental retardation (homozygous intragenic deletion), parents short stature (homozygous intragenic deletion)
			Knockout murine IGF-*I*- profound embryonic and post-natal growth retardation with neurological defects
IGF2	Insulin-like growth factor 2, somatomedin A	Modulation of growth hormone action, stimulation of insulin action, and involvement of development and growth	Overexpression (loss of imprinting) of IGF 2 in Wilms tumor, Beckwith–Wiedemann syndrome
			Targeted disruption of Igf2 gene in mice by line resulted in growth-deficient heterozygous progeny, homozygous mutants were indistinguishable from heterozygous affected
ITGA1	Integrin α1	Cell surface receptor dimerizes with the β subunit to form a collagen and laminin receptor	
ITGA2	Integrin α2, CD49B; α2 subunit of very late activating protein receptor (VLA-2)	Cell surface adhesion receptor dimerizes with the β subunit to form a collagen and laminin receptor	
ITGA3	Integrin α2, CD49C; α3 subunit of very late activating protein receptor (VLA-3)	Cell surface adhesion receptor dimerizes with the β subunit to form a receptor for fibronectin, laminin, and collagen	
ITGA7	Integrin α7, clustering of integrin and Hox genes implies parallel evolution of these gene families	Specific cellular receptor for the basement membrane proteins −1, −2, and −4 provides indispensable linkage between muscle fibers and extracellular matrix, clustering of integrin and Hox genes implies parallel evolution of these gene families	Autosomal recessive congenital myopathy
			Murine homozygous null ITAG7-*I*- mice viable and fertile but develop progressive muscular dystrophy
ITGA10	Integrin α10	Bind to type II collagen expressed in chondrocytes of articular cartilage	
ITGAM	Integrin αM	Dimerize with ITGB2 in vitronectin, fibrinogen, von Willebrand factor, thrombospondin, fibronectin, osteopontin, and collagen	
ITGAV	Integrin αV, vitronectin receptor, cell surface adhesion receptor	Dimerize with ITGB3 in vitronectin, fibrinogen, von Willebrand factor, thrombospondin, fibronectin, osteopontin, bone sialoprotein, and collagen, therapeutic targets for inhibition of angiogenesis and osteoporosis	Murine ablation of ITGAV resulted in V null mice with 80 % dead during embryogenesis but appeared normal and 20 % alive with intracerebral and intestinal hemorrhages and cleft palates
ITGB1	Integrin β1, member of a family of cell surface receptors	Associate with α1 or α6 to form a laminin receptor, with α2 to form a collagen receptor, and with α5 to form a fibronectin receptor	

(continued)

Table 1.8 (continued)

Gene	Protein	Cellular function	Disease
LAR1	Gene not cloned yet		Autosomal dominant Larsen syndrome
LHX2	LIM homeobox protein 2	Positive transcription factor with 2 LIM and 1 Hox domain, may be involved in the development of leukemia by formation of chimeric proteins resulting from chromosomal translocation	Elevated levels of Lhx2 found in patients with T cell leukemias
LOX	Lysyl oxidase	Extracellular Cu-dependent enzymes involving in the cross-linking and maturation of collagen and elastin	Menkes syndrome, X-linked cutis laxa Ehlers–Danlos V syndrome associated with lysyl oxidase deficiency
LUM	Lumiscan keratan sulfate proteoglycan	Play a role in the regulation assembly of fibrils expressed at high levels in adult articular chondrocytes	
LMX1B	LIM homeobox transcription factor 1β	Dorsal/ventral patterning of vertebrae limb	Nail patella dysplasia
			Murine LMX1b-*I*-nail patella syndrome
MADH 1	Mothers against decapentaplegic; drosophila homolog 1	Involve in the BMP signaling pathway, interacting with the activated receptors, undergoing phosphorylation, translocating to nucleus after binding to MADH4	
MADH4	Mothers against decapentaplegic; drosophila homolog 4	Critical mediator of TGFB and BMP signaling pathways, putative tumor suppressor gene mutated or deleted in pancreatic and colorectal carcinoma	Pancreatic carcinoma
			Colorectal carcinoma
			Juvenile polyposis coli
			Head and neck squamous carcinoma
			Murine homozygous Madh4 mice died before embryonic day 7.5. Mutant embryos have reduced size, failure to gastrulate or express a mesodermal marker, and show abnormal visceral endoderm development, heterozygotes show no abnormality
			Murine compound heterozygotes for Madh4 and APC can be generated by meiotic recombination, simple heterozygotes for APC develop intestinal polyps
			Compound heterozygotes for APC and Madh4 develop polyps which then undergo malignant transformation
MADH5	Mothers against decapentaplegic; drosophila homolog 5	Involve in the BMP signaling pathway, interacting with the activated receptors, undergoing phosphorylation, translocating to nucleus after binding to MADH4, involve in the signaling pathway by which TGF-β inhibits the proliferation of human hematopoietic progenitor cells	
MADH6	Mothers against decapentaplegic; drosophila homolog 6	Involve in the TGF-β and BMP signaling pathway express in vascular endothelium	Murine targeted disruption results in MADH-*I*-mutant mice with multiple cardiovascular abnormalities such as hyperplasia of heart valves and outflow tract abnormalities
MADH9	Mothers against decapentaplegic; drosophila homolog 9	Involve in the TGF-β and BMP signaling pathway expressed in vascular endothelium	

(continued)

Table 1.8 (continued)

Gene	Protein	Cellular function	Disease
MAN2B1	Alpha mannosidase B	Enzyme degrades mannosidase, accumulation results in lysosomal storage	α-mannosidosis ((dysostosis multiplex)
MAP3K7/MAPKKK	Mitogen-activated protein kinase 7	Participate in the regulation of transcription by TGF-β involved in the BMP signaling through binding with AP13	
MATN1	Matrillin 1, cartilage matrix protein	Cartilage matrix protein is a major component of the extracellular matrix of non-articular cartilage, it binds to collagen	Rattus, rats immunized with cartilage matrix protein develop polychondritis with erosion of non-articular cartilage
MMP2	Matrix metalloproteinase 2, gelatinase A, 72 kD, type IV collagenase, 72 kD gelatinase	Cleave type IV collagen, the major structural component of basement membranes, catalyzes extracellular matrix degradation	
MMP8	Matrix metalloproteinase 8, neutrophil collagenase	Cleavage of interstitial collagen in the triple helical domain, cleaves collagen type I more so than type III	
MMP9	Matrix metalloproteinase 9, gelatinase B, 92 kD, gelatinase, 92 kD type IV collagenase	Cleave collagen in extracellular matrix, key regulator of growth plate angiogenesis and apoptosis of hypertrophic chondrocytes	Murine homozygous Mmp9-*I*-mice with null mutation exhibit delay and abnormal pattern of skeletal growth plate, vascularization, and ossification. Enlargement of growth plate eventually undergoes remodeling and produces an axial skeleton of normal appearance
MMP10	Matrix metalloproteinase 10, stromelysin 2	Weak cleavage action on collagen types II, IV, and V	
MMP13	Matrix metalloproteinase 13, collagenase 3	Degrade fibrillar collagen probable involvement in the pathophysiology of human osteoarthritis cartilage	
MSX/HOX7	Homeobox 7	Regulate early development of limbs, heart, and teeth	Autosomal dominant hypodontia
			Wolf–Hirschhorn syndrome (gene deleted)
			Murine Msx1-*I*-cleft palate, facial and dental abnormalities
MSX2	MSH (drosophila) homeobox homolog 2	Involved in tissue interaction and implicated in vertebrate-craniofacial development	Craniosynostosis, Boston type
			MSX transgenic mice perinatal lethal with premature suture closure and ectopic cranial bone
NFYA	Nuclear transcription factor Y, α	Stimulate the transcription of various genes by recognizing and binding to the CCAAT motif in promoters of collagen, albumin, and βactin genes	
NFYB	Nuclear transcription factor Y, β	Stimulate the transcription of various genes by recognizing and binding to the CCAAT motif in promoters of collagen, albumin, and βactin genes	
ND	Nitrogen, enactin	Basement membrane protein tightly associated with laminin also binds to collagen	
NOG	Noggin	Bind and inactivate members of the growth factor β superfamily signaling proteins such as the BMPs which are essential for proper skeletal development	Proximal symphalangism
			Multiple synostoses syndrome
			Murine NOG-*I*-stillborn with multiple defects and bony fusion of appendicular

(continued)

Table 1.8 (continued)

Gene	Protein	Cellular function	Disease
PACE	Paired basic amino acid cleaving enzyme, furin, membrane-associated receptor protein	Involved in the processing of TGF-β precursor to the mature form, cleave propeptide of collagen type V, α1	
PDB1	Gene not cloned yet		Paget's disease of bone type I
PDB2	Gene not cloned yet		Paget's disease of bone type II
PEPD	Peptidase D, prolidase, imidodipetidase	Split immunodipeptides, play an important role in collagen metabolism because of the high levels of immunoacids in collagen	Autosomal recessive peptidase deficiency
PEX1	Peroxin 1	Involved in peroxisomal matrix protein import	Zellweger syndrome
			Infantile Refsum disease
PEX2/PXMP3	Peroxin 2	Involved in peroxisomal assembly	Zellweger syndrome
PEX5/PXR1	Peroxin 5	Encode a receptor for proteins with type 1 peroxisomal targeting signal (PTS1) and mediates PTS2 targeted protein import	Zellweger syndrome
			Neonatal adrenoleukodystrophy
			Murine Pxr1-*I*-perinatal lethal with Zellweger syndrome
PEX 6/PAF2	Peroxin 6	Involved in peroxisomal assembly	Zellweger syndrome
PEX7	Peroxin 7	Encode a peroxisomal PTS2 receptor	Rhizomelic chondrodysplasia punctata type I
PHEX	Phosphate regulating protein with homologies to endopeptidases on X-chromosome	Involved in bone development	X-linked hypophosphatemic rickets
			Murine (HYP) X-linked hypophosphatemic rickets
			Murine (GYR) X-linked hypophosphatemic rickets and inner ear abnormalities microdeletion syndrome
PLOD2	Procollagen lysine, 2-oxoglutarate, 5 dioxygenase 2, lysine hydroxylase 2	Form hydroxylysine residues in xan-lys-gly-sequences in collagen, serve as sites for attachment for carbohydrate units, and are essential for stability of intermolecular collagen cross-links	
PLOD3	Procollagen lysine, 2-oxoglutarate, 5 dioxygenase 3, lysine hydroxylase 3	Form hydroxylysine residues in xan-lys-gly-sequences in collagen, serve as sites for attachment for carbohydrate units, and are essential for stability of intermolecular collagen cross-links	
PRTN3	Proteinase 3, serine proteinase, Wegener's granulomatosis autoantigen	Cleave elastin, fibronectin, laminin, vitronectin, and collagen types I, III, and IV	Associated with Wegener's granulomatosis hamster, tracheal insufflation of Prtn3 causes emphysema
PTHRP	Parathyroid hormone receptor or parathyroid hormone-related protein receptor	Involved in calcium homeostasis with hypercalcemia and suppression of PTH levels and exaggerated loss of cortical bone	Mark Jansen metaphyseal dysplasia
SCML1	Sex comb on mid-leg (drosophila like 1)	Involved in transcription expression of HOX genes	
SCML2	Sex comb on mid-leg (drosophila like 2)	Involved in transcription expression of HOX genes	
SEDL	Sedlin	Expressed in fetal cartilage	Spondyloepiphyseal dysplasia tarda, X-linked

(continued)

Table 1.8 (continued)

Gene	Protein	Cellular function	Disease
SMOH	Smoothened (drosophila homolog)	A signaling component of the sonic hedgehog patched complex function as an oncogene in basal cell carcinoma activated by somatic mutation in sporadic nevoid basal cell carcinoma syndrome and primitive neuroectodermal tumors targeting numerous genes (HOX, BMP)	Mutation of SMOH results in sporadic basal cell carcinoma Murine transgenic mice overexpressing SMOH develop skin lesions resembling basal cell carcinoma
SOX9	SRY box 9	Regulates COL2A1 expression and implicates abnormal regulation of COL2A1 during chondrogenesis	Campomelic dysplasia
SPARC	Secreted protein acidic cysteine-rich osteonectin	Bone-specific phosphoprotein binds selectively to hydroxypatite and to collagen fibrils at distinct sites Osteonectin accounts for unique property of bone collagen to undergo calcification	
TBX 1	T box 1, T named after the T or brachyury gene in mouse, member of a family of transcription factors	Involved in the regulation of developmental processes	May be one of the human genes deleted in DiGeorge contiguous gene deletion syndrome
TBX2	T box 2 transcription factor	Involved in the regulation of developmental processes	
TBX3	T box 3	Involved in posterior elements of limb development	Ulnar mammary syndrome
TBX4	T box 4 transcription factor	Expressed throughout developing hindlimb buds	
TBX5	T box 5	Involved in heart and anterior elements of limb development	Holt–Oram syndrome
TBX6	T box 6 transcription factor	Involved in paraxial mesoderm and somite formation, in its absence cells destined to form posterior somites differentiate along a neuronal pathway	Murine creation of a Tbx6 mutation resulted in irregular somites being formed in the neck region but differentiated along neuronal pathway forming neural tube-like structures that flank the axial neural tube
TBX10	T box 10 transcription factor	Involved in the regulation of developmental processes	
TBX15	T box 15 transcription factor	Involved in the regulation of developmental processes in mouse expressed in craniofacial region and developing limbs	
TBX18	T box 18 transcription factor	Involved in the regulation of developmental processes	
TBX19	T box 19 transcription factor	Involved in the regulation of developmental processes	
THBS 1	Thrombospondin 1	Glycoprotein that mediates cell-to-cell and cell-to-matrix interactions can bind to fibrinogen, fibronectin, laminin, and type V collagen	Murine targeted disruption resulting in deficient mice with mild variable lordosis of spine at birth and lung abnormalities with pneumonia
THBS2	Thrombospondin 2	Glycoprotein that mediates cell-to-cell and cell-to-matrix interactions can bind to fibrinogen, fibronectin, laminin, and type V collagen	Murine targeted disruption resulting in homozygous deficient mice with connective abnormalities such as fragile skin with reduced tensile strength, flexibility of tail, increased bone density and cortical thickness of long bones, abnormal bleeding time

(continued)

Table 1.8 (continued)

Gene	Protein	Cellular function	Disease
THBS3	Thrombospondin 3	Glycoprotein that mediates cell-to-cell and cell-to-matrix interactions can bind to fibrinogen, fibronectin, laminin, and type V collagen	
THBS4	Thrombospondin 4	Glycoprotein that mediates cell-tocell and cell-to-matrix interactions can bind to fibrinogen, fibronectin, laminin, and type V collagen	
TRPS1	Gene not cloned yet		Trichorhinophalangeal syndrome type 1
TWIST	Basic helix-loop-helix transcription factor, homolog of drosophila TWIST	Involved in craniofacial and limb development and may function as an upstream regulator of FGFRs	Saethre–Chotzen syndrome
			Murine TWIST ± Saethre–Chotzen syndrome
VDR	Vitamin D hormone receptor	Involved in the synthesis of osteocalcin, the most abundant non-collagenous protein in bone	Vitamin D resistant rickets with end organ unresponsiveness to 1, 25 dihydroxychole-calciferol

Derived from Ho et al. A skeletal gene database. J Bone Miner Res 2000;15:2095–2122

to the adjacent AER to modulate P/D development. Cell division in the progress zone appears to be accurately timed and it is felt that the length of time cells spend in the progress zone specifies the structures they will form. This is generally considered to be 200–300 μm long.

1.13.4 Polarizing Region

The zone of polarizing activity (ZPA) is not distinct histologically but its controlling features were identified on the basis of regional transplant experiments. It became evident that a diffusible morphogen could explain the digit changes evident from transplant experiments. In the limb bud, the highest polarization activity is posterior near the tip of the bud just proximal to the progress zone. The ZPA polarizes the limb along the A/P axis. The polarizing activity is confined to the mesenchyme (Fig. 1.18b). Sonic hedgehog (Shh) appears to be the signal from the posterior polarizing mesenchyme involved in antero-posterior patterning and much of its effect as a morphogen is direct but BMP-2 is also synthesized there and may be a secondary signal.

1.13.5 Dorsal Non-ridge Ectoderm

The signal necessary from the dorsal non-ridge ectoderm to trigger dorso-ventral development appears to come from expression of Wnt-7. It acts by expressing Lmx-1b in the dorsal mesoderm. The AER always forms at and specifically separates the dorsal and ventral (D/V) territories. Radical fringe is preferentially expressed in the ectoderm dorsally and engrailed-1 ventrally and these are thus actively involved with D/V patterning. They are also present in the dorsal and ventral parts of the AER respectively.

1.13.6 Coordinating Multiaxial Development

Interaction between ZPA, AER, and dorsal ectoderm coordinates multiaxial development. Two types of proteins, transcriptional regulators and signaling proteins, play a major role in directing limb development. *Transcription factors* tend to be expressed in specific well-defined regions of the limb. The family of the Hox genes plays a major role controlling early development along both antero-posterior and proximo-distal axes. *Signaling molecules* working between cells and tissues include retinoic acid (RA), a hormone; sonic hedgehog (Shh) which localizes in the zone of polarizing activity (ZPA), the antero-posterior organizer center; the Wnt genes, a large family of extracellular proteins several of which are expressed in the limb; and fibroblast growth factors (FGFs) many of which play a major role in the apicol ectodermal ridge. There is clearly mutual dependence between signaling systems [245, 282–284]. The expression of Shh in posterior mesenchyme maintains FGF-4 expression in the posterior apical ridge and Wnt-7a expression in dorsal ectoderm together with FGF-4 maintains Shh expression in posterior mesenchyme. Current investigation is involved with assessing both positive and negative feedback loops and the developmental cascades to define how the various transcriptional regulators and signaling proteins induce each other and eventually direct cell positioning and the synthesis of extracellular molecules.

Verheyden and Sun have demonstrated one of the limb bud growth controls where a positive Fgf/Shh loop drives outgrowth leading to an increase in FGF signaling which triggers an Fgf/gremlin inhibitory loop [285]. The circuit is considered to represent a self-promoting/self-terminating series of actions.

1.14 Overview of Gene Controls of Limb Development

A large number of molecules are expressed in relation to the developing limbs serving as growth factors, transcriptional regulators, and signaling molecules. Transcription factors are proteins that bind to enhancer or promoter regions and interact to activate or repress the transcription of a particular gene. Most transcription factors bind to specific DNA sequences. The proteins are grouped into families such as homeodomain (Hox, Pac), basic helix-loop-helix, basic leucine zipper, and zinc finger (sox).

Even when an RNA transcript is synthesized several steps remain before a functional protein is created. These include processing of the mRNA by removal of introns, translation from nucleus to cytoplasm, translated by the protein-synthesizing apparatus, and then post-translational modification. Detailed investigations reveal the temporal and spatial aspects of molecular expression indicating the role of each in the developmental cascade and showing in particular interrelationships between the various signaling regions in general and specific molecules in particular. Some of the major factors are listed in Tables 1.8 and 1.9. Many genes encoding regulatory molecules are expressed in the AER. The genes encode two types of proteins: transcriptional regulators and signaling proteins. The hox gene family represents an example of how transcription factors control development. Lmx-1 and engrailed −1 are other transcription factors. FGF-4 is particularly important playing a role in signaling between the AER and underlying mesenchyme. The involved molecules include dlx, Msx-1 and Msx-2, engrailed-1 (en), bone proteins BMP-2 and BMP-4, retinoic acid, retinoic acid receptor-beta, fibroblast growth factors -2 and -4, and FGF receptor 1.

Retinoic acid is a major signaling molecule or morphogen in the zone of polarizing activity. Mesenchymal cells in the progress zone express several genes encoding regulatory proteins such as Msx-1 and Msx-2, Evx-1, Wnt-5A, and AP-2. Mxs-1 and Mxs-2, originally known as Hox-7 and -8, are two related homeobox containing genes which are widely expressed in vertebrate embryos in particular where epithelial–mesenchymal interactions occur. Msx-1 is highly concentrated in the distal mesenchyme in developing limbs with weak expression in the AER while Msx-2 is expressed weakly in mesenchyme but strongly in AER. The mesenchymal cells provide the signals that initiate limb bud development but the molecular trigger that stimulates AER formation is not yet known. There is rapid proliferation of mesenchymal cells which induce the overlying ectodermal cells to form the AER. Early mesodermal induction pre-limb bud stage is the subject of intensive study with members of each of FGFs, TGF betas, and wingless/int-1 (Wnt) families implicated at varying stages and regions.

Tickle and Eichele [244] have listed the genes involved in early vertebrate limb development as reproduced in Table 1.9. Some of the major genes and gene families will be detailed in this section.

1.14.1 Hox Genes

Mesenchymal cells in the limb bud are primed to respond to morphogens by specific genes referred to as homeobox genes. These genes are responsible for initiating regional development by establishing patterns encoding positional information. They do so by producing transcriptional factors which are small proteins that activate genes bound to them. Processes such as cell proliferation, cell differentiation, and cell death are regulated by homeobox genes although these have overlapping functions such that combinations of homeobox genes act on several groups of cells. Hox genes, a subgroup of homeobox genes, are transcription factors that have been identified in vertebrates. There are 39 genes present in four gene clusters on four chromosomes [272, 286, 287]. In humans the four hox gene clusters (A to D) are on four different chromosomes at 7p15, 17q21.2, 12q13, and 2q31, respectively. The gene name “hox” has been limited to use for the cluster genes in vertebrates. The hox genes direct body segmentation and are organized into four clusters termed hox a, b, c, and d in animals and HOX A, B, C, and D in humans. The products of the hox genes are proteins belonging to the transcription factor class which can bind to DNA and regulate gene transcription. There are 39 hox genes in mice and humans. Each complex has 9–11 genes spaced over 100–150 Kb. Sequence comparisons between the four clusters indicate that they evolved from a single cluster of genes. Hox genes within each cluster have direct homologs in the other three clusters. There are 13 sets of related homologs called paralog groups. The entire hox gene family is generally displayed in a 4 (hox a, b, c, d) by 13 (paralog) array with the horizontal axis representing physical linkage and chromosomal position and the vertical axis representing gene similarity. A gene is represented by a letter (chromosome location) and a number (relation to paralogs) [288] (Fig. 1.19).

Each of the 39 Hox genes, which are organized in four different chromosomal complexes, is organized the same way with the genes in each cluster all oriented in the 5′ to 3′

Table 1.9 Genes expressed in early vertebrae limb buds[a, b]

(i) Genes expressed in limb mesenchyme	
Transcription factors encoded by Hox complexes	
Hoxa-10, Hoxa-11, Hoxa-13	Progressively more 5′ genes restricted to more distal mesenchyme
Hoxd-9, Hoxd-10, Hoxd-11	Progressively more 5′ genes are restricted to more postero-distal Hoxd-12, Hoxd-13 mesenchyme
Hoxb-5	Expressed anteriorly in forelimbs
Hoxe-6*	Expressed anteriorly in forelimbs
Other transcription factors	
Evx-1	Postero-distal mesenchyme
Msx-1	Restricted to distal mesenchyme
Msx-2	Anterior and distal mesenchyme
AP-2	Distal mesenchyme
Retinoid receptors and retinoid-binding proteins	
RARαβ	Expressed at low levels throughout mesenchyme
RARβ	Throughout mesenchyme but proximally enriched
RARϒ	Expressed at low levels throughout mesenchyme
RXRαβ	Ubiquitous
CRABP-I	Distal mesenchyme
CRABP-II	Dorsally enriched, higher levels proximally
CRABP*	Anterior to posterior protein concentration gradient with anterior high point
Putative intercellular signaling molecules	
Wnt-5a	Abundant in distal mesenchyme, low levels throughout proximal mesenchyme
Sonic hedgehog	Discrete posterior domain associated with polarizing region
BMP-2	Posterior mesenchyme, approximately coextensive with polarizing region
BMP-4	Anterior and posterior mesenchymal domains
FGF-2*	Mesenchyme beneath ectoderm and apical ectodermal ridge
(ii) Genes expressed in apical ectodermal ridge	
Transcription factors	
Dix	
Engrailed	
Msx-1	
Msx-2	
RARβ	
Putative intercellular signaling molecules	
FGF-2*	Enriched posteriorly
FGF-4	
BMP-2	
BMP-4	
WNT-5a	
(iii) Genes expressed in limb ectoderm	
Transcription factors	
Engrailed	Enriched ventrally
Putative intercellular signaling molecules	
FGF-2*	Dorsally enriched
BMP-2	
Wnt-5a	Enriched ventrally
Wnt-7a	Dorsal ectoderm only

[a]This is a partial list of the best categorized molecules; a comprehensive list would consist of several hundred entries
Expression data based on in situ hybridization analysis except for gene products marked by an asterisk, which indicates that expression pattern has been determined by immunohistochemistry
[b]*Derived from* Tickle and Eichele (Ref. [244])

direction of transcription. There is remarkable conservation of hox gene similarity between drosophila and vertebrate species which begins to explain the molecular basis for structural similarity throughout the animal world. Although some genes have been lost, those that have persisted have a strong degree of structural necessity. There is also a strong correlation between the physical order of genes along the chromosome and their expression along the antero-posterior axis of the embryo. The Hox genes tend to be expressed in specific regions in an ordered array of spatially restricted domains such as the neural tube, neural crest, limbs, hind brain segments, etc. The hox genes play a major role in defining the patterns of development in vertebrate limbs. There is also a relationship based on the time of appearance of expression during embryogenesis. Retinoic acid (RA) induces Hox gene expression along with expression of other developmental molecules. The genes at the extreme 3′ ends of the clusters are activated the earliest, have the most anterior boundaries of expression, and display the highest sensitivity to RA. As one progresses in a 5′ direction, each subsequent gene has a later, more posterior, and reduced RA response pattern of expression. Hox genes are actively expressed in the polarizing region where they appear to convey patterning information. Characteristic of patterning along the limb axis are: the proximo-distal morphogenetic progression; a temporal sequence in the activation of Hox genes; a partially overlapping pattern of Hox expression, especially posteriorly; and concentration in the polarizing region.

There are relatively few naturally occurring mutations in mouse or human Hox genes and their function has been inferred from their position in the developmental sequence. The large number of genes and the overlapping of adjacent areas have led to difficulty in assessing specific functions.

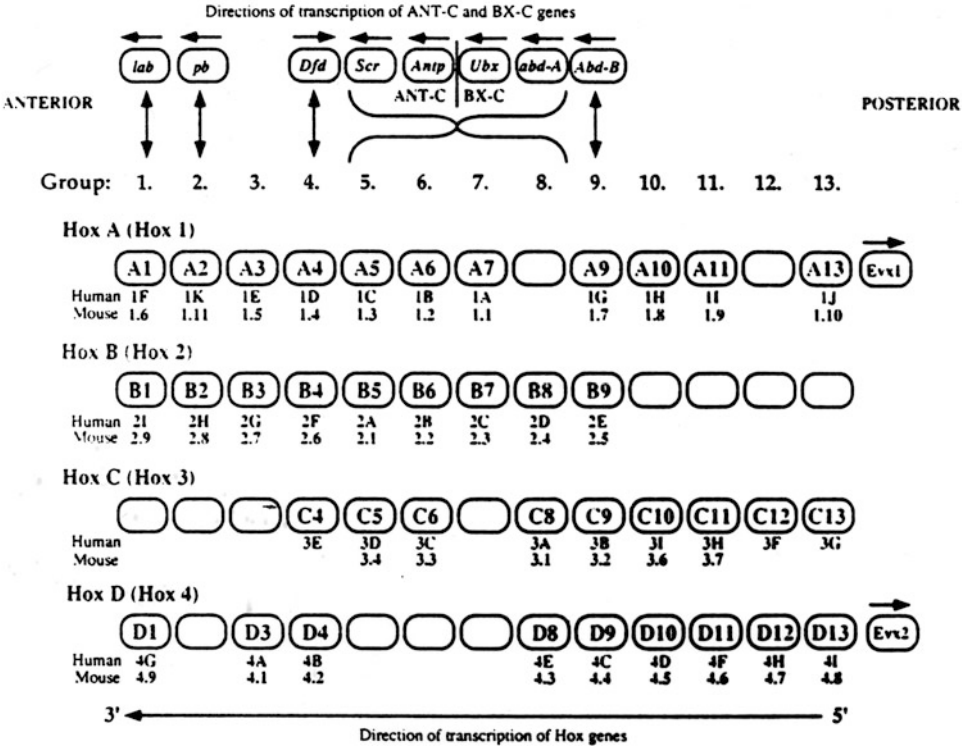


Fig. 1.19 The hox gene family is outlined (from Scott [304]). (Reprinted with permission from Scott MP, Vertebrate homeobox gene nomenclature. Cell 1992:71:551–553. Copyright 1992 Elsevier)

There is substantial overlap in expression domains among the members of a paralogous group and the loss of a single gene can be overcome by functions of adjacent genes. The use of transgenic mutations has led to better definition of specific Hox gene roles. With single gene transformations, however, the abnormal findings are often relatively minimal due to compensation by other Hox genes. There appears to be a requirement for several genes to combine in patterning a structure such that altering a single component may not be sufficient to generate a complete transformation.

The Hox genes are expressed in specific patterns during limb morphogenesis [289]. Hox-8b may define the ability of cells to express sonic hedgehog (Shh). Another gene that might define the competence of cells to express Shh is the basic helix-loop-helix transcription factors dHAND. Evolving patterns of gene expression in the chick limb bud represent temporal and spatial overlap of several distinctly regulated expression domains. The sonic hedgehog (Shh) gene is involved in the regulation of the Hox-d gene expression in the distal mesenchyme. Hox-d gene expression is sequentially expressed. In the early phases, Hox-d-9 and Hox-d-10 genes are expressed across the AP extent of the developing bud. The next phase of limb outgrowth involves activation of Hox-d-11 and Hox-d-12 genes in progressively restricted domains in the posterior half of the bud and finally Hox-d-13 is activated later on. Hox-d-9 and Hox-d-10 appear proximally before sonic is expressed. Abnormal expression of any of these genes can lead to structural abnormalities. When Hox-d-11 expression was altered in limb buds, many changes were noted including a first metatarsal of a deltoid bone shape, abnormal phalangeal structure, and metatarsals abnormal in length. Many of the structural limb abnormalities seen in the human can thus be secondary to abnormalities in Hox gene expression. Gene activity has a temporal sequence which can vary in the sense that the gene may be active early, quieten down, and then reactivate later.

It required all members of the Hox 10 or Hox 11 paralogous groups to be disrupted in mouse experiments to show how these Hox genes are involved in global patterning [290]. In the absence of Hox 10 function, no lumbar vertebrae are formed and ribs project from all posterior vertebrae extending caudally from the last thoracic vertebrae to beyond the sacral region. In the absence of Hox 11 function sacral vertebrae are not formed and these vertebrae show a lumbar identity. The redundancy among these paralogous families is so great that the Hox patterning is not apparent in mice mutant for five of the six paralogous alleles.

All of the Hox genes have specific domains of expression along the anterior–posterior or primary axis of the embryo. They are also expressed in more restricted domains along the secondary axes of the embryo such as the limb buds. The paralogous genes are not expressed in similar domains in the limb bud. Among areas of common expression, the Hox-d genes are centered in the ZPA at the posterior and distal tip of the developing limb bud while the Hox-a genes are expressed in restricted domains along the proximal–distal axis of the limb but are not polarized along the AP axis of the late limb bud. With increasing studies of Hox expression

patterns, it appears that the boundaries of the various genes are not as specific as once suspected. The product of the Shh gene, expressed in the ZPA, along with various FGFs produced in the apical ectodermal ridge is responsible for initiating and possibly regulating Hox gene expression. Signals from the AER and ZPA are coordinated to regulate Hox gene expression in the developing limb bud.

1.14.1.1 Classification and Nomenclature of All Human Homeobox Genes

Holland et al. have revised the classification and nomenclature of all human homeobox genes. They identified all homeobox genes and pseudogenes, named previously unnamed genes, and classified terminology and classification for the rest. They described 300 human homeobox loci dividing into 235 probable functional genes and 65 probable pseudogenes. The new classification defines 11 homeobox gene classes subdivided into 102 homeobox gene families [291]. Homeobox genes possess a particular DNA sequence, the homeobox, which encodes a recognizable protein domain, the homeodomain. Most homeodomains are 60 amino acids long and serve as transcription factors in embryonic patterning and cell differentiation. There are homeobox genes on every human chromosome including the two sex chromosomes. The best-known examples of close linkage between homeobox genes are the 4 Hox clusters on human chromosomes 2, 7, 12, and 17 comprising 9, 11, 9 and 10 genes (=39), respectively.

Gene Classes: The 11 gene classes, written in non-italicized capital letters, are: ANTP, PRD, LIM, POU, HNF, SINE, TALE, CUT, PROS, 2F, and CERS. The two largest classes ANTP and PRD are divided into two subclasses each. *Gene Families*: There are 102 gene families [291].

The human genome has 39 HOX genes arranged into 4 Hox clusters. The classification divides the HOX genes into seven gene families: Hox 1, Hox 2, Hox 3, Hox 4, Hox 5, Hox 6–8, and Hox 9–13. The HOX genes are in the ANTP class which has a total of 37 gene families. The article by Holland et al. [291] names each of the 11 classes and lists the gene families, symbols, names, and chromosomal location for each.

1.14.1.2 Gene and Molecular Controls on Limb Development–the Hox Gene Network

The Hox genes are involved in the establishment of patterns in coding positional information. The vertebrate homeobox-containing Hox genes appear as candidates for pattern formation genes. As development proceeds, cells in the progress zone leave it as proliferation continues there and pushes the tip of the limb bud more distally and laterally. The cells are instructed as to their positional identities, however, while they are within the progress zone. The proximal–distal progression is seen with proximal structures at hip and shoulder developing before those more distally. The information given to the proximal cells is thus different from those more distally both in terms of quality and timing. Those hox genes located at the 3′ extremities of the complexes are expressed earlier and from more anterior positions than genes located at the 5′ position which are expressed later and in more restricted posterior areas. Genes are expressed in cascade fashion from the 3′ to the 5′ regions along the antero-posterior axis. The ordering of the genes and their subsequent expression reflects the temporal sequence of their activation during limb bud outgrowth. The Hox expression domains are also related to establishment of the midline truncal structures. Hox gene expression in the limb as it develops reflects the clustered organization. In limbs the genes located at more 5′ positions are expressed in successively more posterior–distal areas at early stages.

Expression also varies along the rostro-caudal axis. The area in the limb where Hox-d expression domains all seem to overlap is the zone of polarizing activity. Cells of the progress zone will also express various combinations of Hox proteins at different times or positions within the zone. The Hox genes are thus felt to provide patterning information or positional information which is imparted to each cell as it leaves the zone and is then maintained during the next stages of limb development. Each Hox domain overlaps with the one adjacent to it such that there is not rigid direction of one part of one bone by one gene. Hox genes do not specify specific skeletal structures. They are thought to influence not the initial specification of cartilage but rather several steps in the subsequent growth of cartilage. Hox gene expression also leads to characteristic patterning systems. (1) The patterning system operates in a cranio-caudal or proximal–distal temporal progression; (2) the temporal sequence is observed in the activation of Hox genes; (3) a partially overlapping pattern of Hox expression domains is generated with an increasing overlap in the postero-distal areas; and (4) a particular area such as the polarizing region appears to control Hox gene expression. The Hox genes appear to impart information rather than respond to it. They are transcription factors that activate other genes. The progressive activation of more 5′ located Hox genes leads to the addition of segmented structures such as the blastema for the limb bones.

1.14.1.3 Expression of Hox Genes During Normal Limb Development

The earliest Hox-d gene expression is the uniform activation of Hox-d-9 and Hox-d-10 along the entire anterior-posterior extent of the early limb bud. There are three independently regulated phases of gene expression, most clearly seen with the Hox-d genes. During phase 1, Hox-d-9 and Hox-d-10 are expressed uniformly throughout the early mesoderm without apparent anterior–posterior bias while Hox-d-11 through

Hox-d-13 are not expressed. During phase 2, expression of Hox-d-9 through Hox-d-13 is sequentially initiated at the posterior-distal margin of the limb. With phase 3, there is a sequel initiation of transcription of Hox-d-13 through Hox-d-10 in an inverted temporal sequence from that observed during phase 2. Hox-a activation proceeds from Hox-a-9 and Hox-a-10 through Hox-a-11 and Hox-a-13. With the exception of Hox-a-13, the Hox-a genes appear to be activated uniformly along the extent of the limb bud. The timing and positioning of Hox gene expression correlate well with the previously defined proximal-distal segment development from classical embryologic studies. During specification of the upper arm/leg, the non-polar expression of Hox-d-9, Hox-d-10, Hox-a-9, and Hox-a-10 is observed. During specification of the lower arm and leg, there is sequential activation and posteriorly polarized expression of Hox-d-9 through Hox-d-13 and uniform expression of Hox-a-11. Specification of the hand–foot region begins with phase 3 Hox gene expression with Hox-a-13 transcription activated at the posterior border of the limb bud followed by Hox-d-13 and subsequently Hox-d-12, Hox-d-11, and Hox-d-10.

Shh can influence the expression of Hox genes in the limb. The initial phase of limb outgrowth and Hox gene expression occur prior to the onset of Shh expression. The onset of phase 2 expression, however, coincides with the onset of Shh expression and Shh also appears to drive phase 3 Hox gene expression. There is a causal link between Hox gene expression and morphology. Hox gene expression in the limb bud affects both the condensation of skeletal precursors in the limb bud and the subsequent growth and elongation of these elements. There is no obvious correlation between Hox gene expression and specific detailed morphology in the hand and foot. Their expression in the developing limb bud is initiated at a time when pattern is being specified. Hox genes are felt to encode positional information. Hox-a and hox-d genes are expressed in limb bud undifferentiated mesenchymal cells and then are restricted to precartilage areas and perichondrium. When their expression domains are superimposed they prefigure cartilage limb models. It has been suggested that the Hox-a genes are primarily responsible for subdividing the limb along the proximal-distal axis whereas the Hox-d gene exerts influence on the antero-posterior axis. The AER directs limb outgrowth by maintaining undifferentiated proliferating mesenchyme immediately adjacent to it in the progress zone. As the cells leave the P, their fate in a proximal distal sense has been determined. Removal of the AER early leads to proximal limb truncations while later removals involve more distal or digital truncations.

Hox-c clusters are expressed in the anterior–proximal portion of wing or leg [275]. The most 3′ members of the cluster, Hox-c-4 and Hox-c-5, are expressed only in the wing; Hox-c-6 and Hox-c-8 are in both the wing and leg; and the more 5′ members of the cluster, Hox-c-9, Hox-c-10, and Hox-c-11, are expressed only in the leg. In contrast to the changing temporal and spatial patterns of expression of the Hox-a and Hox-d genes in limb development, the Hox-c group in the anterior and proximal region maintains the same relative domains as the limb grows. There is only limited expression of Hox-b genes and the only Hox-b gene expression in the chick limb is Hox-b-9 which expresses specifically in the hind limb in the anterior portion of the developing upper and lower leg. There is also some expression adjacent to the AER.

1.14.2 Retinoids

Retinoic acid (RA), the major active metabolite of vitamin A, was the first molecule identified which profoundly affected the antero-posterior body axis and the pattern of the developing limb [279]. Vitamin A (retinol) is transported through the vasculature bound to carrier proteins and once inside the cell retinol is converted to biologically active retinoic acid. Retinoic acid is known to induce Hox gene expression including Hox-d-11, Hox-d-12, and Hox-d-13 along with FGF-4, BMP-2, and Shh gene expression. The retinoids are small hydrophobic molecules that bind and activate nuclear receptors, which are ligand-dependent transcription factors that control the expression of target genes. Retinoic acid is present in chick and mouse limb buds in particular in the zone of polarizing activity. It is suspected that the concentration of retinoic acid varies in gradient fashion to provide positional information for cell deposition patterns. When RA is applied locally to the anterior margin of a limb bud it induces extra digit formation. The chief observations implicating retinoic acid as a local chemical mediator in normal limb development are that: it occurs in a limb bud; it is enriched in the ZPA; and the concentration of retinoic acid required for digit induction is in the same range as the endogenous retinoic acid concentration [268, 292].

Retinoids have been identified as molecules which can mimic the effects of ZPA grafts on limb patterning. Several RA receptors have been identified in the developing limb. The analysis of retinoid function provides molecular insights into the role of diffusible signals in the control of limb patterning. RA is distributed unevenly across the AP axis of the limb with concentration greater in the posterior region including the ZPA. It appears that secretion of the RA from the ZPA passes into the rest of the limb producing a concentration gradient that can help to define cell position and specify the antero-posterior pattern.

Retinoic acid is not only involved in limb bud differentiation, but also later in the developmental sequence as a major regulator of chondrocyte maturation and matrix mineralization [292, 293]. RA induces collagen X expression in hypertrophic chondrocytes. Tissue culture studies with

chondrocytes also established that 3-week-old cultures treated with retinoic acid rapidly increase expression of the alkaline phosphatase, osteonectin, and osteopontin genes. There is also calcium accumulation in the RA-treated cultures in younger chondrocytes which were cultured. The effect of retinoic acid was different; it did not produce the previously described findings but rather greatly promoted cell proliferation. RA thus appears to react throughout many stages of limb development with specific effects on each. Once cartilage has been formed, the RA appears both to induce expression of late maturation genes and activate mineralization of the cartilage matrix.

1.14.3 Sox9

Sox9 is a transcription factor of the SRY family essential for chondrocyte differentiation from mesenchymal cells and for maintenance and maturation of chondrocytes [294–296]. During embryogenesis it is expressed in all cartilage models. It is needed early in cartilage formation beginning with the stage of formation of chrondrogenic mesenchymal condensation. Sox9 is essential for chondrocyte proliferation and is maximally present in the proliferating (palisading) zone of the growth plate in pre-hypertrophic chondrocytes. Sox 9 maintains the chondrocyte phenotype by inhibiting hypertrophic chondrocyte differentiation and is not present in the hypertrophic zone. Inactivation of Sox9 before the condensation phase in mouse mutants leads to arrest of chondrocyte differentiation. Removal of Sox9 after the condensation phase (i) greatly reduces the proliferation of chondrocytes, (ii) reduces their synthesis of the matrix in the growth plates, and (iii) hastens hypertrophic cell formation and premature matrix mineralization and bone formation. Sox9 binds to and activates chondrocyte-specific enhancer elements in Col 2aI, Col9aI, Col11aI, and aggrecan and is required for expression of Sox5 and Sox6 [297]. Sox5 and Sox6 also contribute to cartilage differentiation including growth plate and articular cartilage formation [298] but are not involved in chondrogenic mesenchymal condensations. Sox 5 and 6 are most involved with chondrocyte differentiation where high levels of Col 2aI, Col 9aI, and aggrecan gene expression are needed. The complete absence of Sox9 in the hypertrophic zone led to the belief that its downregulation allowed for vascular invasion from the metaphysis, cartilage resorption, and bone and marrow formation leading to endochondral bone. This was subsequently demonstrated in transgenic mice where Sox 9 overexpression in the hypertrophic zone halted angiogenesis, cartilage resorption, and endochondral ossification. The study showed that Sox9 also acts as a negative regulator of cartilage vascularization, bone marrow formation, and endochondral ossification [299]. Sox9 acts to inhibit differentiation of *vegfa*, *Mmp13*, and osteopontin in the physeal chondrocytes. These substances enhance angiogenesis, cartilage resorption, and cartilage mineralization, respectively.

Further knowledge of regulation of chondrocyte function was shown by studies showing that Sox 9 itself is regulated by microRNA-145 (miRNA-145). MicroRNA-145 directly inhibits Sox9 expression. Increased levels of miRNA-145 repress Sox9 expression, reduce expression of cartilage synthesis products Col2AI and aggrecan, and increase expression of hypertrophic chondrocyte markers Runx2 and MMP13 [300]. The matrix metalloproteinases are listed in Table 1.10.

Table 1.10 Matrix metalloproteinases

Enzyme	MMP	Enzyme	MMP
Collagenases		*Membrane-type MMPs*	
Collagenase 1	**MMP-1**	*(A) Transmembrane type*	
Collagenase 2	**MMP-8**	MT1-MMP	**MMP-14**
		MT2-MMP	**MMP-15**
Collagenase 3	**MMP-13**	MT3-MMP	**MMP-16**
Gelatinases		MT5-MMP	**MMP-24**
Gelatinase A	**MMP-2**	*(B) GPI-anchored*	
Gelatinase B	**MMP-9**	MT4-MMP	**MMP-17**
Stromelysins		MT6-MMP	**MMP-25**
Stromelysin 1	**MMP-3**	*Others*	
Stromelysin 2	**MMP-10**	Macrophage elastase	**MMP-12**
			MMP-19
Matrilysins		Enamelysin	**MMP-20**
			MMP-21
Matrilysin 1	**MMP-7**	–	
Matrilysin 2	**MMP-26**	CA-MMP-	**MMP-23**
			MMP-27
Stromelysin 3	**MMP-11**	Epilysin	**MMP-28**

MMP 4, 5, 6, 22—no longer used; identical to other members or not found in humans (MMP4)
GPI glycosylphosphatidylinositol (GPI)-anchored proteins are post-transitionally modified glycoproteins
Derived from Nagase, Visse, and Murphy, 2006 (Ref. [387])

1.14.4 Paired Box (PAX) Gene Pathway. Pax1, Pax9

There are nine human genes of the PAX family of transcription factors. Pax1 and Pax9 are transcription factors active in the chondrogenesis sequence. Pax genes are defined by the presence of a paired box, encoding a 128 amino acid

DNA-binding paired domain (PD). The pax genes play a role in regulating organ genesis in widely differing anatomical sites. Pax 1 plays a major role in vertebral column formation. Pax 9 is required for skeletal development of the skull (craniofacial) components, upper and lower extremity digits, and the permanent dentition.

1.14.5 Runx2

Runx2 (also known as Cbfa 1) is a transcription factor required for osteoblast differentiation from the multipotent mesenchymal cell [4]. The mesenchymal cell becomes a pre-osteoblast under Runx2 direction. Runx2 is expressed in osteoblasts of both endochondral and intramembranous bone. Runx2 also stimulates hypertrophic chondrocyte differentiation, a primary step leading to endochondral ossification. Transcription of the type X collagen gene in pre-hypertrophic chondrocytes involves interaction of Smads with Runx2 [301]. It is a member of the Runt-domain family of transcription factors, which includes AML1/Runx1 which regulates hematopoiesis.

1.14.6 Other Transcription Factors Involved in Cartilage and Bone Synthesis Include

1.14.6.1 ATF-2, Pbx-1

Activating transcription factor-2 (ATF-2), a basic region leucine zipper protein, regulates chondrocyte proliferation in the growth plate with mediation by cyclin D1. Pbx 1 is a homeodomain protein that regulates chondrocyte proliferation and delays hypertrophic chondrocyte formation.

1.14.6.2 Osterix

Osterix (OSx) is a transcription factor acting downstream from Runx2 in osteoblast formation. After Runx2 allows mesenchymal cells to differentiate to pre-osteoblasts, it is osterix that enhances the next step to actual osteoblast formation.

1.14.6.3 Msx1, Msx2

These homeodomain-containing transcription factors appear needed for membranous bone formation and may act upstream of Runx2.

1.14.6.4 Dlx5, Dlx6

Dlx5 and Dlx6 are members of the distal less homeodomain-containing family of transcription factors present in developing craniofacial, axial, and appendicular bone.

1.14.7 Hedgehog Proteins. Sonic Hedgehog and Indian Hedgehog

Sonic hedgehog (Shh), a secreted protein, was isolated by Riddle et al. [276] in 1993 in the chick and by Kraus et al. [271] and Echelard et al. [225]. Indian hedgehog (Ihh) was isolated by Lanske et al. [302] in 1996. It is expressed temporally slightly after Shh and regulates chondrogenic differentiation but both Shh and Ihh have similar activities. The hedgehog proteins are a family of secreted signaling molecules that help initiate cell patterning in early embryogenesis and cartilage formation in skeletal development [303]. Shh is a vertebrate homolog of the drosophila segment polarity gene which localizes in the ZPA in chick wing bud, the posterior mesenchyme of mouse limb buds as well as Xenopus and zebra fish [267]. Shh appears to pattern the antero-posterior limb axis. Like all the other signaling molecules, Shh is expressed in many regions of the early embryo long before limb bud formation is initiated [266]. Its expression (in mouse, rat, and chick) coincides with formation of the embryonic floor plate dorsal to the notochord that induces differentiation of neural cells of the central nervous system including the ventral spinal cord. When seen in developing limbs, Shh is expressed in a cluster of posterior mesenchymal cells as noted above. The temporal and spatial pattern of Shh expression suggest a close association between the gene and the organizing activity within the zone of polarizing activity (ZPA), thus serving as the molecular basis of the ZPA.

The hedgehog family of proteins controls cell growth, fate, and patterning of almost every region/organ in the vertebrate body. This variability of a single morphogen is dependent to a great extent on subtle interactions relating to the responding cell and the amount and timing of exposure to hedgehog. The hedgehog gradient is shaped by several interacting proteins for processing, secretion, and transport through tissues. Multiple feedback loops are established. Varjosalo and Taipale have reviewed Shh control of mouse development from embryo to adult in multiple organs and including involvement in such formative activities as vasculogenesis, left–right axis determination, and dorso-ventral axis patterning [304].

Shh regulates the number and type of digits that form in both upper and lower extremities. Shh in the ZPA partially directs digit formation forming a gradient across the limb and acting as a morphogen using mechanisms of differing time periods of exposure. Cells react to the time they reside in the ZPA at maximal Shh concentrations with information on diffusing Shh concentrations recognized after they have left the ZPA. In the mouse, digit 1 formation is Shh-independent, cells of digit 2 and much of digit 3 respond to low Shh diffusing activity, and cells of digits 4 and 5 are exposed to maximal Shh due to a longer period of time in the ZPA. Shh

also plays a role in patterning the interdigital mesenchyme which acts as a secondary signaling center forming digit types through another molecule BMP. In summary Shh stimulates expansion of the limb bud directly and via expression of FGF in the apical ectodermal ridge. Digital progenitors are displaced relative to the ZPA such that cells are exposed to Shh for varying times. This exposure to different total amounts of Shh results in differential patterning of the interdigital mesenchyme which influences digit growth through BMP signaling in metacarpal/metatarsal and phalanx forming regions. In the 5 digits of the mouse this wave of exposure via diffusion with varying concentrations and times of exposure leads to 2 digits derived from Shh-expressing tissue, 2 from lower amounts of Shh, and 1 not exposed to Shh [280, 281]. Shh can induce extra digit formation in the anterior margin of a limb bud. It is currently unclear whether Shh acts as a morphogen itself or exclusively induces the expression secondarily of other signaling molecules. Shh induces FGF-4 in the AER, induces the local expression of Hox-d-13 (needed for limb patterning), and induces the local expression of BMP-2. It has also been found that retinoic acid induces expression of Shh, which then activates Hox d-11 expression.

Indian hedgehog (Ihh) is expressed in the pre-hypertrophic chondrocytes of cartilage where it regulates the rate of hypertrophic differentiation [305]. It works by inducing the expression of a second signal involving PTHrP (the parathyroid hormone-related protein) which then signals to its receptor in the pre-hypertrophic chondrocytes. Ihh has been expressed in developing cartilage. Vortkamp et al. [306] using in situ hybridization in varying stages of chick embryos studied by whole mount preparation detected Ihh in the endoderm of the developing mid-gut, in the lung, and in the cartilage of the developing long bones of the limbs. It was not expressed early in development while sonic hedgehog was expressed in the posterior mesenchyme, suggesting that the two had different roles and that Ihh acted later in the developmental sequence in forming skeletal elements. Type X collagen was expressed only in hypertrophic cells whereas Ihh was expressed in the transitional region between proliferating and hypertrophic chondrocytes and was actually excluded from hypertrophic cells. Ihh was expressed at a specific critical stage of endochondral bone formation. It controls the normal proliferating columns of chondrocytes in the growth plate. Ihh expression, therefore, preceded the hypertrophic state while BMP6 overlapped both the Ihh and the Type X collagen expression domains at each stage. Ihh also acts on the perichondrium to initiate a negative feedback loop that regulates the hypertrophic differentiation process. When Ihh expressing cells underwent the final differentiation steps to become hypertrophic chondrocytes, they turned off the expression of Ihh thereby allowing more cells to commit to the differentiation pathway. Vortkamp et al. felt that the negative feedback loop initiated by Ihh was mediated by the perichondrium and in particular by the parathyroid hormone-related protein expressed there. They concluded that both Ihh and PTHrP repressed hypertrophic cartilage differentiation and that Ihh can induce PTHrP. Ihh plays no role in osteoblast differentiation. A third hedgehog protein, desert hedgehog (dhh), is expressed in the Sertoli cells of the testis [304].

1.14.8 Fibroblast Growth Factors (FGFs)

The fibroblast growth factors (FGFs) are a group of signaling molecules which play a major role in normal developmental and physiological processes [282, 307–310]. The FGF gene family currently comprises 22 members all of which are structurally related and generally encode proteins with a molecular mass of 17–34 kDa [309]. They can generate hundreds of protein isoforms by varying their RNA splicing or initiating codons. FGF-1 and FGF-2 have been studied extensively. FGFs are potent mitogens with cells of mesodermal, neuroepidermal, ectodermal, and endodermal derivatives. Their normal physiological activities in vivo include embryonic and fetal development, neovascularization, and response to wounding. Some FGFs are oncogenes and FGF-4 is one of the most frequently identified oncogenes in cell transformation. The different isoforms generated among certain of these molecules would underlie additional functions and further diversity occurs by a multitude of post-translational modifications. FGFs transduce signals to the cytoplasm through a family of transmembrane receptor tyrosine kinases referred to as the FGF receptors (FGFRs) and four mammalian FGFR genes are known. When an FGFR binds an FGF it activates a dormant intracellular tyrosine kinase to phosphorylate certain proteins and lead to various functions.

In situ hybridization studies show that FGFs are widely expressed during limb development. During the development of the vertebrate limb bud FGF-4 has been found to be synthesized by the apical ectodermal ridge, primarily in its posterior half, which itself has been implicated in outgrowth of the developing limb by maintaining proliferation of underlying cells in the progress zone [282, 307] (Fig. 1.18g). FGF-4 can substitute for the AER in maintaining the polarizing region and can provide almost all the signals necessary for the complete outgrowth and patterning of the chick limb.

FGFs have been shown not only to induce limb bud formation, but also to help maintain the proliferation of limb bud mesenchyme cells. It has been shown that beads soaked in FGF-1, FGF-2, or FGF-4 placed in the presumptive flank of chick embryos induce formation of ectopic limb buds which can then develop into complete limbs. These results suggest that local production of an FGF may initiate limb development. Cohn et al. [311] interpreted their experimental data to

indicate that under the influence of FGF, lateral plate mesoderm cells continue to proliferate and that the FGF led to local activation of sonic hedgehog in cells with potential polarizing activity thus establishing a polarizing region. A progress zone was then established and further maintained by the activation of Hox-d genes. Cells in the progress zones produced a signal that induced formation of a formal AER in the overlying epithelium. The FGF thus served to establish a limb bud not only with a polarizing region, but also with a progress zone and an AER. Newly induced AER then produced FGF-4 which maintained the limb bud and led to the outgrowth and subsequent normal patterning seen.

It is FGF-8 that is responsible for the induction, initiation, and maintenance of chick limb development [312]. FGF-8 gene expression occurs in the ectoderm overlying the prospective limb forming territories after which continuing FGF-8 secretion initiates limb bud formation. This is done by promoting the expression of sonic hedgehog (Shh) in the lateral plate mesoderm. Many studies have indicated that signaling molecules from the AER regulate limb development by their influence on cells at the distal tip of the limb bud mesoderm referred to as the progress zone. The progress zone cells are also influenced by signals from the zone of polarizing activity (ZPA) region of mesoderm at the posterior margin of the limb bud and by signals from the ectoderm coming from Shh and WNT-7A. Evidence indicates that FGF-8 functions to induce limb formation, plays a role in the initiation of limb bud outgrowth, and helps in the establishment of subsequent limb development including maintaining the outgrowth and pattern formation in established limb buds. FGF activity is necessary for the initiation of Shh expression at the limb bud posterior margin. FGF-18 is involved with osteoblast differentiation and FGF-2 plays a major role in angiogenesis.

FGF-9 promotes angiogenesis and has been shown in mice to play a positive role in fracture repair [313]. It does this by initiating angiogenesis through VEGF activation. FGF-2, -9, and -18 and receptors (FGFR 1–3) play a major role in skeletal development.

The mammalian FGF family is composed of 18 ligands that elicit their actions through four transmembrane tyrosine kinase receptors—FGFR1, FGFR2, FGFR3, FGFR4. The FGFs have been used extensively in investigating their repair-enhancing potential. FGF2 in particular has been used in many bone repair models [310].

1.14.9 Wnt Family Proteins

The Wnts are a family of cysteine-rich glycoproteins with 19 members in vertebrates [314]. The Wnt genes encode secreted proteins that act as signaling molecules and associate with cell surface and extracellular matrix. They have been implicated in many embryonic developmental processes including the regulation of cell fate in pattern formation. Wnt signaling controls cell proliferation, stem cell maintenance, cell fate decisions, organized cell movements, and tissue polarity. Wnt 7a was noted to be expressed in the dorsal ectoderm and subsequent studies showed dorsal-to-ventral transformations of cell fate indicating that Wnt 7a is a dorsalizing signal [283]. It was also noted to act not only in the dorsal–ventral plane but also along the anterior–posterior axis. Subsequent studies showed that all three axes (dorsal-ventral, proximal-distal, and antero-posterior) are intimately linked by respective signals Wnt 7a, FGF-4, and Shh during limb development [282]. Wnt signaling has been implicated in several aspects of the endochondral bone formation sequence. Wnt ligands bind to receptors of the Frizzled family of proteins and transduce signals to ß-catenin which enters the nucleus and activates transcription of target genes. Owing to the large number of Wnt proteins (19) as well as frizzled receptors (10 in mice and humans) a huge array of possible reactions can occur. These can be partially categorized as ß-catenin dependent and ß-catenin independent [315, 316]. Wnt/ß-catenin signaling (canonical Wnt signaling) is a key signaling pathway required for normal bone and cartilage formation and for bone homeostasis [317]. The extent to which this pathway (with its multiple normal and abnormal variations re Wnt proteins, receptors, and mutations) contributes to the skeletal system is reviewed and referenced in detail by Baron and Kneissel [318]. WNT signaling plays a major role in chondrogenesis [319] with WNT 9a implicated in regulation of Ihh during chondrogenesis [320] Wnt-5a is expressed in the perichondrium and Wnt-5b in pre-hypertrophic chondrocytes.

1.14.10 Transforming Growth Factors—Beta (TGFβ) Superfamily

Another important group of secreted signaling molecules relating to development in general and that of the skeletal system in particular is the transforming growth factor-beta (TGF-β) family of peptide growth factors [269]. The transforming growth factor-beta superfamily consists of 33 genetically related polypeptide growth factors [321, 322]. They are often subdivided into four groups: (1) TGF-β family (TGF-βs 1–5); (2) Activin/inhibin family; (3) BMP/Dpp/Vg1 family; (4) BMPs 2–8 and the Mullerian inhibitory factor. More recent studies indicate that five distinct TGF-β proteins (1–5) have been characterized from multiple vertebrate sources. The TGF-β family consists of four distinct proteins, TGF-β 1, 2, 3, and 5, with TGF-β 4 subclassified under the TGF-β 1 group. TGF-β localization preceded a marked increase in type II collagen mRNA expression in transitional chondrocytes suggesting a role for TGF-β in the induction and synthesis of extracellular matrix.

TGF-β has a role in the coupling of new bone formation to bone and cartilage resorption during skeletal development. Bone itself represents the most abundant source of TGF-β in the body. It is present and regulative of bone formation, chondrocyte and osteoblast proliferation, and has also been shown to be produced by growth plate chondrocytes. It also plays a role in inhibiting osteoclast formation and activity. Coordinate expression of TGF-β 1 -β 2 -β 3, and -β 4 has been demonstrated in chick embryo chondrocytes in vivo. TGF-β 1, 2, and 3 have been localized to transitional and hypertrophic chondrocytes and osteoblasts, cells that are all involved in the calcification of extracellular matrix [323]. The appearance of TGF-β in growthplate chondrocytes appears to coincide with changes in the morphology of the cells as they pass from the proliferating to the hypertrophic zone. In the growth plate TGF-β functions as a stimulator of proteoglycan synthesis. Other studies have shown that TGF-β 1 prevents terminal differentiation of epiphyseal chondrocytes into hypertrophic cells [324]. In general, the TGF-β molecules stimulate the formation of extracellular matrix in connective tissues by increasing the transcription of genes and coding of many extracellular matrix proteins. The largest amounts of the TGF-β peptides have been found in bone and cartilage matrix. Studies have shown that TGF-β 1 and TGF-β 2 promote the chondrogenic differentiation of chick limb mesenchymal cells in culture.

The signaling pathway for TGF-ß passes from the cell membrane through the cytoplasm into the nucleus. SMADs (also see below) are key components of the signal transduction pathways [322, 325–327].

1.14.11 Bone Morphogenetic Proteins (BMPs)

BMPs are signaling molecules known to induce cartilage and bone differentiation but also to play an important role in early limb patterning and even earlier in generalized embryogenesis [99, 244, 328]. The BMPs are part of the larger transforming growth factor β family and now comprise 20 members. High levels of BMP-4 expression are seen in the embryo in the posterior primitive streak and in ventral mesoderm around the posterior gut and umbilical blood vessels as well as in the body well. BMP-4 thus plays a role specifying posterior and ventral mesoderm. Expression of BMP-4 is subsequently seen in many tissues undergoing mesenchymal–epithelial interactions. In the limb itself, there is expression of BMP-4 throughout the mesenchyme with subsequent strong expression seen in the AER. BMP-2 and BMP-4 are expressed early in limb bud formation and are present both in the ZPA and the AER. BMPs initiate cartilage and bone formation in a sequential cascade. Cartilage and bone differentiation during the endochondral sequence involves a series of steps involving initiation, promotion, maintenance, modeling, and termination events. The various signaling factors are defined at the molecular level with much focus on the BMPs which promote almost every aspect of chondrogenesis from commitment to terminal differentiation [329, 330]. Regulatory signals by the several growth factors precede and control the deposition of the structural macromolecules of the extracellular matrix such as the collagens, proteoglycans, and other glycoproteins. The exact mechanisms of BMP action during chondrogenesis remain unclear but interactions between BMP pathways and other pathways are being identified including with Smad pathways, FGF pathways, and the Ihh/PTHrP pathway [330–332]. BMPs 2, 3, 4, 5, and 7 are expressed in perichondrium and BMPs 2 and 6 in hypertrophic chondrocytes. The BMP family itself, which now includes subtypes, has three distinct subfamilies crucial for bone development, BMP-2, BMP-4, and BMP-5-8.

1.14.12 Parathyroid Hormone (PTH), Parathyroid Hormone Receptor Protein (PTHrP), and PTH/PTHrP Receptor

Parathyroid hormones, parathyroid hormone receptor protein (PTHrP), and the PTH/PTHrP receptor each play a role in modulating skeletal development [302, 306]. These important autocrine/paracrine factors have been identified in the growth plate chondrocytes. PTH and PTHrP also act mitogenically on the growth plate chondrocytes through the PTH/PTHrP receptor. It is also felt that PTHrP inhibits type X collagen expression. It is the Indian hedgehog (Ihh) growth factor which induces secretion of the PTHrP by the growth plate chondrocytes. The PTHrP stimulates proliferation of chondrocytes and prevents their early hypertrophy in the growth plate. It thus regulates the rate at which proliferative chondrocytes leave the cell cylcle and become hypertrophic chondrocytes. The effects of Ihh and PTHrP on chondrocyte differentiation are mediated by the PTH/PTHrP receptor.

1.14.13 Insulin-Like Growth Factor (IGF)

The insulin-like growth factors are regulatory molecules which also play important roles in skeletal development. IGF-1 stimulates longitudinal skeletal growth during the fetal period and throughout postnatal growth until skeletal maturation. It functions by mediating growth hormone actions on the growth plate and independently has the capacity to stimulate both chondrocyte proliferation and matrix synthesis. IGF-2 appears active in fetal life but its post-natal role is uncertain. There is a high degree of interaction between the IGFs and FGFs. The action of IGF-1 is such that it mediates completely the effects of growth

hormone which does not act directly on the cells. The activity involves effects on the IGF-1 receptor. The effects of growth hormone are mediated by their ability to produce growth factors such as the insulin-like growth factors. Receptors for both IGF-1 and IGF-2 have been found in the growth plate.

1.14.13.1 Thyroid Hormones

The thyroid hormones also exert their effects on growth and in particular on the growth plate via mediation of the IGFs. Thyroxine (T_4) and triiodothyronine (T_3) act on the proliferative and upper hypertrophic zone chondrocytes by increasing DNA synthesis in cells and increasing cell maturation, proteoglycan and collagen synthesis, and alkaline phosphatase activity. This effect on cartilage, however, is mediated by the insulin-like growth factors. The effect appears to be mediated almost exclusively via IGF-1. IGF-1 is present in the growth plate where it mediates the action of growth hormone.

1.14.14 Vascular Endothelial Growth Factor (VEGF)

The vascular endothelial growth factor (VEGF) family are glycoproteins that stimulate endothelial cells and induce angiogenesis [114, 115, 333–336]. VEGF plays a major role in endochrondral bone formation immediately preceding vascular invasion of hypertrophic chondrocyte regions with accompanying bone formation at the metaphyseal side of the growth plate and within the epiphysis as the secondary ossification center forms. VEGFA controls both vasculogenesis and angiogenesis [335]. (Vasculogenesis is the de novo formation of vessels and angiogenesis is the growth of new vessels from pre-existing vessels by sprouting). VEGFB plays a role in cardiac and coronary vessel development, VEGFC controls the earliest lymphatic endothelial cell migration in the embryo during lymphangiogenesis, and VEGFD plays a role in vascular development specifically in relation to Sox 18 [334, 336]. VEGFE and VEGFF have also been described [336]. The best studied VEGF and that most specifically relating to bone development is VEGFA, which has four isoforms of 121, 165, 189, and 206 amino acids. VEGF reacts with three specific receptors VEGFR-1, VEGFR-2, and VEGFR-3. Gerber et al. demonstrated that VEGF mediated capillary invasion into the lower hypertrophic zone of the growth plate, an essential component of bone formation via the endochondral ossification mechanism [115]. The hypertrophic chondrocytes themselves expressed the VEGF. VEGF, secreted by the condensing mesenchyme of the forming skeleton in the limb bud, regulates the formation and patterning of the limb vasculature [334]. The vascular development occurs with VEGFmodulating Sox 18 activity [334]. There are a number of VEGF secreted glycoproteins; VEGF-A, VEGF-B, VEGF-C, VEGF-D, as well as VEGF-E, -F, and -b [335]. VEGF-A is the most common variant with isoforms of 121, 165, 189, and 296 amino acids having slightly varying activities regarding proteoglycan binding. VEGF works via three receptors VEGFR-1, VEGFR-2 and VEGFR-3. Maes has reviewed the specific regulation of the vascularization process in endochondral bones [336].

1.14.15 Growth/Differentiation Factor-5 (GDF-5)

Growth differentiation factor-5 (GDF-5) is a protein related to the bone morphogenetic protein (BMP) family and thus a member also of the TGF-ß superfamily. It was previously referred to as BMP 14. GDF-5 plays a major role in joint and cartilage development [337]. It promotes the initial stages of chondrogenesis being involved in cell adhesion, in early chondrocyte differentiation and condensation, and then in increasing proliferation in epiphyseal cartilage adjacent to its expression within the joint interzone. It is most prominent in the distal limbs involving the digital joints where it restricts joint development to the appropriate locations. GDF-5 is also expressed in other joints of the limbs. Joint formation is also directed by Wnt 9a [337]. Recently, Sox 11 has been shown to contribute to the regulation of GDF-5 during joint formation and maintenance [338].

1.14.16 Signal Transduction Pathways

Several molecules respond to the induction influences of the paracrine factors. These molecules include the membrane receptors of the responding cell, which bind the paracrine molecules, and the cascade of interacting proteins that transmit a signal through a pathway to the nucleus. The activated receptor catalyzes reactions that phosphorylate intracellular proteins, activating them to eventually activate or repress a set of genes.

The major signal transduction pathways are briefly outlined.

(i) Receptor Tyrosine Kinase (RTK) Mitogen. Activated Protein Kinase Pathway. This pathway is critical in numerous developmental processes. An RTK binds its specific ligand (such as FGFs, epidermal growth factors, platelet-derived growth factors). The RTK spans the cell membrane and when binding with it the ligand undergoes change enabling it to dimerize with another RTK. A series of reactions occur eventually activating extracellular signal-regulated kinase (ERK) by phosphorylation and ERK can then enter the nucleus and phosphorylate certain transcription factors.

(ii) Smad Pathway. TGF-β ligands activate members of the intracellular Smad family of transcription factors. Smad 2 and Smad 3 are involved with the TGF-β/activin, nodal and myostatin pathways, and Smad 1/5/8 with the BMP and GDF (growth differentiation factors) pathways. The phosphorylated Smads bind to Smad 4 and form the transcription factor complex that will enter the nucleus. Both Smad-dependent and Smad-independent pathways are involved with TGF-β signaling. TGF-β and BMPs both signal through transmembrane serine/threonine kinase receptors. In each pathway there are two kinds of receptors, type I and type II. Ligand binding induces formation of heterotetramers containing two type II and two type I receptors, which allows the active type II receptor to phosphorylate a glycine–serine rich region in the type I receptor. This initiates signaling through the Smad pathway with the phosphorylated glycine-serine region providing a docking site for the receptor-regulated Smad proteins (R-Smads) [322, 325–327].

(iii) JAK-STAT (signal transducers and activators of transcription) is an important pathway transducing information on the cell membrane to the nucleus. Ligand → receptor → Jak (a family of tyrosine kinases) → phosphorylate inactive STATs → dimerized STATS which are then translocated into the nucleus. The STAT pathway is important in regulating fetal bone growth.

1.15 Chemistry of the Extracellular Matrix of Epiphyseal Tissues

The three primary molecular constituents of epiphyseal cartilage are collagens, proteoglycans, and non-collagenous proteins most of which are glycoproteins and phosphoproteins. The connective tissues such as cartilage, bone, tendon, ligament, and fascia are composites in a material sense of insoluble fibers and soluble polymers. The principal fibers are collagen and elastin while the principal polymers are proteoglycans and glycoproteins. Tissues such as tendon which must withstand large tensional forces are rich in collagen while those like cartilage which are subject to compressive forces contain high levels of proteoglycans. Type II collagen and the proteoglycan aggrecan make up 90 % of the organic cartilage matrix.

1.15.1 Collagen

At present 28 genetically distinct types of collagen have been defined [339] (Table 1.11). Approximately 80 % of the total body collagen is types I and II. The common structural feature of the collagens is a triple helix that ranges from most of their structure, 96 % in collagen I, to <10 % in collagen XII. Some molecules, not formally defined as collagens, contain a collagen-like one triple-helical domain and are referred to as "soluble defense collagens" or membrane collagens (such as gliomedin). The collagen specific for cartilage including the epiphyseal growth plate is type II collagen [340]. Several of the defined minor collagens, so named because they are present in relatively small amounts, have been localized to cartilage in particular types IX, X, and XI where they are crucial for tissue structure. Types VI, XII, and XIV also have a small cartilage presence. Type X collagen is localized in the matrix of the hypertrophic zone and has been hypothesized to play a major role in allowing for mineralization of the cartilage matrix which occurs at that specific level.

The collagen molecule is composed of three polypeptide chains which are defined as alpha chains and are assembled into a triple helix with a coiled coil conformation [341–343] (Fig. 1.20a). In the major fibrillar collagens, including types I, II, and III, each alpha chain is composed of approximately 1,055 amino acids. In type I collagen, there are two identical alpha 1 chains and one distinct alpha 2 chain assembled into the triple helix. Type II collagen is composed of three alpha 1 (2) chains. The primary structure of the protein is a repeating sequence of GLY-X-Y triplets with glycine (gly) present in every third position. Glycine is the smallest amino acid and its position is crucial for appropriate folding of the molecule. Glycine thus occupies a restricted space where the three helical alpha chains come together in the center of the triple helix. The most common amino acid in the X position is proline and the most common in the Y position is hydroxyproline. In collagen from mammals, approximately 100 of the X and 100 of the Y positions are proline and hydroxyproline, respectively. They are rigid amino acids which serve to limit rotation of the polypeptide backbone and thus contribute to the stability of the triple helix. The enzyme prolyl-4-hydroxylase converts approximately 100 proline residues in each polypeptide chain to 4-hydroxyproline. Ascorbic acid is a required cofactor for the reaction. Type II collagen is composed of three alpha 1 (2) chains.

The fibril-forming collagens are synthesized first as larger precursor molecules called procollagens. Each chain is originally synthesized intracellularly as a longer component involving both C-terminal propeptides and N-terminal propeptides referred to pro-alpha chains (Fig. 1.20b). The pro-alpha chains undergo proteolysis with severing of either propeptide following assembly, folding, and secretion of the procollagen molecule. The pro-alpha chain N-and C-propeptides at the amino- and carboxy-terminal ends of the molecule, respectively, are connected to the central triple

Table 1.11 Collagen types and the location of their genes on human chromosomes

Type	Gene	Chromosome	Expression
I	COL1A1	17q21.3-q22	Most connective tissues, including bone, tendon, ligaments, skin (dermis)
	COL1A2	7q21.3-q2	
II	COL2A1	12q13-q14	Cartilage, vitreous humor
III	COL 3A1	2q24.3-q31	Extensible connective tissues, e.g., skin, lung, vascular system
IV	COL4A1	13q34	Basement membranes
	COL4A2	13q34	
	COL4A3	2q35-q37	
	COL 4A4	2q35-q37	
	COL4A5	Xq22	
	COL4A6	Xq22	
V	COL5A1	9q34.2-q34.3	Tissues containing collagen I, quantitatively minor component
	COL5A2	2q24.3-q31	
	COL5A3		
VI	COL6A1	21q22.3	Most connective tissues
	COL6A2	21q22.3	
	COL6A3	2q37	
VII	COL7A1	3p21	Anchoring fibrils
VIII	COL8A1	3q12-q13.1	Many tissues, especially endothelium
	COL89A2	1p32.3-p34.3	
IX	COL9A1	6q12-q14	Cartilage; (tissues containing collagen II)
	COL9A2	1p32	
	COL9A3		
X	COL10A1	6q21-q22	Hypertrophic cartilage
XI	COL11A1	1p21	Cartilage; (tissues containing collagen II)
	COL11A2	6p21.2	
	COL12A1	12q13-q14	
XII	COL12A1	6	Tissues containing collagen I
XIII	COL13A1	10q22	Many tissues
XIV	COL14A1		Tissues containing collagen I
XV	COL15A1	9q21-22	Many tissues
XVI	COL16A1	1p34-35	Many tissues
XVII	COL17A1	10q34-35	Skin hemidesmosomes
XVIII	COL18A1	21q22.3	Many tissues, especially liver and kidney
XIX	COL19A1		Rhabdomyosarcoma cells
XX	COL20A1		FACIT
XXI	COL21A1	6p 11.2-12.3	FACIT
XXII	COL22A1	8q24.2	FACIT, at tissue junctions
XXIII	COL23A1	5q35	Transmembrane
XXIV	COL24A1	1p22.3	Fibril-forming, embryonic bone, and cornea
XXV	COL25A1	4q25	Brain-specific membrane associated
XXVI	COL26A1		Beaded-filament forming
XXVII	COL27A1	9q32	Fibril-forming
XXVIII	COL28A1	7p21.3	Beaded-filament, von Willebrand factor a domain-containing protein

From Prockop, Kivirikko Ann Rev Biochem 1995;64:403–434 (Ref. [348]), Kadler et al. J Cell Sci 2007;120:1995–1958 (Ref. [339]), and Ricard-Blum Cold Spring Harb Perspect Biol. doi:10.1101/csgoersoect.a004978

helical collagen domain by short sequences which are themselves non-triple helical that contain cleavage sites for the proteinases that process pro-collagen to collagen in the extracellular matrix. A folding into the triple helix occurs by spontaneous self-assembly in a specific zipper-like fashion from the carboxy (C-) terminal toward the amino (N-) terminal end of the molecule for fibrillar collagens (Fig. 1.20c). For the membrane collagens (XIII, XVII, XXIII, and XXV) the triple helix is initiated from the amino terminus. As noted above, the stability of the triple helix is dependent greatly on the presence of glycine residues at every third position in each of the three pro-alpha chains. Once the pro-alpha chains have been synthesized, significant post-translational changes occur which are integral to normal collagen formation [340, 342, 343].

Intracellular steps in procollagen synthesis include: (1) hydroxylation of the proline residues to hydroxyproline and of lysine residues to hydroxylysine; (2) glycosylation of hydroxylysine residues to form galactosyl hydroxylysine and glucosyl-galactosyl-hydroxylysine; (3) addition of a mannose-rich oligosaccharide to one or both propeptidases; (4) association of C-terminal propeptides; and (5) disulfide bonding to enhance chain association. Each of the above-listed post-translational changes occurs in the intracellular position with the subsequent changes extracellular (97). In the amino-terminal propeptides of Type I procollagen, cysteine is present and forms intrachain disulfide bonds whereas in the carboxy-terminal propeptides, the cysteine is involved in both intrachain and interchain disulfide bonds. The propeptides account for one-third of the bulk of the procollagen molecule. They serve to direct assembly of the triple helix. After the C-propeptides have associated the triple helix begins to form in zipper-like fashion towards the N-terminus. The protein, which is assembled in the rough endoplasmic reticulum, then passes through the Golgi complex before leaving the cell.

The extracellular conversion of procollagen to collagen requires two enzymes, a procollagen amino protease that removes the amino-propeptides and a procollagen carboxy protease that removes the carboxy-propeptides. Once cleavage of the procollagen ends occurs, the collagen

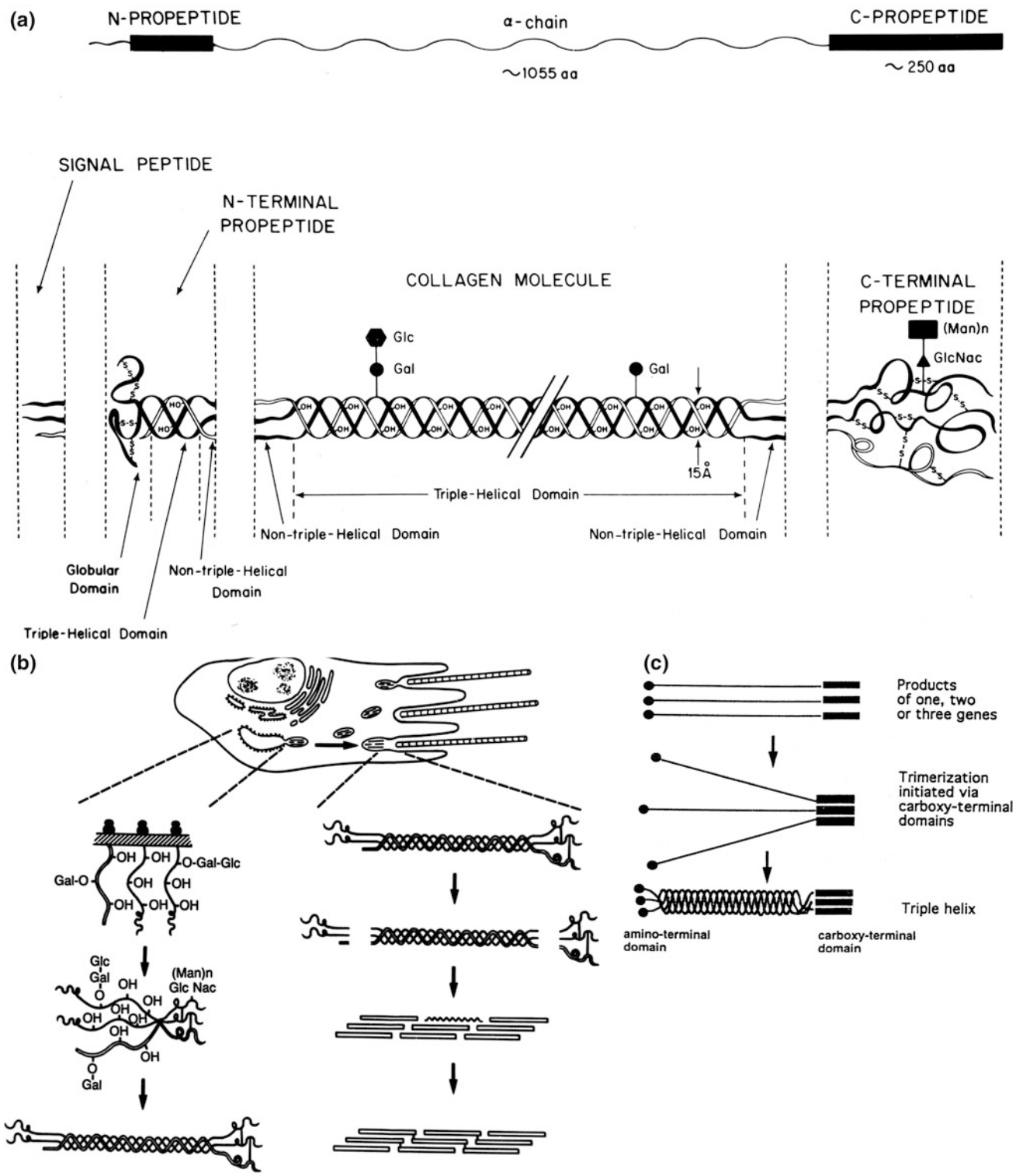
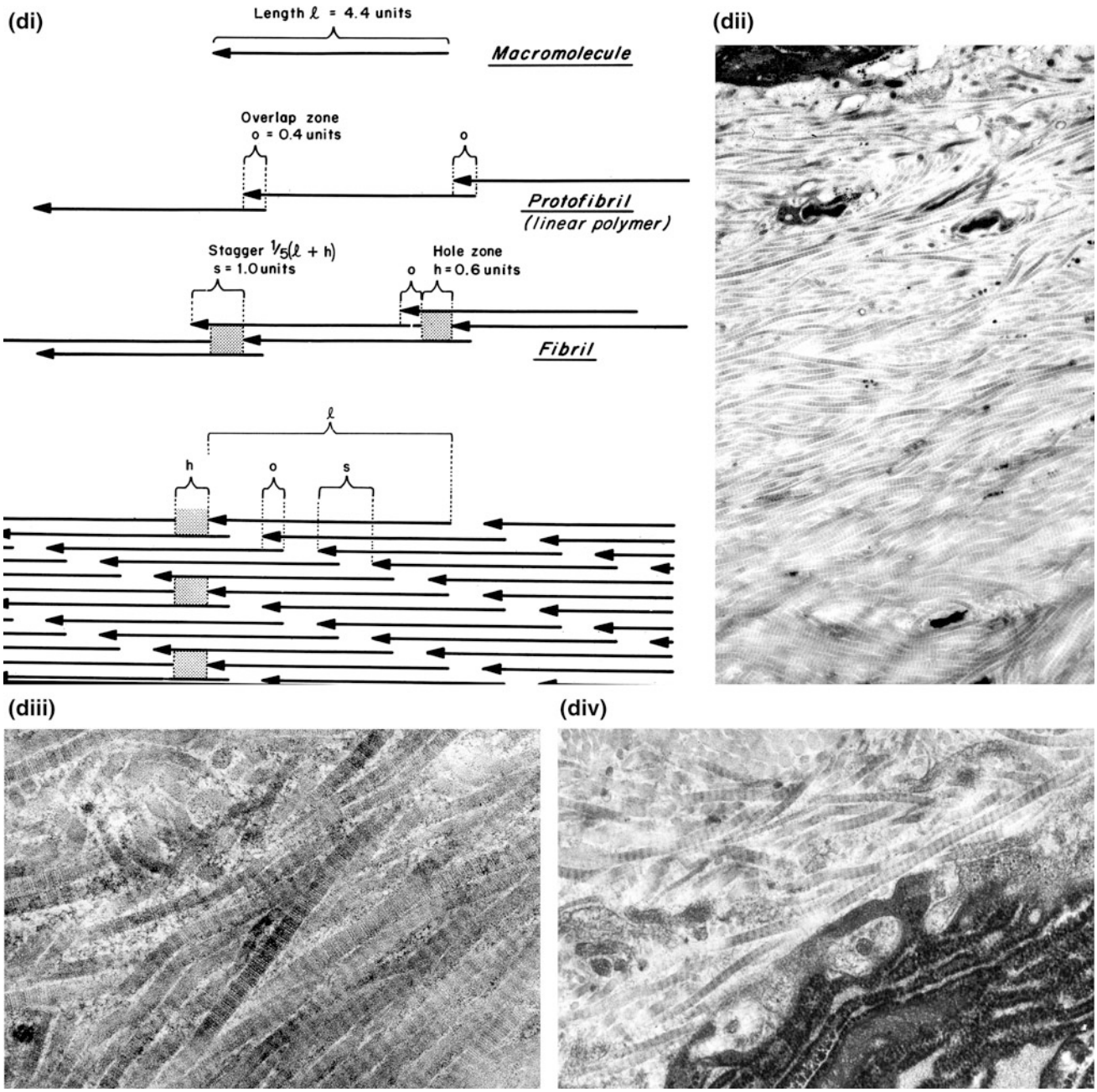


Fig. 1.20 (continued)



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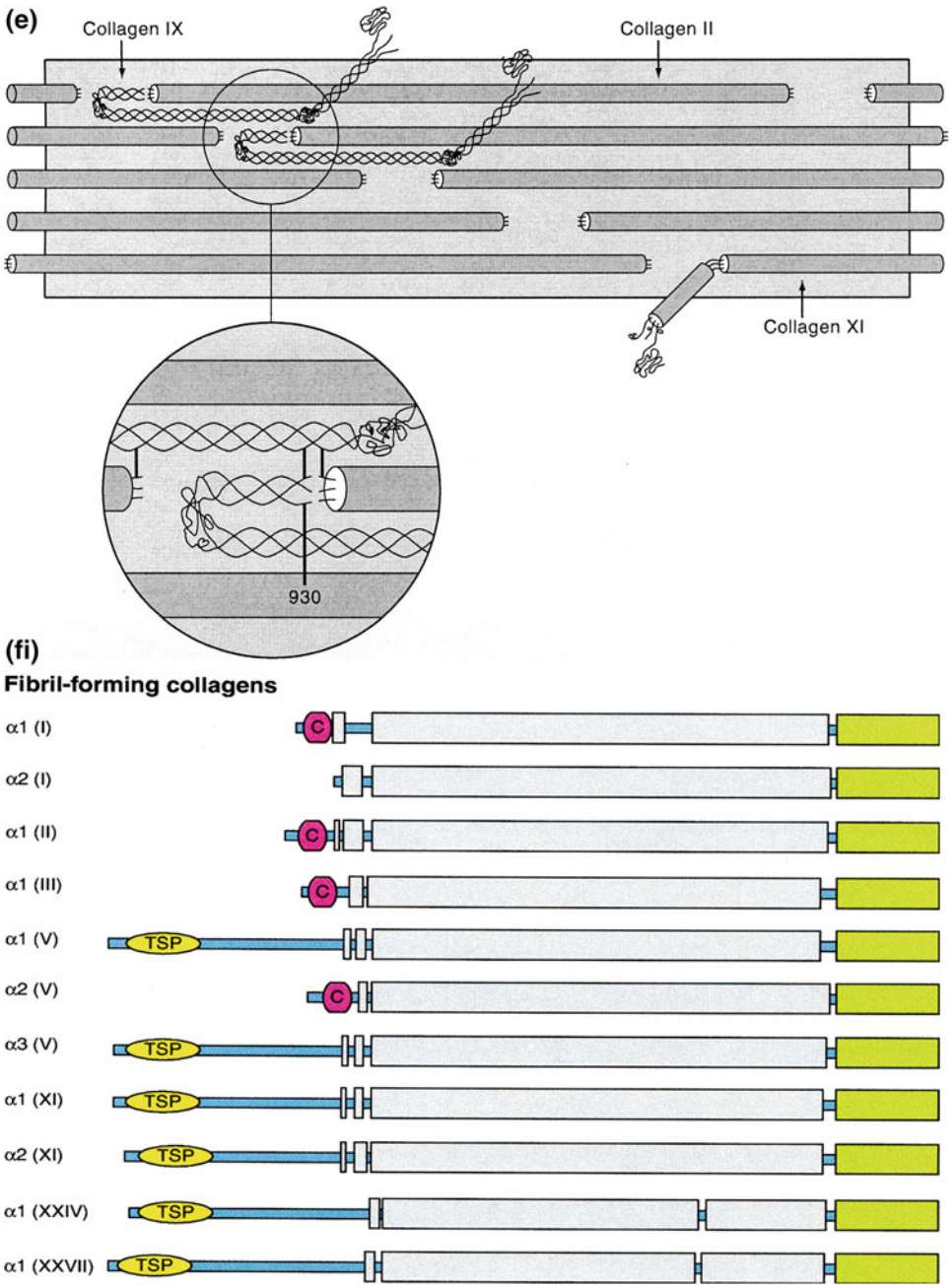


Fig. 1.20 (continued)

molecules remain free in the extracellular matrix and then spontaneously assemble into fibrils (Fig. 1.20b). Extracellular processing involves (1) conversion of procollagen to collagen; and (2) cross-linking which is mediated through lysine and hydroxylysine residues [340, 342–346]. Lysyl oxidase allows for conversion of small lysyl and hydroxylysyl residues of collagen to reactive aldehydes. Two major types of cross-links then form. The first are referred to as intramolecular cross-links that join alpha chains of the same molecule and are formed by aldol condensation of two of the aldehydes. Intermolecular cross-links involve condensation between an aldehyde derived from lysine, hydroxylysine, or glycosylated hydroxylysine and the amino group of a second lysine, hydroxylysine, or glycosylated hydroxylysine. They are Schiff bases. The main reducible cross-link is dihydroxylysinonorleucine. The major cross-links in skeletal tissues are the three hydroxypyridinium cross-links derived from three hydroxylysyl residues [344]. They are particularly abundant in adult bone and cartilage. The dihydroxylysinonorleucine cross-links decrease progressively with tissue maturation while the hydroxypyridinium molecules increase with time (Table 1.12).

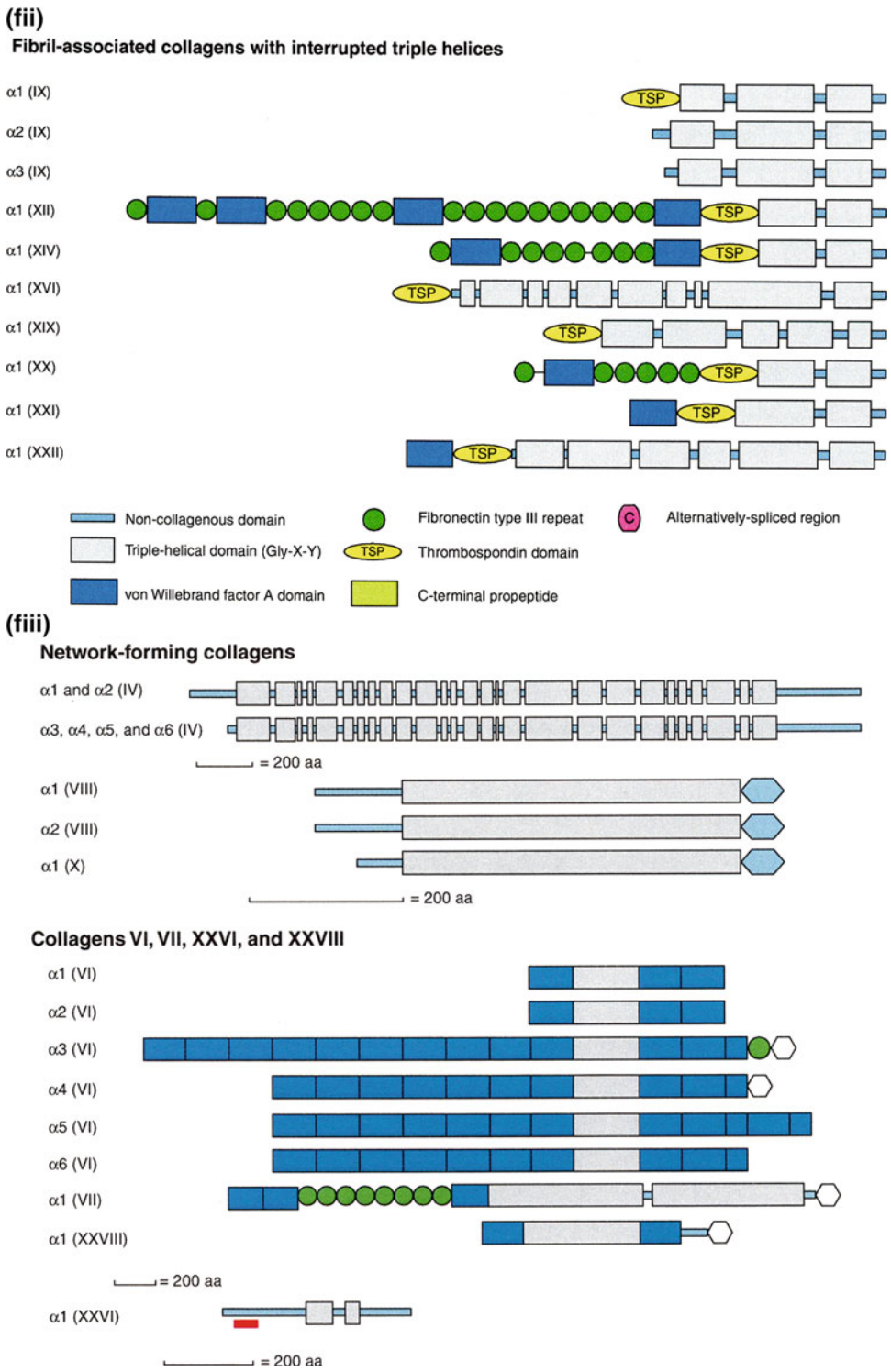


Fig. 1.20 (continued)

After secretion from the cell, the procollagen molecules are enzymatically cleaved to collagen and the collagen then self-assembles into fibrils. The triple helical collagen molecule is approximately 300 nm long and 1.5 nm in diameter. Fibrils are formed by the lateral and longitudinal association of the triple helical molecules to each other. Each type I collagen molecule relates to the adjacent molecule in a quarter-staggered array such that the composite fibril by electron microscopy appears as a striated pattern (Fig. 1.20d). The cross-striations represent surface staining of the cylindrical

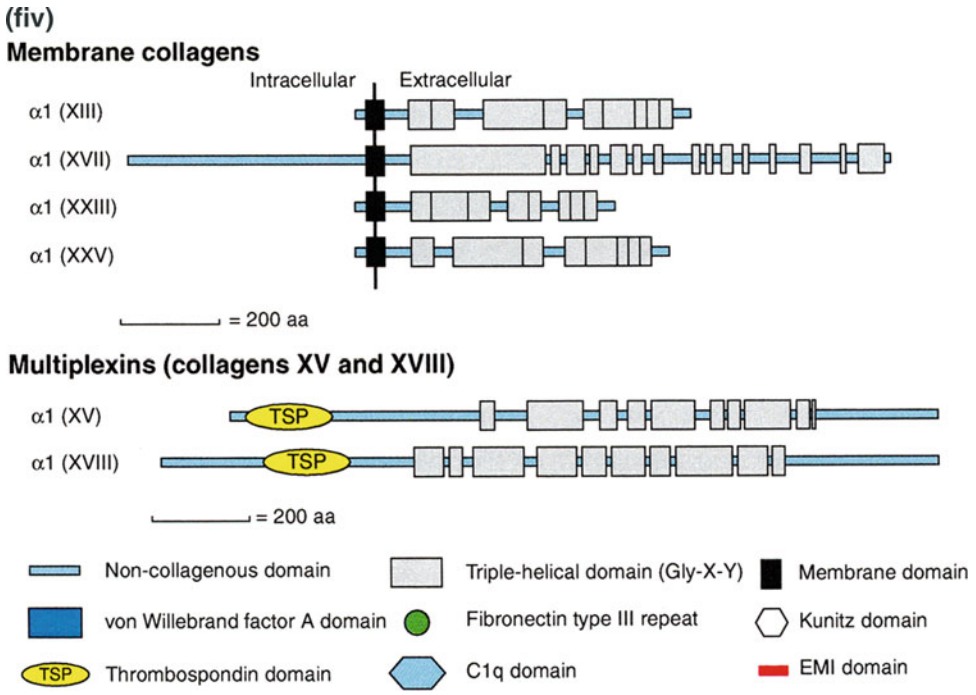


Fig. 1.20 Various aspects of collagen formation are shown. **a** The components of a characteristic fibrillar collagen molecule are shown (from Olsen, BR, In: Cell Biology of Extracellular Matrix. Ed ED Hay, 2nd edition, Plenum Press, New York). (Reprinted with permission from Olsen BR, Collagen biosynthesis in ED Hay (ed): Cell Biology of Extracellular Matrix. 2nd edition. Copyright 1991 Springer Science + Business Media). **b** The intracellular (*left*) and extracellular (*right*) steps in collagen synthesis are shown. (Reprinted with permission from Prockop DJ, Mutations in collagen genes as a cause of connective-tissue diseases. New Engl J Med. 1992;326:540–546. Copyright 1992 Massachusetts Medical Society). **c** Mechanism of post-translational assembly of fibrillar collagen is shown. (Reprinted with permission from Francomano CA, Key role for a minor collagen. Nature Genet. 1995;9:6–8. Copyright 1995 Nature Publishing Group). **d** The characteristic ultrastructural appearance of type I (fibrillar) collagen is shown. **di** Characteristic staggered packing of collagen fibrils leads to development of hole zones where mineralization is initiated. These fibrillar arrangements contribute to the cross-banding seen in collagen fibers when sectioned along the longitudinal axis and viewed by electron microscopy after demineralization. **dii**, **iii**, **iv** Electron micrographs of newly synthesized bone collagen show woven pattern and typical fiber cross-banding. These individual fibers are usually in the 70–120 nm range (diameter). An active osteoblast in this figure **div** is adjacent to collagen fibers just synthesized by the cell. **e** Type IX and type XI collagen are closely related in position to the much larger type II collagen molecule. These are primary components of type II collagen in cartilage. (Reprinted with permission from Olsen BJ, New insights into the function of collagens from genetic analysis. Curr Op Cell Biol. 1995;7:720–727. Copyright 1995 Elsevier). **f** The structural organization of the many collagens is outlined. **fi** fibril-forming collagens, **fii** fibril-associated collagens with interrupted triple helices (FACIT), **fiii** network-forming collagens and collagens *VI*, *VII*, *XXVI*, and *XXVII*, and **fiv** membrane collagens and multiplexins (collagens *XV* and *XVIII*). (Reprinted with permission from Ricard-Blum S, The collagen family, Cold Spring Harb Perspect Biol. 2011; 3:a004978(p. 1–19). Copyright 2011 Cold Spring Harbor Laboratory Press)

fibril which in cross-section is composed of several hundred individual collagen molecules. The hole zone is roughly 67 nm wide. The longitudinal staggering of the molecules involves slightly less than one-quarter of the length of the molecule and leaves a "hole" between the end of one triple helix and the beginning of the next. It is widely felt by some that this hole zone in type I collagen of bone provides a site for the deposition of hydroxyapatite crystals in bone formation [347].

Cleavage at the N-terminal end is done by procollagen N-proteinases belonging to the ADAMTS family (Disintegrin And Metalloproteinase with Thrombospondin Motifs) and at the C-terminal end by BMP-1 (bone morphogenetic protein-1).

The three polypeptide chains of the collagen molecule are called alpha chains with these and then coiled into a left-handed helix with about three amino acids per turn. Each of the three helical chains together is then twisted around each other into a right-handed superhelix. These actions lead some to refer to collagen as a "coiled coil." In the mammalian collagens, approximately two-thirds of the x and y positions are occupied by a variety of amino acids which help provide stability during the next higher level of hierarchical organization at the fibrillar level.

In summary, synthesis of collagen has both intracellular and extracellular components [342, 343, 348] (Fig. 1.20b and Table 1.12). The procollagen in the molecule is assembled and then secreted from the intracellular region while in the extracellular environment the procollagen is converted to collagen and then incorporated into stable and cross-linked collagen fibrils. The first act of synthesis involves transcription and then

Table 1.12 Steps in collagen synthesis

Interacellular
1. Gene selection, transcription, mRNA processing, translation
2. Post-translational processing
• Hydroxylation of proline and hydroxyproline residues to 4-hydroxyproline, 3-hydroxyproline, and hydroxylysine
• Glycosylation of hydroxylysine residues
(a) galactosyl hydroxylysine
(b) glycosyl galactosyl hydroxylysine
• Assembly of pro-alpha chains, glycosylation of propeptides, disulfide bonding between pro-alpha chains
• Folding into triple helix
• Secretion from cell to extracellular region
Extracellular
3. Cleavage of pro-collagen extension peptides at C- and N-terminal ends of molecule to leave collagen
4. Self-assembly of fibrils
5. Intermolecular cross-linking. Conversion of lysine and hydroxylysine side chains to aldehydes and reactions of addetudes to form covalent cross-links

Adapted from Eyre (Ref. [341]) and Olsen (247), Prockop et al. (Ref. [342, 343])

translation of the collagen as the amino acids line up in the polypeptide sequence characteristic of the protein. There is initially a signal sequence at the amino-terminal end which for the pro-alpha chain is long, containing about 100 amino acid residues. Post-translational changes are extensive involving both the propeptide domains and the collagen itself in the pro-alpha chain. The signal sequences are removed as the amino-terminal ends of the pro-alpha chains enter the rough endoplasmic reticulum. Hydroxylation then occurs within the RER forming hydroxyproline and hydroxylysine. These actions are partially mediated by enzymes including prolyl-hydroxylase and lysyl hydroxylase. The hydroxylases act only on non-helical substrates and not on collagen which has reached the helical conformation. The next post-translational change relates to glycosylation. Sugar residues are added to hydroxylysyl residues. Enzymes involved here are galactosyl transferase and glucosyl transferase. The first adds galactose to the hydroxylysyl residues and the second adds glucose to the galactosyl hydroxylysyl residues. Cleavage from procollagen to collagen occurs with mediation by two enzymes, procollagen amino protease to remove the amino propeptides and procollagen carboxy-protease to remove the carboxy propeptides. Cross-linking then occurs in the extracellular domain.

1.15.2 Collagen Groups

The collagens are divided into differing groups based on slightly differing molecular constituents [338, 341, 349] which lead to different types of polymeric structures or differing structural features (Fig. 1.20e, f). These include: (i) Collagens. Collagens capable of forming linear fibrous structures are of types I, II, III, V, XI, XXIV, and XXVII; their main function is to resist tensile stresses on tissues; (ii) FACIT collagens. Collagen molecules found on the surface of other collagens are referred to as FACIT collagens (fibril-associated collagens with interrupted triple helices) include types IX, XII, XIV XVI, XIX, XX, XXI, and XXII. They are associated with collagens but do not form fibrils by themselves; (iii) Network-forming collagens. Collagen types IV, VIII, and X are involved in the formation of sheets or protein membranes having the ability to form regular hexagonal lattice structures. Type IV is seen in basement membranes, type VII in Descemet's membrane, and type X in the hypertrophic zone cartilage matrix (although there is no evidence that type X actually assumes a membrane conformation; (iv) Beaded filament forming collagen. Type VI collagen forms beaded filaments which appear to be independent and are present in many extracellular matrices including cartilage; (v) Collagen of anchoring fibrils. Type VII collagen forms anchoring fibrils present primarily in skin and act in dermal–epidermal adhesion linking epithelial basement membranes to the underlying stroma. Type XXVIII also belongs to this group; and (vi) Collagens with a transmembrane domain. Collagens with a transmembrane domain (types XIII, XVII, XXIII, and XXV) have both a cytoplasmic and extracellular domain (Fig. 1.20f).

Some collagen types have very restricted functions. Collagen XXII is present only at tissue junctions such as the myotendinous junction in skeletal and heart muscle. Collagen XXIV is a marker of osteoblast differentiation and collagen XXVII appears to be restricted to cartilage calcification-associated cartilage-to-bone transition. The fibril-forming or fabrillar collagens present in bone, cartilage, skin, and tendon have similar features shared by all members of the family including a highly conserved C-terminal non-collagenous domain and a long collagenous domain of $\sim$1000 amino acid residues. There are however three related but distinct groups within this family. These are type A pro α 1(I), pro α 2(I), pro α 1(II), pro α 1(III), and pro α 2(V); type B containing the remaining chains of type V and XI collagens; and type C, the more recently defined type XXVII and type XXIV collagen genes [338].

Individual collagen types are rarely found in isolation in extracellular matrices and usually are grouped together. The cartilage-specific collagens are of types II, IX, X, and XI along with the more ubiquitous collagen type VI and most likely types XII and XIV. Although the structures of the various collagens vary and many are hybrid molecules, where the collagen domain may only be small in comparison to the non-collagenous part of the molecule, there are certain

characteristics shared by all collagens. These include the triple helix in which three left-handed helices, alpha chains, twist around each other to form a right-handed supra-helix. Each alpha chain contains glycine at every third residue and approximately 10–12 % of each of the remaining X and Y residues of the repeating sequence GLY-X-Y are proline and hydroxyproline, respectively. Hydroxyproline is essential for the formation of hydrogen bonds that stabilize the helix. The fibrillar collagens are synthesized as large precursor procollagen forms with non-collagenous propeptides at the N–C termini. The propeptides are completely removed in type I, II, and III collagens by specific proteinases before and during self-assembly and cross-linking of the triple helix.

Collagen organization in cartilage fibrils shows evidence of structural intermixture of several collagen types involving primarily type II but also definable amounts of types IX and XI forming what is referred to as a heterotypic fibril [350–353]. Type II collagen represents about 80 % of the cartilage fibril with the remaining 20 % distributed between type IX and XI (Fig. 1.20e). Type XI fibrils are buried within the type II fibrils indicating a firm intermixture. It is felt that type XI collagen initially forms a core filament and that collagen type II is deposited around it. When the diameter reaches about 17 nm, the structure is such that the perimeter of the fibril serves as a binding site for type IX collagen, which is thus deposited on the surface. Attachment of type IX collagen prevents further growth in the diameter of the fibril and limits adherence of adjacent fibrils. In summary, a core of quarter staggered molecules of the fibrous collagen type XI is coated by molecules of the fibrous collagen type II. When a certain diameter is reached, which appears to be in the area of 17 nm, type IX collagen is attached to the fibril surface. There are hydroxylysine-derived cross-links between type IX collagen and type II collagen. In addition, the type IX molecules are attached to chondroitin sulfate chains of variable length. The alpha-2 (IX) chain carries a covalently attached chondroitin sulfate chain making this collagen a proteoglycan as well. The surface type IX plus the proteoglycan helps to prevent adjacent fibrils from aggregating. The collagen fibrils of cartilage are therefore much thinner than those of bone, averaging about 20 mm in width. The dispersed state of the fibrils prevents formation of a thicker fibril with quarter staggered array which explains why cartilage collagen by ultrastructure is not cross-banded.

Collagen fibrils in skin are made of I and III and in cornea of I and V.

Many of the more recently defined collagens are in effect complex molecules in which the collagen is only one component. Several collagens (IX, XII, XIV, XV, XVIII) carry glycosaminoglycan chains (chondroitin sulfate and/or heparan sulfate) and are considered also as proteoglycans. Type XVIII collagen is both a collagen and a proteoglycan with recent definition of heparan sulfate side chains. Type XVIII collagen has typical features of a collagen with sensitivity of its core protein to collagenase digestion but it also has the characteristics of a proteoglycan in particular heparan sulfate since it has long heparitinase-sensitive carbohydrate chains and a highly negative net charge [354]. Collagen XVIII is abundant in the basal laminae and after collagen type IV is the second commonest collagen in the basal laminae. At the C-terminal globular domain the collagen XVIII molecule contains the angiogenesis inhibitor endostatin [355]. This segment of the type XVIII collagen molecule has been shown experimentally to inhibit endothelial cell proliferation and to suppress angiogenesis. It is the focus of much investigation in terms of therapeutic potential to minimize tumor growth.

1.15.3 Detailed Review of Specific Cartilage Collagens

1.15.3.1 Collagen Type II

This is the major fibrous collagen of cartilage and is also present in the vitreous humor of the eye and the intervertebral disks. It represents 80–90 % of the collagen content of the cartilage matrix. It is a homotrimer of three type II alpha chains [α1(II)]3. It is processed by N- and C-proteinases in the same fashion as procollagen Type I. It is closely associated with type XI collagen which accounts for <5 % of the cartilage collagen. Type II collagen has a higher hydroxylysine/lysine ratio and increased levels of glycosylated hydroxylysine than collagen types I and III. The degree of glycosylation also contributes to the thinness of the type II collagen fibril in relation to type I.

1.15.3.2 Collagen Type XI

Collagen Type XI is also a fibrous collagen. It is a heterotrimer of three chains [α1 (XI) α2(XI) α 3 (XI)]. Type XI collagen has been shown to form heterotypic fibrils with type II and their retention of the N-terminal non-collagenous domain is felt to restrict the overall diameter of these fibrils (Fig. 1.20e).

1.15.3.3 The FACIT Collagens: Types IX, XII and XIV

Collagen fibers in cartilage form a stable meshwork to counteract the swelling pressure generated by the hydrated proteoglycan aggregates. This is done by interaction of the collagen type II fibers with other matrix components such as type IX collagen [356, 357] (Fig. 1.20e, f). Type IX collagen is found along the surface of type II collagen fibrils. It is composed of three distinct polypeptide chains [α1(IX)α2 (IX)α3(IX)] assembled in a 1:1:1 ratio. The type IX collagen molecules have a long triple-helical arm running along the fibril and a short triple-helical arm, extending into the

peri-fibrillar space where it terminates with a globular domain, and four non-collagenous domains one of which has a glycosaminoglycan side chain. Type IX is present throughout cartilage tissue and is thus secreted by all chondrocytes. Type IX is associated with a glycosaminoglycan (GAG) side chain consisting of either chondroitin sulfate or dermatan sulfate [358]. The more recently described type XII and XIV collagens are similar to type IX collagen and are felt to associate on the surface with type I collagen containing fibrils [359, 367]. The presence of glycosaminoglycans has also been connected to type XII and XIV collagens. Type XII collagen has been localized to the perichondrium at the articular surface and around cartilage canals while type XIV collagen is found throughout the matrix.

1.15.3.4 Type X Collagen

Type X collagen is a short chain collagen which is expressed exclusively by hypertrophic chondrocytes at sites of endochondral bone formation [120, 122, 341, 360, 361]. Its triple-helical domain is capable of forming a hexagonal lattice-like structure. It is a homotrimeric molecule [α1(X)]3. It is seen initially in the developing embryonic long bones in the central part of the diaphysis (where chondrocyte hypertrophy initially occurs), whereas type II collagen is seen earlier and throughout the cartilage model. The type X is then expressed further toward each end of the developing bone as cartilage maturation and hypertrophy move in those directions. Eventually it is concentrated in the physes in the matrix adjacent to the hypertrophic cells. The amino acid sequence, gene structure, and molecular organization closely resemble those of type VIII.

1.15.3.5 Type VI Collagen

Type VI collagen forms into beaded microfibrils which occur in cartilage and many other tissues. It is most commonly present as a heterotrimer [α1 (VI)α2 (VI) α3(VI)]. Its function is still unknown but its interactive properties suggest that it may have a bridging role between cells and their extracellular matrix. The fibril diameters in cartilage are in the 17–20 nm range.

1.15.4 Proteoglycans

The other major group of molecular constituents in the connective tissues and the group which plays a major role in all cartilage tissue are the proteoglycans (PGs) [362–372]. They are a diverse family of molecules made of a core protein to which are attached one or more glycosaminoglycan (GAG) side chains (Fig. 1.21ai, ii). The following basic molecules comprise the GAG group in cartilage: chondroitin sulfate (CS), dermatan sulfate (DS), heparan sulfate (HS), keratan sulfate (KS), and hyaluronic acid (HA) (Fig. 1.21b). Each of these GAGs is sulfated except for hyaluronic acid. Only the sulfated GAGs become part of a proteoglycan. Combinations of these primary molecules form five specific proteoglycan macromolecules of hyaline cartilage; aggrecan, decorin, biglycan, fibromodulin, and type IX collagen. Aggrecan is the largest in size and most abundant by weight. The term aggregating refers to the ability of single proteoglycans to interact non-covalently with hyaluronic acid to form large proteoglycan aggregates. The aggregating proteoglycan of hyaline cartilage is aggrecan. This large aggregating CS–PG is composed of about 85 % CS, 6 % KS, and 7 % protein and accounts for 10 % of the dry weight of cartilage. The primary role of aggrecan is to provide cartilage with its osmotic properties, to swell and hydrate the collagen fibrillar framework giving cartilage its ability to resist compressive loads.

The term non-aggregating proteoglycan refers to all molecules that do not interact specifically with hyaluronic acid. This family of molecules interacts with collagen molecules. The following are in this category. Biglycan (small CS/DS proteoglycan) is the predominant small proteoglycan of cartilage possessing two dermatan sulfate chains and localized in the peri-cellular matrix. Decorin is a small CS/DS proteoglycan with one dermatan sulfate chain. Fibromodulin (small CS/KS proteoglycan) bears many keratan sulfate chains and is present in many tissues including cartilage where it binds to type II collagen. Type IX collagen is considered to be a proteoglycan as well since one of its chains bears a glycosaminoglycan chain. Type IX is present on the outer surface of type II collagen.

Aggrecan synthesis and breakdown in the growth plate at varying depths and different stages of development have been assessed in the distal tibia of fetal calf tissue [371]. The rates of aggrecan synthesis and turnover were highest in the resting/proliferative zone compared to either the upper or lower hypertrophic zones. Aggrecan gene expression in the cells of the resting/proliferative zone and the upper hypertrophic zones was similar, but the levels were reduced in the deepest cells of the lower hypertrophic zone. Approximately 90 % of the newly synthesized proteoglycan and the total proteoglycan population was able to aggregate and the monomers were relatively large. Aggrecan is a complex macromolecule consisting of an extended core which contains several distinct domains: N-terminal G-1 domain adjacent to the G-2 domain, keratan sulfate rich region, and an extended chondroitin sulfate rich region and a C-terminal G-3 domain. The G-1 domain binds to hyaluronate stabilized by a separate link protein such that many proteoglycans can

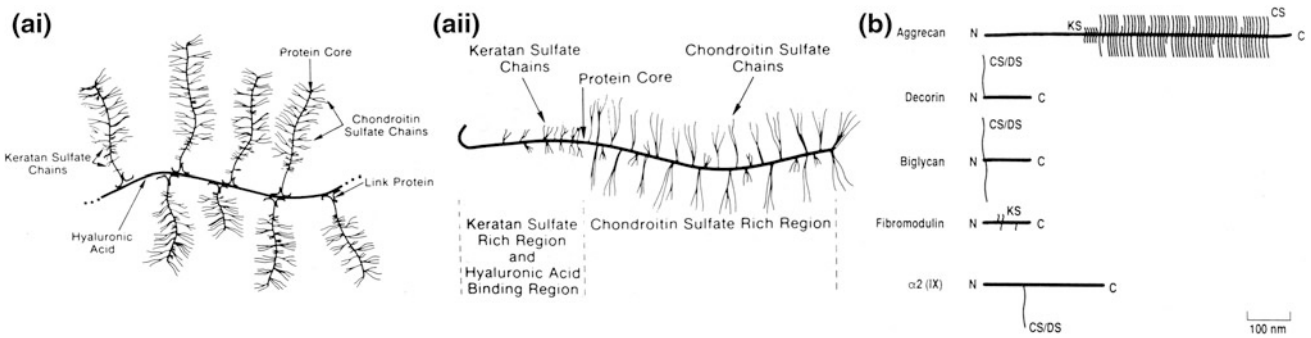


Fig. 1.21 **ai**, **ii** The basic structure of the proteoglycan molecule is shown. (Reprinted with permission from Buckwalter JA, Proteoglycan structure in calcifying cartilage. Clin Orthop Rel Res 1983;172;207–231. Copyright 1983 Wolters Kluwer Health). **b** The major proteoglycan molecules of cartilage are shown. (Reprinted with permission from Roughley et al. Cartilage proteoglycans: structure and potential functions. Microsc Res Tech. 1994;28:385–397. Copyright 1994 John Wiley and Sons)

bind to a chain of hyaluronate to mobilize themselves in a dense collagenous network.

Proteoglycan synthesis, studied by 35S-sulfate incorporation into the glycosaminoglycan chains, showed heterogeneity of synthesis through the depth of the tissue. The major proteoglycan in the growth plate is aggrecan, which is also found in high concentrations in articular cartilage. Other proteoglycans present in the growth plate in smaller amounts include biglycan, decorin, and type IX collagen [373]. Assessment comparing the upper resting proliferative zones and the lower hypertrophic zones shows that the cell volume per total tissue volume increases five to tenfold and the matrix volume per cell also increases up to threefold. In the lower hypertrophic zone, the extracellular matrix may occupy only 10 % of the total tissue volume compared with over 60 % in the upper zones. There is thus an overall loss of extracellular matrix and proteoglycan. The composition of the ECM also changes with depth. Aggrecan is distributed throughout the growth plate. Proteoglycan concentration in the ECM increases toward the lower hypertrophic zone, but the total amount of the proteoglycan per tissue volume decreases. There is little variability in the size of the proteoglycan monomer with depth. The rate of proteoglycan synthesis per cell is dramatically reduced only in the lower hypertrophic zone. The mRNA levels of type II collagen and osteonectin are also reduced in the hypertrophic zone compared to chondrocytes in the resting zone, but there are high levels of type X collagen and hypertrophic chondrocytes associated with the onset of mineralization. The proteoglycans are summarized in Tables 1.13 and 1.14.

1.15.5 Glycoproteins, Non-collagenous Proteins

A large number of proteins other than collagens and the proteoglycans are present although in much smaller amounts in the extracellular matrix [374, 375]. These are generally referred to as non-collagenous proteins, a term that reflects their highly variable chemical nature. These molecules interact with cells, with other macromolecules of the extracellular matrix, and with the mineral phase of bone and calcifying cartilage. Many of these proteins are phosphorylated leading them to be described as phosphoproteins and many are glycosylated, and thus referred to as glycoproteins. Many have subsequently been given names based on their presumed function. One of the most abundant non-collagenous proteins of bone is osteonectin, a phosphorylated glycoprotein.

The principal bone associated non-collagenous proteins are anionic. Several extracellular glycoproteins have been isolated and these molecules have been shown to interact both with cells and with other macromolecules and even the inorganic phases of bone. Post-translational modifications include phosphorylation of serine and threonine.

Groups of glycoproteins in cartilage include: cartilage matrix protein, cartilage oligomeric matrix protein, link protein, and matrix gla protein. Cartilage matrix protein has recently been found to localize primarily at the lower part of the proliferating zone of the endochondral sequence between the cells of the upper proliferating zone and the hypertrophic zone cells. It has been suggested that CMP is a marker for post-mitotic chondrocytes which will shortly progress to the hypertrophic stage [376]. It is present in articular cartilage. Cartilage oligomeric matrix protein is a glycoprotein found in cartilage in particular during periods of chondrogenesis. It is preferentially localized in the peri-cellular territorial matrix. Other glycoproteins seen in cartilage but more prominent in bone and other non-cartilage tissues include: “adhesive glycoproteins” interacting with cells: fibronectin, vitronectin, laminin, thrombospondin, von Willebrand factor, and fibrinogen; “skeletal tissue associated glycoproteins”: bone sialoprotein, osteocalcin, osteopontin, osteonectin, osteogenin [377], and other phosphoproteins

Table 1.13 Properties of cartilage proteolycans

Proteoglycan type	GAG type[b]	GAG #	Protein size[c]	Chromosome location	Gene size (kb)	Exon #
Aggrecan	CS and KS	>100	2297	15	>50	15
Decorin	CS/DS	1	329	12	>38	8
Biglycan	CS/DS	2	331	X	8	8
Fibromodulin	LS	4	357	–	–	–
Type IX collagen	CS/DS	1	677	–	–	32

[a]All data refer to human proteoglycan except that for fibromodulin, which is bovine and α2(IX), which is chick
[b]*CS* chondroitin sulfate; *DS* dermatan sulfate; *GAG* glycosaminoglycan; *KS* keratan sulfate
[c]Protein size is represented as the number of amino acid residues present in the secreted proteoglycan
Derived from Roughley et al. (Ref. [370])

Table 1.14 Proteoglycans of extracellular matrix

Name	Prior names	GAG	Core size[a]	Comments
Decorin	PG-11, PG-S2, PG-40	DC/CS	45 K (36,383)	Small PG of fibrous tissue, leucine repeats
Biglycan	PG-1, PG-S!	DS	45 K (37,983)	Leucine repeats
Fibromodulin		KS	50 K (42,200)	Leucine repeats
Lumiscan		KS	50 K (38,640)	KSPG of cornea
				Leucine repeats
Pg-Lb		DS	43 K (35,854)	Leucine repeats
Aggrecan	PG-H	CS, KS	225–250 K	Large PG of cartilage, aggregates with hyaluronic acid
Versican	PG-400	CS	400 K (262,744)	Fibroblast large PG
Neurocan		CS	150 K (136,000)	Large aggregating PG of brain
Perlecan		HS	400 K (396 K)	HSPG of basement membrane
Type IX collagen	PG-Lt	CS	320 K	3 Alpha chains

GAG glycosaminoglycans; *DS* dermatan sulfate, *CS* chondroitin sulfate; *KS* keratan sulfate; *HD* heparan sulfate; *PG* proteoglycan
[a]Approximate size determined by SDS-PAGE after enzymatic digestion of GAG chains. Figure in parentheses is MW
Derived by Vogel (Ref. [372])

such as phosphoserine and phosphothreonine; and the "elastin associated glycoproteins" fibrillin and MAGP. Both bone sialoprotein and osteopontin have been defined in hypertrophic chondrocytes and the adjacent mineralized cartilage matrix. The fixed negative charge of many of the bone-associated molecules is due to the fact that many are rich in acidic amino acids such as aspartic and glutamic, some contain stretches of consecutive aspartic acid residues (osteopontin), and others stretches of consecutive glutamic acid residues (bone sialoprotein). Other molecules contain gamma-carboxyglutamic acid residues (osteocalcin and matrix gla protein). Other post-translational changes include sulfation of tyrosine residues (bone sialoprotein).

Many of these molecules have been implicated in calcification and calcium ion binding although it has been difficult to specifically pinpoint function. The non-collagenous gamma-carboxyglutamic acid containing proteins (bone gla or osteocalcin and matrix gla protein) have been associated with the calcification process. Bone sialoprotein has a restricted tissue distribution being found primarily in bone and mineralized connective tissues. It is expressed by osteoblasts at high levels. The molecule is extensively glycosylated, about one-half of its serine residues are phosphorylated and it contains extended sequences of acidic amino acids in particular glutamic acid, glycine, and aspartic acid. Matrix gla protein is a vitamin K dependent protein isolated initially from bone matrix but subsequently found also in cartilage. Bone gla protein also known as gamma-carboxyglutamic acid containing protein or osteocalcin is a low molecular weight protein found primarily in bones. It contains three gamma-carboxyglutamic acid residues providing the molecule with calcium-binding properties. Osteocalcin binds tightly to hydroxyapatite and may play a role in regulating crystal growth. Its synthesis is also vitamin K dependent.

Osteocalcin is the most abundant non-collagenous protein in mineralized bone matrix. It is a small protein containing 49 amino acids. Three amino acids are gamma-carboxylated via mediation of vitamin K, a property which allows for its close relationship to hydroxyapatite. It is abundant in bone tissue being approximately 20 % of all non-collagenous protein but its precise function is still uncertain. Bone sialoprotein 1 (BSP1) is now referred to most commonly as osteopontin [378, 379]. It is expressed early in bone development, at high levels at sites of bone remodeling, and is also seen to bind to hydroxyapatite. Its finding in relation to bone remodeling is associated with an apparently increased attachment to osteoclasts. Bone sialoprotein (BSP) is

synthesized by osteoblasts and is a glycosylated phosphoprotein rich in sialic acid.

1.15.6 Cell Surface Proteoglycans

Proteoglycans have recently been found as abundant molecules of the cell surface where they play major roles in morphogenesis [380–382]. Virtually all epithelial cells express cell surface proteoglycans. The major transmembrane proteoglycans of the cell surface are syndecans which contain both chondroitin sulfate and heparan sulfate. Syndecan 3 is a member of the family of heparan sulfate proteoglycans which function as extracellular matrix receptors mediating the interaction of cells with extracellular components and as signaling molecules that control cell shape, adhesion, proliferation, and differentiation. Syndecan 3 responds to AER signals, mediates cell–matrix and cell–cell interactions involved in the onset of chondrogenesis, and plays a role in regulating epiphyseal chondrocyte proliferation during endochondral ossification.

1.15.7 Temporal and Spatial Changes in Specific Molecular Expression Within the Endochondral Sequence

Virtually all structural changes are or presumably will be found to be associated with changes in molecular synthesis by the participating cells. With increasing sophistication of molecular identification, the specific cascade of changes is being clarified. Indian hedgehog (Ihh) is secreted by pre-hypertrophic chondrocytes and induces another factor from the perichondrium, parathyroid hormone-related protein (PTHrP). A number of changes have been identified specifically during the chondrocyte hypertrophy phase of the endochondral sequence. These include the acquisition of collagen-type X synthesis capability by the hypertrophic chondrocytes, the loss of synthetic capacity for types II and IX, a decrease in some proteoglycan synthesis, and an increase in the activity of metalloproteinases as well as alkaline phosphatase. Recent studies on cultures of hypertrophic tibial chondrocytes helped characterize as many as 18 upregulated genes during chondrocyte hypertrophy [383]. The identified genes included translational and transcriptional regulatory factors, ribosomal proteins, the enzymes transglutaminase and glycogen phosphorylase, type X collagen, and the carbohydrate-binding protein galactin. Temporal and spatial differences in expression have also been defined for the proteoglycan core protein, aggrecan, and cartilage proteoglycan link protein [366]. These were expressed in the same regions and were confined to chondrocytes of the developing skeleton and other cartilaginous structures. The highest expression was found in the lower proliferative and upper hypertrophic zones of the physeal regions whereas the resting zones showed less expression. In addition, cartilage which was calcifying and thus close to the osteochondral junction showed no expression. The phenomenon of loss of expression in the area of calcification was found throughout the subsequent stages of skeletal development. It is felt by some that the large aggregating proteoglycan of cartilage inhibits mineralization and thus may well prevent calcification in the proliferative and upper hypertrophic zones.

The final stages of endochondral ossification are associated with matrix metalloprotein expression, in relation to cartilage resorption, with MMP-9 and MMP-13 seen, and with angiogenic regulators such as vascular endothelial growth factor (VEGF) in relation to vascular invasion bringing in osteoprogenitor cells [384].

Studies have been done to assess the synthesis of type IX collagen during skeletal formation. The type IX collagen began to accumulate at the onset of overt chondrogenesis during the early condensation phase of the process in which mesenchymal cells became closely packed prior to depositing the cartilage matrix. The type IX collagen synthesis coincided with the production of cartilage proteoglycan core protein and type II collagen accumulation.

Expression and localization of the proteoglycans biglycan and decorin was also assessed in human tissues (28). Tissue sampling involved femur, tibia, and humerus. Although both proteoglycans were found in developing cartilage, there was a marked difference in their location in the developing epiphyseal regions. Biglycan core protein was localized to an outer cap of prospective articular cartilage at each epiphyseal end while decorin was not detected at these sites but was found within the more deeply located resting cartilage in which staining for biglycan was weak. The cartilage matrix remained unstained for both around the vascular canals which grew in from the perichondrium to the epiphyseal cartilage regions. Within the physeal regions, there was a highly segregated staining pattern in the upper proliferative zone where biglycan was restricted to the territorial capsules of the chondrocytes and decorin restricted to the interterritorial matrix. Staining for both was virtually absent in the lower proliferative, hypertrophic, and mineralizing zones of the growth plates. High levels of biglycan were detected in the region in the forming growth plates and in perichondrium-derived mesenchymal inside vascular canals. Low levels of decorin were found in articular cartilage with a very high level detected near a rim of cartilage at the peripheral sub-perichondral locations and in chondrocytes arranged around vascular canals. In growth plates, low levels of biglycan and lower undetectable levels of decorin were observed in proliferating cartilage and high levels in

hypertrophic chondrocytes. The biglycan gene was expressed at high levels in pre-osteogenic cells both in the periosteum and in morphologically undifferentiated mesenchymal cells and vascular canals thought to be recruited for development of secondary ossification. Decorin was maximally expressed at the sites of appositional growth in the sub-perichondrium whereas biglycan expression predominated at the site of formation of growth plates.

Specific localization of the gene for cartilage matrix protein (CMP) has also been found within the physis. Chen et al. [376] identified that it was the post-proliferative chondrocytes which make up the zone between the zones of proliferation and hypertrophy that specifically transcribe the gene for CMP. This is referred to as the zone of maturation. CMP translation products were present in the matrix surrounding the non-proliferative chondrocytes of both the zones of maturation and hypertrophy such that CMP is a marker for post-mitotic chondrocytes. This provided further indication that chondrocytes in each zone reside in an extracellular matrix with a unique macromolecular composition. The results were thought to be compatible with the demonstration of distinct switches at the proliferative–maturation transition and at the maturation–hypertrophy transition during chondrocyte differentiation. The chondrocytes themselves synthesize new matrix molecules to modify their pre-existing micro-environment as differentiation progresses. Type X collagen synthesis is specifically related to the hypertrophic chondrocyte which can be shown in tissue culture to stop type X collagen synthesis, resume proliferation, and re-initiate aggrecan synthesis when they leave the hypertrophic zone. The data are consistent with "a high degree of plasticity in the chondrocyte differentiation program."

The expression of I, II, X, and XI collagens along with aggrecan synthesis by bovine growth plate chondrocytes in situ and by human fetal tissue has also been defined [121].

1.15.8 Matrix Metalloproteinases (MMPs) and Tissue Inhibitors of Matrix Metalloproteinases (TIMPs)

Synthesis and resorption are both involved in long bone growth and development. Molecules involved in the remodeling processes of the extracellular matrix have been identified. The proteolytic enzymes involved in the extracellular matrix degradation are grouped into a family referred to as the matrix metalloproteinases (MMPs) which play a major role in resorption of collagen and other macromolecules in normal prenatal and postnatal development and in pathological disorders such as malignant tumor invasion, joint destruction in rheumatoid arthritis, and resorption of periodontal structures in dental disease. The MMPs are members of a sub-family of zinc-dependent endopeptidases that show enzymatic proteolytic activity outside the cell [385–387]. The initial MMP identified was collagenase which is now referred to as MMP-1. As many as 28 MMPs have now been identified. Four major families of MMPs are the collagenases (MMP-1, -8,-13,-18), gelatinases (MMP-2 and -9), stromelysins (MMP-3, -10, and -11) (including matrilysin MMP-7 and -26), and the membrane type MMPs (MMP-14 to 17, -24, and -25) (Table 1.10). The metalloproteinases are essential for a breakdown of the extracellular matrix in normal development where their activity is strictly regulated by an additional set of molecules referred to as tissue inhibitors of metalloproteinases (TIMPs). Imbalances in functions of the MMPs and/or their control by the TIMPs are associated with such pathological processes as tumor metastasis, rheumatoid arthritis, and osteoarthritic cartilage where there is excessive tissue destruction. There are four major groups of protease inhibitors of the TIMP family (TIMP-1, TIMP-2, and TIMP-3, and TIMP-4). There is considerable specificity for tissue components for the various MMPs although there is not an absolute tissue or molecule specificity. The collagenases are the only members of the MMP family which cleave fibrillar collagens, showing activity against type I, II, and III collagens. The collagenase family includes MMP-1, MMP-8, and MMP-13. Collagen II is a preferential substrate of MMP-13 and collagens I and III are preferentially cleaved by MMP-1 and MMP-8. The stromelysins (MMP-3and MMP-10) can degrade many extracellular proteins including the proteoglycans (MMP-3, MMP-7, MMP-10, and MMP-11). Gelatinases are effective in degrading type X and type XI collagens along with some of the other collagens. The more recently defined membrane type MMPs also have proteoglycan degradative activity. Gelatinase B (MMP-9) is present in osteoclasts. Three specific MMPs, MMP-9, MMP-13, and MMP-14, contribute to vascular invasion and connective tissue remodeling during calcified cartilage resorption. MMP-9 and MMP-13 proteins and enzymatic activity can be quantified in urine. Their original use is to assess tumor angiogenesis. They can also be used to assess bone turnover and repair.

Haeusler et al. studied human growth plates by immunohistochemistry to assess MMP and TIMP presence. MMP-14 was the most prominent and was present within all zones of the growth plate [388]. MMP-1, MMP-13, MMP-9, MMP-10, and MMP-11 were positive in hypertropic chondrocytes (as well as osteoblasts). TIMP-1 was also present in all zones of the growth plate (as well as osteoblasts and

osteoclasts) and TIMP-2 was found in hypertrophic chondrocytes (and osteoblasts).

1.15.9 Matricryptins of Collagen

Matricryptins are biologically active fragments released by proteolytic cleavage of collagens, which regulate a number of physiological and pathological processes including development, angiogenesis, tumor growth and metastasis, and tissue repair [389]. Most of them possess biological functions different from those of the intact parent molecule. A single collagen type can give rise to several matricryptins. Most of the matricryptins identified so far have originated from basement membrane collagens (IV, VIII, XVIII) or are located in the basement membrane zone (XV, XIX). Endostatin, the carboxy-terminal fragment of collagen XVIII, has anti-tumor and anti-angiogenic properties and has been adapted for medical use. These bioactive fragments are also released from proteoglycans and glycoaminoglycans.

1.16 Mineralization

Mineralization is an integral part of the terminal stages of the endochondral sequence when the cartilage becomes mineralized and of the formation of bone by either the endochondral or intramembraneous sequences in which the newly synthesized osteoid is mineralized. The process of adding mineral to matrix is the mineralization process.

1.16.1 Vitamin D

Vitamin D is integral to the mineralization process. It is a steroid made in the skin by the action of sunlight. It is biologically inert and must undergo two successive hydroxylations in the liver to 25-dihydroxy vitamin D and then in the kidney to the biologically active form 1, 25-dihydroxy vitamin D [1, 25(OH)2D]. The renal production of 1, 25(OH)2D is closely regulated by serum calcium levels through the action of parathyroid hormone (PTH) and phosphorus. The major biologic function of vitamin D is to maintain normal circulating levels of calcium. This is done by two mechanisms, one involving the efficiency of the small intestine to absorb dietary calcium and the other to allow for mobilization of calcium from bone when dietary calcium alone is inadequate to maintain normal levels. The 1, 25(OH)2D induces monocytic stem cells in the bone marrow to differentiate into osteoclasts which then perform the resorptive activity. Several different metabolites of vitamin D have been identified including 24, 25(OH)2D but it is 1, 25(OH)2D that is believed to be the major if not exclusive active agent for the biologic effects of vitamin D on calcium and bone metabolism. Vitamin D is important for bone mineralization although it appears not to participate directly in the process. Instead it promotes the mineralization of osteoid and physeal cartilage by maintaining the extracellular calcium and phosphorus concentrations in the normal range which then allows for the deposition of calcium hydroxyapatite into the matrices.

Recently however vitamin D has been found to play a more active role in growth plate cartilage development. All target tissues for vitamin D contain a vitamin D receptor (VDR) for 1, 25(OH)2D. Such receptors have been found also in growth plate cartilage for both the 1, 25 and 24, 25 metabolites.

1.16.2 Matrix Vesicles and the Collagen Matrix and Their Relationship to the Initiation of Mineralization

1.16.2.1 Matrix Vesicles

Matrix vesicles are extracellular 100 nm diameter membrane invested particles selectively located within the matrix of bone, cartilage, and predentin. They serve as the initial site of calcification in all skeletal tissues in the view of Anderson who first described them in 1969 [390] and has studied them extensively since [391, 392]. He describes matrix vesicle biogenesis occurring by polarized budding and pinching off of vesicles from specific regions of the outer membrane of chondrocytes, osteoblasts, and odontoblasts. (The discussion in this section will subsequently be limited to the cells of cartilage and bone.) The diameter of the vesicles has a range from 20 to 200 nm (1 μ). Seeding of selected areas of matrix with matrix vesicles explains the localized distribution of subsequent zones of mineralization. The vesicles have a single covering membrane. Anderson considers biomineralization to be a two phase process. The formation of initial hydroxyapatite crystals occurs within the matrix vesicles during phase 1. This is controlled by phosphatases (including alkaline phosphatase) and Ca-binding molecules. The first electron microscopically observable crystalline apatite mineral is seen as a needle-like dense precipitate within the matrix vesicle often in close apposition to the inner part of the membrane. Matrix vesicles are restricted to those areas of the matrix in which mineralization will begin. Phase 2 begins with the breakdown of the matrix vesicle membranes exposing the preformed hydroxyapatite to the extracellular fluid after which mineral crystal enlargement is controlled by extracellular conditions such as the levels of ionic CA^{2+} or PO_4^{3-} in the extracellular fluid, the pH, and molecules influencing crystal deposition (+ or 1) such as proteoglycans and non-collagenous proteins.

Most evidence indicates that matrix vesicles do not contain crystals of mineral when initially budding from the

chondrocyte or osteoblast but, rather, form the crystals when in the matrix with the vesicle membrane intact. The matrix vesicles contain the molecules needed to induce the initial mineral crystals, including annexin V and II, lactic dehydrogenase, phosphatases, type X collagen, CA ATPase, carbonic anhydrase, and proteoglycanase. Crystals arising within matrix vesicles then perforate the vesicle membranes to serve as templates for crystal proliferation (growth). As part of the second phase, Anderson comments on the role of non-enzymatic extracellular molecules including collagen which provide a "supportive framework on which mineral is deposited but also regulates the rate of mineral propagation into the matrix once initiated" [391]. Anderson has continued to believe that "collagen fibrils of cartilage, bone, dentin and turkey tendon matrices appear not to be the initial site of mineral formation …" [392]. Anderson noted that the biphasic nature of mineralization had been noted by others in bone, cartilage, turkey tendon, and dentin with the deposition of mineral occurring first within matrix vesicles and subsequently, in phase 2, around them. The mineral proliferation then continued outward forming radial clusters that eventually permeated the collagenous matrix.

1.16.2.2 Primary Association of the Majority of Extracellular Mineral Particles with Collagen Fibrils

Landis and Glimcher and colleagues stressed the initial deposition of mineral in the hole regions of collagen and although recognizing the existence of matrix vessels they did not find them at all sites of mineralization. Based on detailed studies of embryonic chick bone, as well as other tissues, they commented that the vast majority of the extracellular mineral particles were associated with collagen fibrils in all chick bone tissues at all ages. They felt that the presence of only small numbers of (matrix) vesicles, restricted to specific regions and ages of bone tissue undergoing active mineralization, argues against an obligatory requirement for matrix vesicles in the calcification of extracellular bone matrices [393]. Subsequent high voltage electron microscopic tomography by Landis et al. further confirmed that platelet-shaped crystals were arranged in channels or grooves which are formed by collagen hole zones in register [394].

1.16.3 Mineralization of Cartilage in the Endochondral Sequence

Calcification of the cartilage cores in the hypertrophic cell region of the endochondral sequence is an essential step in endochondral ossification at physes and secondary ossification centers. The calcification occurs in the longitudinal cartilage columns immediately adjacent to the final three or four hypertrophic cells at the lowest part of the physis. The region calcified, which is actually in the central portion of the longitudinal septae, is referred to as the interterritorial matrix. The transverse septae are rarely calcified. The calcified septae persist in the metaphysis as cartilage cores and serve as a scaffold on which the metaphyseal bone is synthesized. Vascular invasion from the metaphyseal side stops abruptly after entering the lowest of the hypertrophic cell lacunae and passing only two or three cells upwards. The vessels bring undifferentiated mesenchymal cells with them and these cells soon differentiate to osteoblasts and synthesize osteoid on the calcified cartilage cores. The exquisite control and patterning of mineralization in relation to the endochondral sequence in the lowermost parts of the hypertrophic zone are the focus of study in terms of causation. Mineralization is concentrated in the longitudinal septae of the hypertrophic zone. Recent studies have identified molecules specific to the physeal cartilage and some even to the hypertrophic zone and these molecules are considered to be involved in the mineralization front. The overall cartilage matrix is composed primarily of type II collagen and proteoglycans in particular aggrecan but other molecules have been identified including type IX and XI collagens, osteonectin, osteocalcin, osteopontin, and bone sialoprotein. In addition, type X collagen is localized specifically to the hypertrophic zone matrix and is not found either in cartilage which does not calcify or intramembranous bone [122].

The cartilage matrix in the calcifying region contains matrix vesicles containing alkaline phosphatase. These are involved in deposition of mineral although the exact mechanism is still uncertain [347, 390, 391, 393]. Release of inorganic phosphate as a result of the activity of alkaline phosphatase can lead to the displacement of proteoglycan bound calcium and its precipitation. The regulation of inorganic pyrophosphate is also considered to be of importance. Alkaline phosphatase hydrolyzes the inorganic pyrophosphate, an inhibitor of mineralization, to release the inorganic phosphate which enhances hydroxyapatite formation. Inorganic pyrophosphate [PP_i] is a molecule of two phosphate ions linked by an ester bond that binds to hydroxyapetite crystals and prevents further incorporation of P_i ions into the crystals. The C-propeptide of type II collagen becomes concentrated in the mineralizing sites. The synthesis of type II collagen and the C-propeptide together with alkaline phosphatase is regulated by vitamin D metabolites. The association of alkaline phosphatase with calcification was first reported in the 1920s [395]. Studies by Poole et al. indicated that when calcification starts in the lower hypertrophic zone, it is not initiated within the matrix vesicles and indeed most calcification occurs in focal sites where there are no detectable vesicles [395]. They are still quite

important however since they represent the location where alkaline phosphatase, the enzyme associated and responsible for calcification, is present.

Much interest has centered on type X collagen and its possible relationship to mineralization but no clear answer has been provided. Many have proposed a positive relationship of type X collagen to mineralization since type X collagen appears in the mineralizing region at the appropriate time and is not present elsewhere. Schmid et al. [122] point out that type X collagen has been isolated from hypertrophic cartilage before mineralization, from the mineralizing front, and from regions of calcified cartilage. Synthesis occurs by hypertrophic chondrocytes in the upper regions of the hypertrophic zone before mineral is detectable histologically. Type X collagen persists in the cartilage cores after their mineralization and after bone has been deposited upon them. Gerstenfeld and Landis [396] showed an increase in type X collagen by chondrocytes cultured in the presence of beta-glycerophosphate.

On the other hand, Poole and Pidoux [360] have suggested that type X collagen does not enhance mineralization but rather inhibits it. Their ultrastructural studies of type X collagen could not identify its association near early mineral foci or in association with matrix vesicles. They suggested that a coating of type X collagen on the cartilage fibrils actually directed early mineral formation away from those fibrils to interfibrillar sites. In close analysis type X collagen appears to be deposited preferentially in the immediate peri-cellular chondrocyte region where mineralization does not occur. This finding is consistent with the observation that the initiation of calcification does not occur in the transverse septae which are in the immediate peri-cellular region because of their narrowness but rather occurs in the longitudinal interterritorial septae of the growth plate which are relatively further from the cell.

Attention has also been directed to the proteoglycans and their relationship to mineralization primarily because they are so extensively present in the physeal areas. Buckwalter has defined the two theories of the role of aggrecans and aggregates in physeal mineralization [362, 364]. The first theory is that aggrecans/aggregates bind the calcium and inhibit the formation of mineral clusters in the matrix while proteoglycanases prepare the hypertrophic zone matrix for mineralization by degrading the aggrecans. The second theory also proposes that the aggrecans/aggregates bind calcium but that they act as sites of mineral formation in the hypertrophic zone by increasing the concentration of calcium. This current impression is that they inhibit mineral growth throughout the uppermost parts of the physis and that an alteration in their structure subsequently serves to enhance mineral formation in the lower hypertrophic zone.

The calcium–phosphorus (CaP) mineral phase has been studied extensively in relation to the cartilage mineralization of the epiphyseal growth plate [362, 364, 397]. In a study of the calcified cartilage of the epiphyseal growth plate of young calves, x-ray diffraction of the samples revealed very poorly crystalline apatite [397]. Fourier transform infrared spectroscopy and 31P nuclear magnetic resonance spectroscopy revealed significant amounts of non-apatitic phosphate ions. Their concentration increased during the early stages of mineralization but then decreased as the mineral content rose. The initial studies characterized the calcium phosphate mineral phase as a very poorly crystal ion, immature calcium phosphate apatite which was rich in labile non-apatitic phosphate ions with a low concentration of carbonide ions compared with bone mineral of the same animal. These studies were performed on the very young and mostly newly deposited mineral. It is felt that the maturation process of the mineral phase of calcified cartilage appears to proceed as it does in bone mineral but some distinctive differences were found in concentration of ions and in the temporal changes that occurred in the mineral phase. One of the main characteristics of the mineral phase of calcified cartilage was the relatively large concentration of non-apatitic ions. Other important characteristics involved its low carbonide content. Its difference from mature bone mineral could be based on the fact that the mineral in calcified cartilage was less mature than in bone owing to its more rapid turnover. At all stages of calcification in the cartilage including the earliest phase the only crystalline solid detected by x-ray diffraction was apatite with no evidence of a non-apatitic solid phase found. There is no evidence that the very earliest solid phase of CaP was amorphous. In the final stage of mineralization the characteristics of the mineral phase in cartilage tended to approximate more closely those of bone mineral.

Mineralization of the endochondral sequence is also dependent on circulating levels of calcium and phosphorus. These in turn are uniquely determined by functions of the parathyroid hormone (PTH) and vitamin D. Disorders of vitamin D metabolism in particular are associated with major abnormalities of the endochondral sequence referred to as rickets. Vitamin D of exogenous or skin origin accumulates in the liver and is converted to the circulating form of 25 dihydroxy vitamin D [25(OH)2D] which is further activated in the kidney within the renal tubular cell mitochondria to the active metabolite 1, 25 dihydroxy vitamin D [1, 25(OH) 2D] or calcitriol. This metabolite passes from the kidney by the bloodstream to the intestine, bone, elsewhere in the kidney, and other organs where it is physiologically active. It stimulates absorption of the intestinal calcium and phosphate as well as the mobilization of calcium from bone so as to normalize the serum calcium concentration. The kidney also produces a second metabolite 24, 25 dihydroxy vitamin D (24, 25(OH)2D). The concentrations of calcium and phosphorus, which form the mineralized portions of the skeleton,

are closely regulated by the vitamin D-PTH system whose purpose is to maintain the concentration of these minerals in a relatively narrow range in the extracellular fluid.

1.16.4 Mineralization of Bone

Mineralization of bone tissue involves the deposition of hydroxyapatite (HA) crystals of calcium phosphate in the organic matrix composed of type I collagen and a variety of non-collagenous proteins including proteoglycans, glycoproteins, phosphoproteins, and GLA-containing proteins. The process thus involves organic matrix interactive proteins and the transport of ions to the mineralization site. Although the initial mineral crystals are deposited between and within the collagen fibrils, there is fairly widespread acceptance that collagen itself is neither the promotor nor the inhibitor of mineralization. The primary molecular factor that appears to be involved in the mineralization process is alkaline phosphatase but many others are also involved including proteoglycans, fibronectin, thrombospondin, and the primary non-collagenous proteins bone sialoprotein, osteopontin, osteonectin, and osteocalcin (matrix gla protein). They are both promoters and inhibitors of mineralization. A specific phosphate concentration in bone promotes mineralization but the level is lowered by pyrophosphate, an inhibitor of mineralization. Mineralization of the extracellular matrix occurs in bone due to the co-expression in osteoblasts of type I collagen and Tnap (tissue non-specific alkaline phosphatase), the enzyme that cleaves pyrophosphate to free and thus elevate tissue levels of phosphate. Another protein, PHEX, also modulates mineralization. Evidence is increasing that it is not osteoblast-specific genes that explain the limitation of normal mineralization to bone [398]. Murshad et al. have indicated that matrix mineralization occurs only in bone because of the exclusive co-expression in osteoblasts of type I collagen and Tnap, an enzyme that cleaves pyrophosphate. (Normal type mineralization occurs at a particular phosphate concentration. Pyrophosphate is an inhibitor of mineralization and loses that function if cleaved allowing bone formation to occur [398]). (i) Tnap is neither osteoblast specific nor bone specific, (ii) Phex affects serum mineral ion balance primarily, (iii) deletion of osteoblast-specific genes does not inhibit bone mineralization, and (iv) ectopic extracellular matrix mineralization can occur in the absence of osteoblasts. There are differing schools of thought as to the initial nucleation site in relation to the collagen and to the specific molecules which trigger that nucleation. In view of some it is the hole region within the collagen that serves as the initial focus of mineralization based on the presence of phosphoproteins and the physical mechanical gap which allows the nucleation to occur [347]. Others feel that deposition is not site specific other than being related to the collagen fibrils and that initial nucleation is involved with the association of matrix vesicles which are small membranous structures derived from both hypertrophic chondrocytes and osteoblasts [390, 392].

Much effort has been made both to identify the non-collagenous molecules of bone and to determine their temporal and spatial relation to the bone formation process specifically mineralization both in the hypertrophic chondrocyte matrix and in the early osteoid of bone. Alkaline phosphatase is a specific product of osteoblasts and is expressed at high levels during bone development [399]. Osteoblasts actively synthesizing extracellular matrix are always strongly positive for alkaline phosphatase activity while older mature osteocytes are not. Alkaline phosphatase activity is found within the matrix vesicles where it is felt that initial hydroxyapatite formation occurs [392]. Several groups have defined the fact that fibronectin is one of the earliest and most widespread of the extracellular matrix proteins whose expression occurs with the formation of pre-osteoblasts prior to calcification and which is seen in diminished amounts after mineralization has occurred. Thrombospondin is another glycoprotein found to bind to calcium, to hydroxypatite, and to osteonectin. Most agree that bone sialoprotein and alkaline phosphatase appear earliest following fibronectin in the developing mineralization cycle with osteonectin and osteocalcin formed relatively later. Cowles et al. concluded that fibronectin is one of the earliest matrix proteins expressed being rapidly followed by type I collagen, bone sialoprotein, and alkaline phosphatase with osteocalcin, osteonectin, and osteopontin having synthesis coinciding with mineralization [400]. Roach has also indicated that osteopontin and bone sialoprotein are localized ahead of the mineralization front suggesting that both proteins are necessary for the initiation of bone mineralization [401]. Hultenby et al. showed that BSP was expressed to a great extent in the osteoid synthesized by invading osteoblasts during the endochondral synthesis of bone on calcified cartilage [378]. Osteopontin was most pronounced at sites different from those of BSP with the largest amount observed in cells close to the metaphyseal/diaphyseal border where osteoclastic bone resorption was particularly active [402, 403]. Although these two proteins occur early in synthesis of bone, they appear to have different roles with bone sialoprotein present during the initial phases of bone formation whereas osteopontin was particularly enriched at sites of osteoclast bone resorption [401]. The other phosphoproteins, osteocalcin and osteonectin, are generally not present in areas of initial crystal formation but are clearly found in areas of fully mineralized matrix. It has been postulated therefore that they are more important for controlling the size and speed of crystal formation rather than initiating the crystals. Osteocalcin recruits osteoclast precursors to resorption sites. The initiation of calcification begins with the formation of individual small CA–P crystals within

collagen fibrils and the whole zone regions. When studies were made including the expression of osteopontin and osteocalcin in growth plate cartilage, both proteins first appeared related to calcified cartilage in the hypertrophic zone with both molecules found concentrated at the periphery of the calcified cartilage at the future bone-calcified cartilage interface [403]. Both were also found throughout the mineralized bone matrix.

The predominant mineral phase in bone is hydroxyapatite which contains calcium (CA) and inorganic phosphate (Pi) ions ($Ca_{10}[PO_4]_6[OH]_2$). Landis has done extensive studies on mineralization and organic matrix interaction in particular using the mineralizing leg tendons of the turkey [394]. This model is analogous to the mineralization of bone but is simpler to study and thus specific events of mineral–matrix interaction can be visualized. The final event in mineralization of vertebrate tissues is deposition of a calcium phosphate salt, hydroxyapatite, associated with the organic matrix composed primarily of collagen. The crystals are shaped as thin plates, referred to as platelets. The size of individual crystals varies from 30 to 45 nm while crystal thickness is uniform at 4–6 nm. Crystals eventually fuse to form larger platelets. Extensive study has attempted to determine the initial site of crystal deposition. It has been postulated that the hole zone within the collagen fibril is the initial site of re-nucleation and much of the study revolves around the size and shape of the hole region and the size and shape of the individual crystal. In a 3-dimensional high voltage electron microscopic tomography and graphic image reconstruction study by Landis et al. it was shown that the earliest mineral deposition is within or along the characteristic banding pattern of the collagen. Some crystals appear to traverse adjacent hole and overlap zones but much of the material is located principally within collagen hole zones. The 3D study confirmed that the mineral is of platelet or tablet shape and all the individual crystals lie parallel to one another. The authors concluded that the mineral consisted of irregularly shaped thin platelets rather than rod-shaped components. Width and length were variable but the crystals appeared limited in thickness. The crystals appeared preferentially in the hole zones of collagen but also in overlap zones. Eventually crystal size outgrows dimensions of a collagen hole zone but may be accommodated by channels or grooves in collagen formed by adjacent hole zones in register. The crystal platelets have their long axes nearly parallel to one another and to the long axes of the collagen fibrils they are associated with. As to the site of nucleation, many crystals appear preferentially in the neighborhood of the collagen hole zones but other crystals, spatially separate from those in the hole zones, are present in the collagen overlap zones. Nucleation events occur at different, spatially discrete sites and regions of collagen. This observation by Landis and colleagues is interpreted to argue against the influence on collagen mineral interaction of other matrix components such as extracellular or matrix vesicles.

1.16.5 Continuing Assessments of Biomineralization

Extensive work continues on biomineralization. Anderson et al. continue studies on the mechanisms of matrix vesicle biogenesis and their role in matrix initiation [391, 392] continuing to stress the calcification initiating function of the vesicles in the extracellular specific matrix environments. Two recent reviews by Golub have updated knowledge on matrix vesicles [404] and biomineralization overall [405]. Matrix vesicles are membrane bound organelles now considered to be a lipid bilayer with a composition different from the chondrocyte and osteoblast membranes from which they are derived. They contain TNAP (tissue non-specific alkaline phosphatase), nucleotide pyrophosphatase phosphodiesterase, annexins II, V, and VI, and phosphatidylserine, along with other molecules. Golub comments that MV (matrix vesicles) play some role in the calcification of cartilage, bone, and dentin is now generally accepted although the exact nature and extent of that role remains controversial and the mechanisms through which MV initiate mineralization in these tissues remainunclear. The primary matrix calcified is collagen but non-collagenous proteins play a role. These are proteoglycans, glycoproteins, phosphoproteins, and gamma-carboxyglutamic acid-containing molecules. These include osteopontin (OPN), bone sialoprotein (BSP), and matrix extracellular phosphoglycoprotein (MEPE). In calcifying cartilage type X collagen, fibronectin and matrix gla protein are involved. These molecules may either stimulate or inhibit calcification. Once initiated, the mineral platelets slot into the hole regions and adjacent sites in the collagen molecule. While some postulate the matrix vesicles as forming the initial mineral, others feel that initial mineralization is essentially a self-assembly process based on the physico-chemical environment with deposition beginning at the hole regions. Both views thus incorporate the obvious facts that mineral is deposited within collagen fibril and that non-collagenous proteins are involved in some way. The biphasic representation of mineralization involves an initial formation of appatite with the MVs and then a propagation phase within the matrix.

Other researchers continue to assess the initiation of biomineralization as essentially a self-assembly process with

little to no implication of matrix vesicles as being an essential component of the process. Landis and Jacquet have reviewed these concepts recently as well [406]. This approach focuses on the type I collagen fibrils as the template for apatite mineral formation with collagen polypeptide stereochemistry underlying the binding of these CA and PO_4 ions at sites within the collagen hole and overlap regions leading to nucleation of crystals. Crystal growth and development then proceed. They also propose that the side chains of charged amino acid residues might point toward and into the hole and overlap spaces to provide the initiating binding sites for the Ca and PO_4 ions [407]. Landis and Silver detailed this latter approach in previous articles [407, 408] leading to their contention that type I collagen appears to provide a molecular framework for direct formation of apatite without the necessary intervention or mediation of other molecules in extracellular matrices of calcifying tissues.

Nudelman et al. have extensively reviewed the in vitro models of collagen biomineralization concentrating on the various imaging techniques and the physico-chemical nature of the process. Matrix vesicles are not included in their discussion. They indicate that the two important steps in mineralization controlled by collagen involve (i) the infiltration of the mineral phase in the form of an amorphous calcium phosphate (ACP) precursor into the fibril and (ii) its transformation into oriented apatite crystals. They also indicate that the nucleation of apatite is induced by nucleation sites formed by clusters of charged amino acids present throughout the collagen [409]. They conclude that collagen is not a passive scaffold but rather, that it actively controls and templates apatite formation by directing infiltration of ACP and mediating its nucleation into crystals.

Li and Aparicio have modeled mineralization in vitro with a polymer-induced liquid precursor process [410]. Studies of mineralized collagen fibrils by ultrastructure led them to postulate a hierarchical mineral–matrix accumulation. Hydroxapatite nanocrystals are embedded within collagen fibrils with their c-axes arranged roughly parallel to the long axis of the fibrils. Mineralized collagen fibrils are visualized as bundles of subfibrils with approximately 10 nm diameter, each one with an organic–inorganic core-shell structure. The HA nanocrystals were specifically grown along the longitudinal direction of the collagen microfibrils and encapsulated them within the crystal lattice. The mineral phase surrounded the surface of collagen microfibrils forming an interdigitated network. They consider this to be the basic building block of mineralized collagen. They did not consider the crystals of bone as a bunch of parallel platelets all synchronously nucleated at the gap zones of a fibril but rather considered the crystals as fragments deposited on the surface of collagen microfibrils.

1.17 Epiphyseal Growth

1.17.1 Physeal Chondrocyte Metabolism

Brighton and colleagues focused on the chondrocyte metabolism as well as structure in the physeal regions [98, 411]. The zone of proliferation was characterized by high oxygen content, high glycogen storage within chondrocytes, and high levels of mitochondrial ATP production. As the physeal sequence progressed, cells in the hypertrophic zone had a low oxygen tension, progressive consumption and lowering of glycogen levels until depletion at the lowest levels, and a switching of mitochondrial metabolism with cessation of ATP formation. The matrix of the hypertrophic zone was increasingly laden with calcium.

1.17.2 Studies of Cell Proliferation in Physeal Cartilage Using Tritiated Thymidine Autoradiography

The development of tritiated thymidine autoradiography and its application to the study of physeal chondrocytes allowed for the determination of individual cell contribution to physeal growth. The titrated thymidine autoradiography technique is an accurate indicator of cell proliferation patterns and serves as a way of assessing the dynamics of growth. Thymidine, a specific precursor of DNA, labels cells only in the process of DNA synthesis and allows those cells to be followed through division and early differentiation. Thymidine is taken up from the circulation quickly with labeling reaching a maximum in 1–2 h [412, 413]. Uptake during bone development has previously been demonstrated in the upper regions of the physis [413–415], in secondary ossification center and metaphyseal bone, in epiphyseal including articular chondrocytes [225, 226], and in cells of the perichondrial ossification groove of Ranvier [1]. Kember was one of the first to develop this technique in relation to physeal studies [412–414]. His initial studies were performed in the proximal tibia of the rat. Studies were done from 1 h to 7 days at eight time periods. Kember was able to note cell localization initially in the upper reaches of the proliferating zone of the growth plate with subsequent labeling in progressively lower regions with concentration in the hypertrophic zone by 7 days. This study indicated not only the areas of rapid cell proliferation but also the rate of cell differentiation and passage to each of the chondrocyte cycles including the hypertrophic region. The basic measurement with tritiated thymidine was the percentage of cells labeled in an animal sacrificed at 1 h after injection for any of the cells in synthesis would have divided. The autoradiographic studies were a far more convenient and accurate way of measuring the portion of cells in division than by

mitotic counting. The zone of active cell proliferation was clearly noted to be in the region of columnar or proliferating cells. He was able to identify the stem cell compartment of the germinal zone of the physis owing to the fact that proliferation in this region and thus labeling was less than that immediately below it. The progression of the label through the various regions of the physis toward the lower hypertrophic zone with time was clearly illustrated. While labeling with tritiated thymidine allowed for initial identification of proliferating cells and subsequent assessment of their passage through various sequences towardchondrocyte hypertrophy, the method did not allow for assessment of the contribution of hypertrophy itself to longitudinal growth.

1.17.3 Kinetics of Epiphyseal Growth

The description of the epiphysis given so far has concentrated on molecular and supra-molecular structure but it is extremely important to document the dynamic growth phenomena as these represent the primary function of the epiphyseal region. The epiphyseal growth plate maintains its height at the same extent throughout the vast majority of the period of growth owing to coordinated functions of matrix synthesis at the epiphyseal end and resorption at the metaphyseal end. The epiphysis must also increase in width which it does by interstitial growth of the epiphyseal cartilage immediately above the growth plate and by addition of chondrocytes from the zone of loosely packed cells within the groove of Ranvier. The narrowing by resorption in the metaphyseal region was previously described. Longitudinal growth is also partially controlled by the elastic forces exerted by the surrounding periosteum.

More detailed studies outline the specific features of cell and matrix activity which underlie longitudinal growth. It has been determined that such growth is due to three specific factors which may vary from time to time during the cycle of physeal development and function. Growth by which is meant increase in length is a function of (1) chondrocyte cell proliferation; (2) matrix synthesis; and (3) chondrocyte hypertrophy. In relation to changes in shape, it is felt by Hunziker and Schenk [112] that there is “a high degree of coordination between matrix remodeling and chondrocyte shape change.” They feel that during both acceleration and deceleration of linear growth, it is the changes in hypertrophic cell activities that appear to play an important regulatory role. It is not simply changes in proliferative activity alone that modulate longitudinal growth. Indeed the importance of cell hypertrophy in regulating growth rate lies in the fact that it is a much quicker mechanism than new cell production. In a careful study, they documented that a proliferating chondrocyte would need approximately 54 h (cell cycle time) to duplicate its own volume whereas during hypertrophy, the corresponding volume increase would be achieved in a period as short as 5 h. Hypertrophy was a far more efficient mechanism for bringing about columnar linear growth than cell proliferation alone. Actual matrix synthesis is felt to play a role in effecting but not in regulating longitudinal growth (since it does not contribute directly to acceleration or deceleration of this process by column prolongation). Matrix increase is more related to retaining the biomechanical properties of growth plate cartilage and to integrating chondrocytes in a highly ordered fashion rather than to triggering growth itself. The duration of the hypertrophic phase at approximately 48 h was found to remain constant irrespective of animal age or growth rate indicating that changes in duration would not be the triggering growth factor but, rather, changes in cell shape and size. These findings were somewhat contradictory to previous assessments of longitudinal bone growth which had been determined upon measurement of bulk parameters such as growth plate height, cell proliferation activity as determined by tritiated thymidine incorporation, or matrix production evaluated by autoradiography of matrix components. They concluded that “growth acceleration was achieved almost exclusively by cell shape modeling, namely increase in final cell height and a decrease in lateral diameter.” Even during varying rates of growth, the cell proliferation rate in the longitudinal direction and net matrix production per cell remained unchanged. “Physiological increase in linear growth rate thus appears to be based principally upon a controlled structural modulation of the chondrocyte phenotype.” Cell matrix production in particular “appears to play a subordinate role in regulating longitudinal bone growth rate. The duration of the hypertrophic cell activity phase remains constant at approximately 2 days under the various growth rate conditions.”

1.17.4 Amount of Growth at Each Epiphyseal Plate

It was recognized in the mid-1800s that growth was not uniform at each epiphysis. Ollier undertook experimental studies to assess the contributions to growth of each end of the major long bones [51, 61, 62]. He implanted a lead nail in the middle of a long bone in rabbits, chickens, and lambs and then assessed their relative position several weeks to months later. He concluded that the proximal end of the humerus grew far more extensively than the distal end but that it was the distal ends of the radius and ulna that grew far more extensively than their proximal ends. In the lower extremity, the relationships were reversed. In the femur, most of the growth was at the distal end and in the tibia, along with the fibula, there was more growth at the proximal than at the distal end. He thus clearly understood and

documented that growth was most extensive at the shoulder, wrist, and knee. He also indicated that it was the most actively growing epiphyses that fused latest. He indicated, however, that those epiphyses which provided more longitudinal growth did not do so because of the fact that they continued growing longer, but rather that they contributed more throughout the entire period of growth. He then identified the clinical importance of these varying growth features in terms of resections for disease which were commonly performed in those days. The obvious conclusion was that resections in the elbow area had relatively little consequences for longitudinal growth whereas at the knee, they would lead to quite extensive limb shortness if done during the active growing years. Similar major growth limitations would occur with early resections at shoulder and wrist.

The contributions to growth of each plate in each of the long bones were established by Digby [416] in a brief publication in 1916 as follows: proximal humerus, 80 %; distal humerus, 20 %; proximal radius, 25 %; distal radius, 75 %; proximal ulna, 20 %; distal ulna, 80 %; proximal femur, 30 %; distal femur, 70 %; proximal tibia, 57 %; distal tibia, 43 %; proximal fibula, 60 %; and distal fibula, 40 %. These relative amounts of growth persist at a uniform level throughout growth.

Pritchett [417] has reported a detailed study of upper extremity long bone growth in 100 males and 100 females between 1 and 19 years of age and lower extremity long bone growth in 123 males and 121 females from age 7 years to skeletal maturity. His data indicate that the percentage of growth plate activity at each long bone epiphysis is not constant throughout the growth period. He used the location of the nutrient artery as the fixed point for measurement. He concluded in agreement with Digby that the proximal growth plate of the humerus contributed 80 % of the growth, the distal plate 20 %, the proximal radius 25 %, and the distal radius 75 %. He differed from Digby in attributing the proximal ulna contribution at only 15 % and distal ulna 85 %. The proximal humerus (40 %) and distal radius–ulna (40 %) accounted for 80 % of upper extremity growth with the elbow region (10/10 %) only 20 %. Pritchett was able to assess growth at various ages with the very interesting finding that growth plate activity was not proportionately constant throughout growth. In the humerus before the age of 2 years <75 % of growth occurs proximally increasing to 85 % at age 8 and remaining constant at 90 % after age 11. At the distal ulna, 85 % of growth occurred but 90 % by age 5 years and 95 % by age 8 years. At the distal radius, growth was 80 % overall but 85 % after age 5 years and 90 % by age 8 years. In the lower extremity the overall growth contribution was the same as noted by Digby. As in the upper extremity growth plate activity was not constant throughout growth [418]. Although approximately 70 % of growth of the femur occurs distally in both males and females the proportion in the distal femoral growth plate in girls varies from 60 % at 7 years of age to 90 % at age 14 while in boys the contribution of the distal femoral growth plate varies from 55 % at 7 years of age to 90 % at age 16. The overall contribution of the proximal tibia growth plate is approximately 57 %. This varies from 50 % at 7 years of age to 80 % at age 14 in girls and in boys from 50 % at 7 years of age to 80 % at age 16. The amount of growth remaining in the distal femur and proximal tibia in males and females has been documented in greatest detail by Green and Anderson [419, 420]. Pritchett has also developed similar charts from his data. The amount of growth, which can be expected to occur throughout childhood or is currently remaining in the proximal femur and distal tibia, can also be calculated from these charts by defining the distal femoral growth as 70 % leaving the proximal femoral as 30 %. Similar calculations can be made for the distal tibia.

Karrholm et al. [421] have calculated the longitudinal growth rate of the distal tibia and fibula in children from 9 years of age to skeletal maturity in 30 boys and 31 girls. The patients were studied with Roentgen stereophotogrammetric analysis (RSE) with examinations quite frequently at intervals of 1–12 months with most patients observed at 3–6-month time periods. In the distal tibia in boys and girls, the average growth rate decreased from a plateau of about 10–11 years, respectively. The decreasing growth rates were found somewhat later in the distal tibia than in the distal fibula in both boys and girls. The growth rates, however, were close to 0 at about the same time in distal tibia and fibula in both sexes. Growth charts were established to provide clinical guidelines. The group also calculated the average daily growth rate of differing skeletal maturity measuring micrometer level values at distal fibula and distal tibia. Charts were produced for the calculated remaining growth in the distal fibula and distal tibia in girls from 8 years of age and in the distal fibula and distal tibia in girls from 9 years of age. The data were expressed in charts with mean values as well as one and two standard deviation values above and below the mean.

Several sets of growth data are available covering lengths of major long bones followed longitudinally in groups of normal patients [417–420, 422]. These include the work of Maresh [422] who published length data for males and females separately for humerus, radius, ulna, femur, tibia, and fibula from 2 months to 18 years of age. Measurements were made between the epiphyseal plates up to and including 12 years of age and entire bones including the epiphyses from 10 years of age upwards. Green and Anderson published values for femur and tibia in males and females.

Approximate estimates of growth per year in the distal femoral and proximal tibial growth plates have been described by other observers; (i) Pritchett [418]: average of

1.3 cm per year of growth from the distal femur (half that amount in the final 2 years of growth); average of 0.9 cm per year of growth from the proximal tibia (half that amount in the final 2 years of growth) and (ii) White and Stubbins [423]: 3/8″ growth per year at distal femur; 1/4″ growth per year at proximal tibia.

Pritchett [418] has also summarized growth phenomena reviewing concepts derived over decades of investigation going as far back as Ollier in the nineteenth century. (1) Growth contributions from each of the upper and lower extremity growth plates are not equal. One dominant growth plate makes the major contribution to length in any particular bone throughout growth; in the humerus the proximal growth plate, in the forearm the distal radial and ulnar growth plates. In the lower extremity the major contributions are at the knee involving the distal femoral and proximal tibial growth plates. (2) Growth is not constant at all ages. The activity of the growth plate varies with age, with the more active growth plate assuming greater importance with increasing age. (3) The nutrient foramen marking the entrance of the nutrient vessel into the cortex provides a fixed point in the long bone and growth of each end can be measured in relation to it. (4) The more active growth plate is thicker than the less active growth plate. (5) The more active growth plate closes later than the less active growth plate and virtually all growth during the last 2 years before growth plate closure occurs at the more active growth plate. (6) The nutrient canal is directed away from the more active growth plate and toward the less active growth plate.

1.17.5 Growth Slowdown and Growth Arrest Lines (Harris Lines)

Harris demonstrated transverse radiodense lines across the metaphyses of growing children who had been subjected to either generalized illness or localized bone disorders from which a recovery had occurred. Harris was a British radiologist who clearly delineated the phenomenon although he was inaccurate in the histopathologic interpretation as he felt the disorder was due to the deposition of calcium within the physis itself. Since that time, studies of clinical material by Ogden [424] and experimental assessments by Siffert and Katz [425] have shown that the transverse metaphyseal line is bone and represents thickened transversely interconnected trabecular networks with the normal longitudinally oriented trabecular bone on either side. With the slowdown in physeal growth during the time of illness, the normal endochondral patterning is thrown off and bone accumulation at the outer reaches of the metaphysis is increased. The growth arrest line is parallel to the adjacent physis. With the slowdown or complete cessation of growth, the trabeculae become thickened and fuse with each other transversely. They contain central cores of cartilage but are primarily bone. When the child enters a recovery phase, physeal growth increases and the normal pattern of metaphyseal bone is resynthesized with the trabeculae oriented along the long axis of the bone. With increasing time between the period of growth slowdown and the time of reassessment, the physis grows away from the transverse metaphyseal line. Histologic studies show the bone thickening to be present throughout the transverse diameter of bone within the metaphysis and not to be concentrated as an inner thickened rim of the cortex. If there are recurrent episodes of poor health, then the patient will often demonstrate multiple growth arrest lines. These are most prominently seen at the distal femur and proximal tibia where growth is most rapid and infrequently seen around the elbow where growth is extremely slow. They can also be seen at the proximal humerus and distal tibia where growth is also more marked. The growth arrest lines are seen with many types of childhood illnesses. They are on occasion seen, however, in the absence of serious disorders. Transverse lines related to one physeal area are also frequently seen following fractures of the adjacent bone. They can serve as valuable indicators of the state of physeal function since the distance between the physis and the growth arrest lines should be the same throughout the entire width of the bone. If there is a partial or complete focal physeal arrest, early demonstration of this can be seen by angulation of the growth arrest line with diminished distance between physis and the line at the area of tethering. While growth arrest lines are clearly identified on plain radiographs, they are seen with a much higher degree of resolution and in earlier states of formation on MR imaging.

1.18 Responses of Developing Bones and Epiphyses to Mechanical Stresses

1.18.1 Normal Responses to Mechanical Factors

The importance of mechanical or physical factors in stimulating bone development has been commented on from the early years of scientific investigation. As early as 1815 Howship felt that “mechanical pressure” was the principal agent in bringing about progressive changes of structure in growing bone [50]. King (1844) [426] observed “that pressure and tension affect the evolution of all parts, scarcely requires proof at this time.” In commenting on the replacement of the cartilage model of the developing bone by bone

tissue itself, he indicated that "the precise site of this 'bony' deposit seems to be determined by a certain excessive degree of pressure or tension, as in the center of a cubicle bone or an epiphysis or in the middle of a parietal or cylindrical bone. The continual depositions which succeed seem also strictly determined by the directions of pressure or extension or of both." He felt that internal absorption would seem to depend on the removal of pressure from the center to the circumference. In terms of the structuring of the internal bone, he felt that "every bone has most to resist on its surface, and least internally. In proportion as the exterior is strained and excited, so is it nourished, so does it grow; while as the inner parts are the more removed from physical tensions, they are carried off by absorption." That much depends on tension seems corroborated by the remark that "when tension is removed from the center, it becomes absorbed which explains the excavation of bone, the course of simple atrophy, and the modeling of definitive callous." "The cause which fixes the precise spots of incipient fetal ossification are conceived specific. The event takes place in a solid nidus at a point where many convergent forces and pressures are concentrated. The continuance of ossification (being as it were a columnar growth against gravity) follows a similar rule for it is a deposition where pressure is greatest; and whether we regard the order in which the nuclei of all the bones begin or the order of rapidity with which each one grows, the activity is evidence in dependence on the tension of the parts. The form of every bone and process of bone, and even the arrangement of every fiber of cancellus seems to me to be regulated by the above principle." D'Arcy Thompson reviewed the mechanical structure of bone in his classic work "On Growth and Form" [427]. He referred to several studies pointing out the trabecular pattern of the proximal femur where the curving trabeculae were found so that "each intercrossing is as nearly as possible an orthogonal one: that is to say that one set of fibres (trabeculae) or cancelli cross the other everywhere at right angles." The arrangement of the bony trabeculae was essentially a diagram of the lines of stress (or directions of tension and compression in a loaded structure.) Within his 10-page discussion (pp. 975–985) he also referenced several major studies from 1827 to 1930 on the topic.

It was the works of Hueter [428] and Volkmann [429], published separately in 1862, focusing on the effects of pressure on cartilage growth and of Wolff [430], summarized in his classic book in 1892, focusing on bone structure in relation to extrinsic forces and functional patterns that firmly implanted the concept of mechanical or biophysical effects on cartilage and bone structure (Table 1.15). The Hueter–Volkmann principle refers to skeletally immature bone growth via cartilage regions with suppression due to excess compression loading and acceleration to reduced loading. Wolff was relating to the adaptation of bone as a tissue to its mechanical environment with bone apposition stimulated by increased stress and bone resorption by reduced stress.

Table 1.15 "Laws" of Bone and Cartilage Development

Re: *Bone structure*	
Wolff's Law (1870, 1892)	(Extrinsic forces on a bone modify the internal trabecular architecture and the external shape)
	"Every change in the form and function of the bones, or of their function alone, is followed by certain definite changes in their internal architecture, and equally definite secondary alterations of their external conformation, in accordance with mathematical laws"
Re: *Cartilage growth tissues*	
Hueter–Volkmann "law" (1862)	There is an inverse relationship between compressive forces along the long axis of epiphyseal growth and the rate of epiphyseal growth
	(Increased pressure on the concave side interferes with normal bone growth while on the convex side less than normal pressure leads to overgrowth.)
	(Pressure beyond the normal on growth cartilage leads to growth retardation.)

Parsons in 1905 [224] defined "epiphyses which occur at the articular ends of long bones, by which the pressure is transmitted from bone to bone" as pressure epiphyses. He contrasted these with epiphyses into which tendons are inserted which he referred to as "traction epiphyses" [431, 432]. Traction epiphyses were noted by a projection from one end of a shaft of a long bone into which a tendon was inserted and which had a separate center of ossification. Both Haines [433] and Barnett and Lewis [434] felt that traction epiphyses were derived from pre-existing sesamoids.

As early as 1911, Schaffer [435] and Gebhardt [436] used photo-elastic models to assess mechanical stresses and their relation to ossification in developing cartilaginous epiphyses. Similar studies were subsequently shown by Pauwels decades later also in an effort to relate mechanical forces to bone development [437]. These contributions have been reviewed by Carter and Wong [438, 439]. Gebhardt concluded that the central region of the developing cartilaginous epiphysis contained the greatest accumulation of stress which then led to the formation of the bony epiphyseal nucleus. Pauwels' studies were interpreted to indicate that Gebhardt was incorrect and concluded that the secondary ossification nucleus formed in areas of "pure and high hydrostatic pressure." More recent studies by Carter and coworkers felt this conclusion also to be inaccurate, primarily because of the use of incorrect assumptions for boundary and loading conditions.

1.18.2 Biophysical Effects Underlying Bone Development, Maintenance, and Repair. Mechanotransduction

Experimental studies are now allowing for biophysical [440] understanding of the mechanical effects on normal and abnormal bone. The intercellular communication system of bone, mediated through the lacunar-canalicular system, allows for biophysical control mechanisms essential to tissue development and maintenance. In a work primarily relating to bone as a tissue, it was indicated how ***mechanotransduction*** (the conversion of a biophysical force into a cellular response) encompasses four distinct steps: ***mechanocoupling***, where mechanical loads cause bone deformations that stretch/compress cells and create fluid movement within canaliculi; ***biochemical coupling***, mediated by force transduction through the integrin–cytoskeleton–nuclear matrix structure (cell as mechanosensor); ***transmission of biochemical signal***, via surface osteoblasts and lining endothelial cells reacting to cyclic mechanical bending or osteoblasts/osteocytes communicating via gap junctions linking cell process to adjacent cell process and transmitting small messenger molecules or electric signals; and an ***effector cell response*** where the effects of the former three features direct or inhibit the cell response [441]. Bone cells in a physiologic strain range have an equal balance of ***bone formation*** and ***bone resorption***. Decreased strain (disuse) favors resorption over formation, increased (but still physiologic) strain favors formation over resorption whereas massively increased strain (pathologic) leads to structurally less effective woven bone formation.

The biophysical effects in limb morphogenesis on mesenchymal tissue, including muscle and cartilage, have been assessed [442]. The combined cellular activity of the growth process generates deformations and pressures caused by the developing tissue itself, which influences morphogenesis by modulating growth rates, modulating tissue differentiation, influencing the direction of growth, or deforming tissues. A target cell responds in four basic ways to incoming signals by: ***direct contact*** from a touching cell or from extracellular matrix, ***diffusible molecules*** that bind with surface receptors or intracellular molecules, ***gap junctions*** between adjacent cells, or ***imposed tensions and pressures*** wherein growth generated strains and pressures from the mechanical environment induce the target cells into specific synthetic functions. Studies on cultured osteoblasts allow for quantitative assessments of applied strains that alter matrix synthesis [443].

The mechanical principles controlling the internal architecture of bone were assessed in detail in the last half of the nineteenth century by many authors and codified by Wolff in his classic “Das Gesetz der Tranformation der Knochen” (1892) [430] [translated into English as “The Law of Bone Remodelling” (1986)]. In these works the trabeculae of bone were considered to be arranged for appropriate structural support along the lines of pressure and tension trajectories. There was early awareness that mechanical principles operated to guide differentiation of mesenchymal tissues into bone, cartilage, or fibrous tissue. Roux (1912) felt that undifferentiated tissues would respond differently in terms of the developing connective tissue phenotype depending on whether they were exposed to tension, shear, or compression [444]. Krompecher (1937) [445] related cell response to the specific mechanical environment provided [445]. He stressed that mechanical factors were involved with bone formation in normal development (1934) [446] and with fracture repair (1956) [447]. Moderate tension forces applied to fractures caused intramembranous bone rather than cartilage formation. He demonstrated direct bone formation from fibrous tissue (desmoid tissue) in the presence of blood vessels, a mechanism he contrasted with endochondral bone formation, and referred to as primary angiogenic bone formation (primare angiogene Knochenbildung).

Pauwels considered that there were only two different types of mechanical stimuli that influenced differentiation of mesenchymal cells. These stimuli caused either pure ***distortion of shape*** by stretch or pure ***change of volume*** by hydrostatic pressure. The nature of the stress determined the cell differentiation pathway. Distortion of shape was due to stretch which led to collagen fibril production whether the stretching arose from compression (external and unequal), tension, or shear stress. The nature of the deformation (shape change) was dependent on the plane of change as the force was applied. The collagen fibril production in tension led to fibrous tissue which could then differentiate to intramembranous bone while compression led to cartilage formation which could then differentiate to endochondral bone. In his conception bone could only form from cells protected from intermittent stretching by either the fibrous tissue or cartilage. Change of volume was due to hydrostatic pressure which produced uniform (equal throughout) and extreme stress within the cell whether applied externally or internally. Hydrostatic pressure (compression) caused cells to differentiate into cartilage. He recognized that shear caused a change in cell shape and stimulated fibroblast formation whereas hydrostatic compression which changed cell volume but not shape stimulated chondrocyte formation; when these two forces were combined in a tissue area the combined stress favored mixed tissue formation such as fibrocartilage. In his mechanical construct, soft tissues were necessary in repair to stabilize the mechanical environment and only when this happened could bone formation occur (Pauwels 1976, English translation [448]; Weinans and Prendergast 1996 [449]).

Understanding which mechanical force leads to what tissue type remains a matter of intense investigation. ***Stress*** is a general term defined as force exerted between contiguous bodies and ***strain*** is a slightly more specific term referring to a pull or a stretching force that tends to counteract the stability of a structure or region. There are three forces of differing types that eventually translate into tissue differentiation to different specific phentotypes. (i) ***Tension*** refers to a state of being pulled or stretched tight; a ***tensile force*** serves to stretch or draw out an object or region. (ii) ***Compression*** refers to a state of being squeezed together to occupy less space. ***Hydrostatic*** (often referring to compression) defines the pressure exerted by liquids at rest. (iii) ***Shear*** refers to a state produced by pressure such that each layer slides over the next; a shear force distorts or breaks a structure usually by an oblique or rotatory force. There is general agreement today that tensile stress leads to intramembranous ossification; compression favors chondrocyte formation: constant hydrostatic compression leads to cartilage formation while intermittent compression favors actual endochondral ossification; and high shear stresses favor fibrous tissue formation [450]. These descriptions refer to primarily uniaxial forces but in reality many forces on developing or repairing bones are multiplanar. Pauwels developed the concept of mixed forces, recognizing that the combination of shear and hydrostatic compression led to fibrocartilage formation. Cyclic motion and shear tend to a large external callus production.

Claes and colleagues have quantified the magnitudes of the hydrostatic pressure and strain that select either the intramembranous or endochondral sequences. By analysis of experimental callus geometry they determined that if compressive hydrostatic pressure (negative) exceeded 0.15 MPa endochondral bone formation occurred whereas if hydrostatic pressure was below this threshold intramembranous bone formed [451]. Perren has focused attention on the interfragmentary repair tissues themselves, developing the interfragmentary strain (IFS) theory that the fracture gap could only be filled with a tissue capable of sustaining IFS without rupture [452]. If IFS is high, only fibrous granulation tissue can form; if it is intermediate, cartilage is present and when low, bone formation follows. The formation of a large soft tissue callus stabilizes the gap peripherally, decreasing motion, decreasing IFS, and allowing progressive tissue differentiation from fibrous to cartilaginous to bone. The elongation potential of granulation tissue was considered to be +100 %, cartilage +10 %, and bone only 2 %.

Awareness is increasing that the mechanical effects on tissue differentiation are mediated at the individual cell level and that the cells respond to cell level deformations and to fluid flow. Fluid flow can cause mechanical stimuli within tissues at the cell level by further increasing cell deformation. Bone cells (osteocytes) communicate with each other, with overlying osteoblasts and with cells lining intraosseous vessels via the lacunar-canalicular system. Consideration is growing that tissues should be analyzed as solid–fluid mixtures. Owan et al. (1997) have gone so far as to consider that responsiveness to fluid flow may be more important than mechanical strain in bone cells [453]. Prendergast and van der Meuler (2001) point out that biomechanical stress on cells is high if fluid flow is high and that both matrix deformation and fluid flow taken together define the mechanical milieu of the cell [454].

In summary, for intermittently imposed loading in repair tissues: (i) direct intramembranous bone formation occurs in areas of low stress and strain, (ii) hydrostatic compressive stress is a stimulus for chondrogenesis, (iii) high tensile strain is a stimulus for the net production of fibrous tissue, and (iv) tensile strain with a superimposed hydrostatic compressive stress will stimulate the development of fibrocartilage.

Carey wrote a series of studies on the dynamics of musculoskeletal histogenesis in which he sought to relate the biophysical forces generated by growth phenomena to the structure of the tissues they were associated with [455–458]. He indicated that "the biophysical aspect is as important as the biochemical one in the problem of bone origin." He was particularly interested in the effect of developing muscle on the developing skeleton. He was one of the first to attempt to assess growth from a dynamic viewpoint in which interaction of forces resulted in transference of energy. The forces generated were major factors in histogenesis. He referred to his concept as the "growth motive force" which he defined as "any agency which tends to produce a transfer of kinetic energy from an active to a less active group of cells and of potential energy from a less active to an active group, and a cellular field of differential growth until equilibrium is established." Although the work postulated mechanical effects of tissue subsets on each other, no experimental work was done and some of the conclusions, while theoretically attractive and convincingly presented, have never been experimentally validated. His work did not specifically discuss the types of mechanical sources, although frequently mentioning their importance; it was strongly based on histologic and radiographic studies. He referred to active and less active zones in reference to the rate of cell division per millimeter of cross-section as determined histologically. He sought to assess how the increase of cellular components and their transformation led to the perfection of form out of the relatively formless antecedents (by which he means undifferentiated mesenchymal cells). Along with many investigators at that time, cellular differentiation was considered to be influenced by the environment in the sense that it was partly dependent upon an interaction of the developing parts before external form and internal structure were perfected. He referred to the relationship of differing tissue groups to

each other in development and used the term "inductive" to imply that some changes were produced without cell–cell contact and "conductive" in which there was change produced with contact. He thus felt that through conduction of the developing skeletal and muscular tissues upon each other, the factor of force was inherently involved. As the skeleton underwent its most rapid growth during early embryogenesis, a tensional elongating or stretching action was bound to be exerted upon the surrounding and less actively growing continuous syncytial mesenchyme. He defined his theory of the relationship between muscle and skeletal development in simple terms:

(i) There is a force manifested by rapid skeletal growth; (ii) this force exerts a tensional or stretching action upon the surrounding mesenchyme influencing the first steps of myogenesis; and (iii) the first differentiated muscles react upon the primordial blastemal skeleton resulting in a definite series of changes. These are seen in the formation of the condensed cartilaginous skeleton and later, as the muscles become more developed and vigorous, serve as a physiological foundation in the formation of the osseous skeleton.

He thus defined a degree of equilibrium of the musculature and skeleton during any stage of development established between opposing myogenic and skeletal forces. His theory indicated that "mechanically, skeletal and the related muscular tissues are inter-dependent, one relying upon the other for its initial and continued differentiation." Stated another way, he felt that force was exerted in certain regions of the embryo by the genesis of a rapidly dividing group of cells upon a less active or relatively passive group of cells. In turn, the relatively passive group reacts upon the former. This action/reaction response was shown by alterations in the rate of growth or by changes produced in the external form or internal structure of groups of cells. He derived the term "growth motive" and defined it as any agency which tends to produce a kinetic and potential energy in a cellular field of differential growth.

In attempting to relate biomechanical features to changes in shape and form, Carey provided brief definitions. He defined any definite alteration in the form or dimensions of an elastic body as a strain with the simplest strain being the linear one. Elongation was defined as the ratio of change in length to the initial length. A negative elongation or shortening was called compression; a positive elongation or lengthening was called tension. He then related skeletal development from the limb bud stage on to the associated myogenesis in relation to the reciprocal forces of each. The core of his argument is that mechanical forces play a major role in cell differentiation as the limb bud progresses from mesenchymal condensation to the cartilage model of the developing bone to formation of the primary ossification center with hypertrophy of cells in the cartilage mass and finally to cortical bone formation. He postulates that centrally there is more cell activity within the developing cartilage mass than there is at the periphery. As the central core of the limb pushes forth more rapidly than the mesenchymal cells at the periphery there is a tendency for the latter to be pulled out, stretched, or elongated by the former. "The traction force of the rapidly growing appendicular core exerted upon the surrounding mesenchyme is the internal stimulus of a correlated part, resulting in the elongation of the nuclei of the pre-muscular mass in the direction of the long axis of skeletal growth." As differential growth continues, the growth motive force becomes more and more in evidence and there is a drawing out or stretching of the peripheral syncytial cytoplasm in the direction of skeletal growth. The myofibril is formed roughly parallel to the long axis of the developing bone. The formation of the embryonic skeletal muscles is felt to represent a definite reaction to the growth of the skeleton and in turn these muscles "tend to restrict the growth of the skeleton in length. This is manifested by an increasing condensation of the skeletal core." Cartilage then forms within the skeletal model to provide greater stability to counteract the formation that would occur as the primitive muscles begin to contract. He thus postulates continual interplay between muscle and skeletal development. As the growth motive force of differential growth continues, the musculature becomes too vigorous even for the cartilage base which then leads to supplanting of the cartilage model by the osseous skeleton.

Carey produced a series of drawings relating to the cell and matrix deposition patterns of the developing bone and the associated muscle in an effort to show how the various strains helped modulate cell differentiation (Fig. 1.22a–d). He concluded that there was a direct transference of kinetic energy from the more rapidly growing skeleton to the less actively growing primitive musculature and then a reactive transference of potential energy from the latter to the former tending to an equilibrium state. When muscle differentiated to the state that it began functioning, there was a direct transference of kinetic energy from this tissue back to the growing skeleton tending to retard or alter its motion or growth. The active and passive play of the muscles led first to a stiffening of the skeletal model by cartilage formation and then further stiffening by bone formation. In regard to bone formation, he noted in particular a subperiosteal osteogenetic and constricting cell zone at the center of a developing long bone which quickly encircled the shaft. Formation of the osseous skeleton was part of a feedback mechanism based on the stimulus of the functionally active thigh muscles and the stimulus of the restriction to growth at the ends of the rapidly elongating cartilage model due to passive muscular resistance. The interactive forces also explained in a mechanical or biophysical sense why the bony epiphyses or secondary ossification center formed. The centrifugal expansion of centrally confined epiphyseal

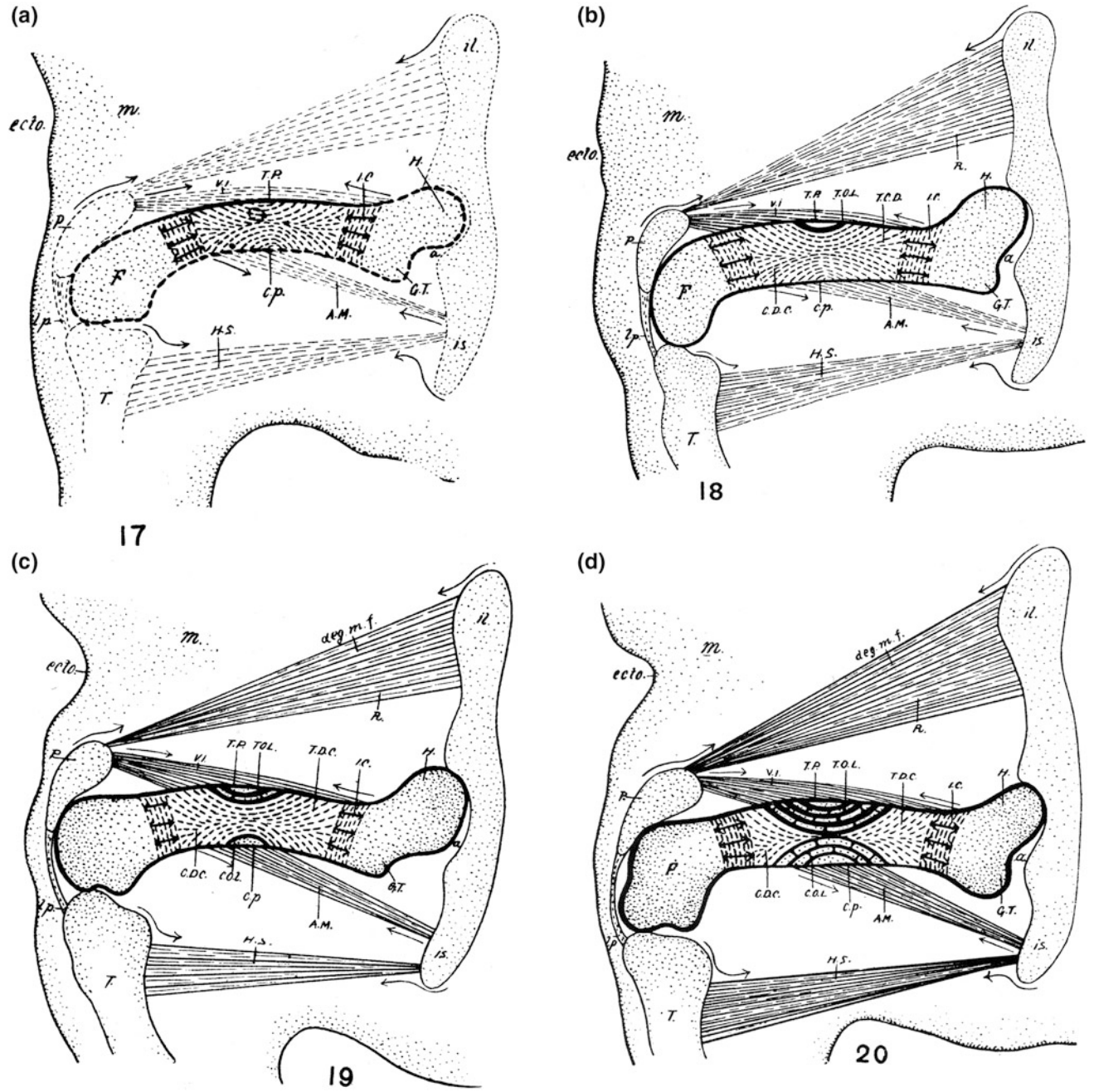


Fig. 1.22 Illustrations from the work of Carey demonstrate his efforts to correlate the embryologic development of bone and muscle in relation to the feedback effects of the two tissue types. The work also demonstrates at a theoretical level how the mechanical actions of one tissue affect the developmental pattern of the adjacent tissue. The sections are from the developing hind limb of the embryonic pig. The developing pelvis in each figure is shown at right with "il" representing the ilium and "is" representing the ischium. The head of the femur (H) is shown at right and the distal femur (F) and proximal tibia (T) are shown at left. Changes in tissue types are shown progressively from figure **a** the 18 mm stage (*upper left* number 17), to figure **b** the 25 mm stage (*upper right* number 18), to figure **c** the 32 mm stage (*lower left* number 19), and to figure **d** the 50 mm stage (*lower right* number 20). The stress lines as conceived by Carey. The *stress lines* as conceived by Carey are outlined on the developing femur. The initials IC represent the growth plate which he refers to as intermediate growing cartilage. At progressive time periods the diaphyseal cartilage, surrounding perichondrium, and early periosteum are converted to areas of bone formation. The letters TP outline the tensile periosteum on the anterior surface of the femur and the letters cp outline the compressible periosteum on the posterior surface. As bone is formed on the dorsal or anterior surface the orientation listed as TOL refers to the tensile osseous lamella while on the posterior surface the letters col refer to the compressor osseous lamella. As illustrated by Carey, the bone is formed initially on the anterior surface and subsequently on the posterior surface. While Carey illustrates stress lines in the developing embryonic model of bone his work remained theoretical with little to no published experimental work either by himself or others to verify his interpretations

cartilage cells was resisted by the centripetal effect of the peripheral muscles, ligaments, and tendons together producing the "adequate compression of differential growth." The epiphyseal bone thus represents a terminal pressure system segmented from the diaphysis.

Carey indicates that muscle differentiation in the thigh shortly after the formation of the cartilage model of the bone is not a coincidence but a mechanically mediated cellular response to the traction or tension to which the continuous peripheral mesenchyme is subjected during the rapid growth of the femur in length. Carey then relates the rapid growth of the skeletal model of individual bones to what happens between them at the joint interface. Resistance during femoral growth, for example, is met at first at the proximal end in the centers of opposing growth for the triradiate cartilage (ilium, ischium, and pubis) and at the distal end in the centers of opposed growth for the tibia. The regions of cell concentrations between opposing developing bones are referred to as the interzone where joints will eventually form. The appearance of the joints, however, is felt by Carey to be the mechanical result of the opposed growth of contiguous accelerating growth segments. Early resistance to expansion of the femur in two directions, by associated growth of the hip region and knee region, combined with the constraints of the peripheral muscle, leads to normal rotation of the limb plus slight bending of the bone. He feels that formation of periosteum around the cartilage model is also mediated by mechanical events. The perichondrial fibrosis becomes modified into a periosteal membrane. The osteoblasts form a matrix which is mechanically situated to serve effectively as a cellular reaction to the great strain to which the bent femoral beam is subjected. The appositional growth of bone strengthens the femoral beam at its weakest part. The mechanical result of this cellular reaction of bone differentiation is the progressive formation of a more stable base for the application of muscular forces. The proximal femoral–acetabular hip joint is formed owing to different rates of growth of the femur and the acetabular cartilages. The head of the femur is seen to, relatively speaking, advance farther and farther into the acetabulum formed by the ilium, ischium, and pubis. The force of longitudinal interstitial growth of the femur per square millimeter of cross-section is calculated to be 12 times greater than that of the acetabulum. This fact associated with muscular restrictions to longitudinal femoral growth and a femur rendered more stable by primary ossification center bone, leads to the structural elaboration of the hip joint. Joints are not hereditary structures alone but rather the mechanical resultants of opposing centers of accelerated growth.

Overall, limb development is a feature both of intrinsic self-differentiation of the cell mass plus an extrinsic mechanical interaction due to differential growth. The idea is presented that shaping of bones, even in the embryonic time, is "an immediate mechanical resultant of the force of its own interstitial growth and the intermediate resistance encountered to this growth." Both growth and resistance are inseparable and both play major roles in morphogenesis. The formation of a joint is a resultant along the lines of juncture between the zones of accelerated growth of neighboring segments in opposite dimensions. That segment presenting the greater force of growth possesses the convex element whereas the segment with a lesser force is concave in relation to the moveable joint. Joint form is not solely an inherited pattern of skeletal segmentation, but rather occurs owing to the mechanical resultants of compressive and shearing stresses of prior centers of accelerated growth opposing each other in the blastemal skeleton. The histogenesis and morphogenesis of the musculoskeletal regions therefore are as much dependent upon the mechanical factors extrinsic to the cells of the region as upon the intrinsic faculty of the tissue itself to grow. Each of the three structural forms of the skeleton, sclero-blastemal, cartilaginous, and bony, represents advancing degrees of consolidation reacting to a gradient increase of pressure.

Carey provided an excellent description of the development of the thigh of the pig encompassing both the bone and muscular tissues. This is excellent as an embryologic description itself although he utilizes his theory of growth motive force to comment on the reasons for the differentiative patterns. While the mechanical theory is attractive, the ability of organ culture to demonstrate entire bone growth in vitro and in the absence of limb musculature did much to eclipse interest in the work. In our opinion, however, much of value is provided warranting renewed exploration with the far more sophisticated micro-technology now available.

1.18.3 Mechanical Stresses and Their Differences and Effects on Skeletal Development

Carter and associates [438, 439, 459–461] have defined a model which suggests that mechanical loading histories greatly influence bone morphogenesis beginning from the embryonic stages of endochondral development and continuing throughout life. Carter and associates have developed theoretical models of new bone formation in general and the endochondral ossification mechanism in particular based on assessments of mechanical stresses and the use of finite element analysis. Integral to their theoretical basis is the belief that "the progression of endochondral bone formation in the diaphysis and metaphysis, the formation of the secondary ossification center, and remodeling of the new bone may all be influenced by the mechanical forces created from an increasingly active muscular system." Their feeling is that the entire internal structure of long bones is governed

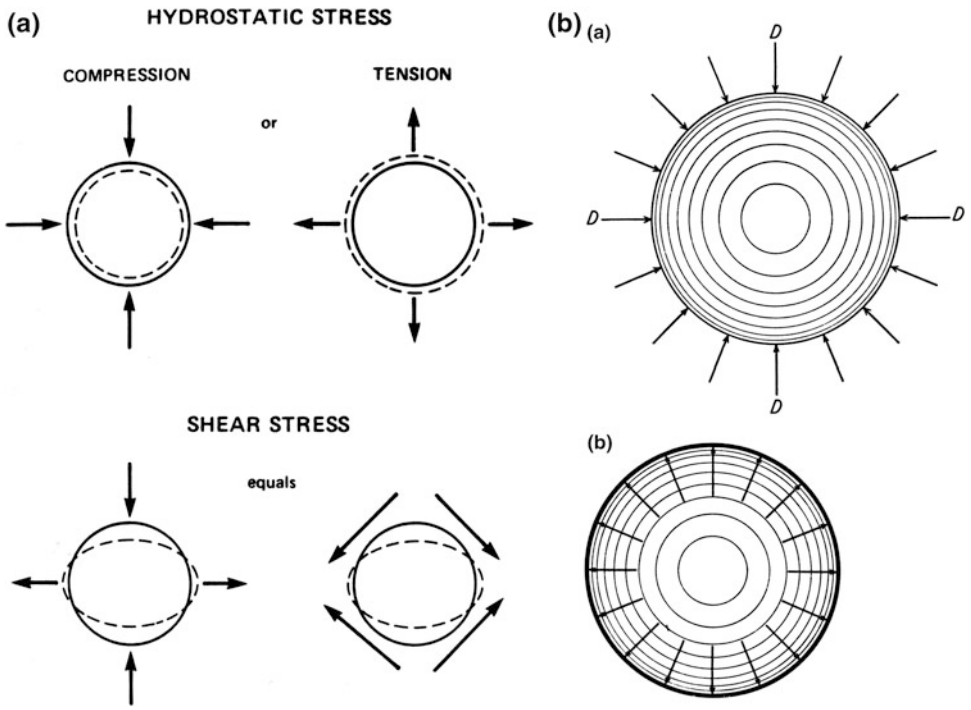


Fig. 1.23 Diagrammatic illustration of stresses on a developing bone which tend to influence certain types of synthetic patterns. Both hydrostatic (dilational) stresses and distortional (shear) stresses play a role. **a** Dilational stress causes change in the volume of compressible materials and shear stress results in distortion of the material. The *thick lines* represent unloaded, underformed shape and thin lines represent loaded, deformed shape (from Wong and Carter [461]). (Reprinted with permission from Wong and Carter, A theoretical model of endochondral ossification and bone architectural construction in long bone ontogeny. Anat Embryol. 1990;181:523–532. Copyright 1994 Springer Science + Business Media). **b** Hydrostatic pressure in mesenchymal tissue arises due to external forces (*arrows*) or from internal growth forces (*arrows*) caused by increases in tissue volume encountering resistance peripherally (from Pauwels [437]). (Reprinted with permission from Pauwels F, A new theory concerning the influence of mechanical stimuli on the differentiation of supporting tissues in *Biomechanics of the Locomotor Apparatus*, p. 388, 1980. Copyright 1980 Springer Science + Business Media)

by loading or tissue stress histories which the bones are exposed to during growth and development. Their studies seek to emulate the influence of cyclic mechanical stresses on bone development to show how these would correlate with the endochondral ossification sequences. Using 2-dimensional computer models, they conclude that mechanical stresses caused by intermittent loads influence the formation of the endochondral ossification patterns. Both the ossification of the diaphysis and the formation of the secondary ossification center of the epiphysis are predicted by locating regions of high intermittent shear stresses. Their model interprets the stresses on the developing bone as being primarily hydrostatic or shear. Hydrostatic or dilatational stress causes a change in the volume of compressible materials on the basis of either compression which decreases the volume or tension which increases it while distortional stress causes no change in volume but causes changes in shapes (Fig. 1.23a, b). They propose that endochondral ossification within the cartilage model is accelerated by cyclic shear stresses and slowed by cyclic compressive dilatational stresses. They recognize that the complete state of stress in any material is best described by specifying six stress components of three principal stresses and their orientation with respect to a reference frame, but it is often "more informative to summarize the state of stress in terms of a dilatational (hydrostatic) component and a shear component." They use standard convention with compressive dilatational stress as negative and tensile dilatational stress as positive. They express their theory of the influence of mechanical stress on endochondral ossification by assuming that the application of intermittent shear stress or strain energy accelerates ossification while intermittent compressive hydrostatic stresses retard or arrest ossification. They utilize their data to calculate the distribution of a stress-dependent "osteogenic index" using a 2-dimensional computer model of a cartilage diarthrodial joint with five loading conditions applied along the joint contact surface. They conclude that regions of high osteogenic index correspond to the site and shape of the secondary ossification centers while regions of low osteogenic index correspond to the site where articular cartilage and growth plate would form and persist. The osteogenic index is a mathematical parameter for these theories which summarizes the local mechanical stimulation to endochondral ossification over a

time period as a weighted mathematical sum of the accelerative effects of cyclic shear stress and the inhibitory effect of cyclic hydrostatic pressure. Finite element stress analyses of the femoral cartilage model indicate their theory to be consistent with features of bone morphogenesis including the development of the primary ossification site, the tubular diaphysis with marrow cavity, metaphyseal and epiphyseal trabecular bone, location and geometry of the growth plate, the appearance and location of the secondary ossification center, and the presence and thickness distribution of articular cartilage. They are able to model each of seven stages of ossification passing from the cartilage model of the developing bone to the fully developed bone at the termination of skeletal growth with obliteration of the physis [461]. Their staging involves: stage 1, all cartilage; stage 2, primary ossification front; stage 3, front migration; stage 4, further front migration; stage 5, secondary ossification center formation; stage 6, expansion of secondary ossification center; and stage 7, growth plate closure. Their theory indicates that cartilage degeneration and subsequent ossification are promoted by intermittently applied shear stresses which are calculated to be highest at the center of the epiphysis where the secondary ossification center is formed. High shear stresses are also noted at the sides of the bottom edge of their model where the ossification groove of Ranvier is formed. Intermittently applied hydrostatic compression inhibits or prevents cartilage ossification and this was found at the periphery of the cartilage model over the joint surface. Their work indicates that mechanical stresses play a critical role in early skeletal growth and ossification in particular in relation to embryonic and early post-natal tissue differentiation. They again stress that "the reality of our model of long bone skeletal morphogenesis assumes that the muscular system has begun to exert mechanical stresses on the skeletal anlagen prior to or at the time at which endochondral ossification commences." It is interesting to note the correlation between the views of Carter and associates and those expressed by Carey over 50 years earlier. Much of Carey's work was disregarded when tissue culture and organ culture experiments began to reveal the development of cartilage models of the bone in vitro without muscle influences, although it is now apparent that the effects of muscle on bone development in vivo are real.

In summary, Carter and associates show that the ossification of the diaphysis and the formation of the secondary ossification center can be predicted by locating regions of high intermittent shear stresses. They define stress-dependent osteogenic indices using a 2-dimensional computer model of a cartilaginous joint. Regions of high osteogenic index correspond to the site and shape of the in vivo secondary ossification centers and regions of low osteogenic index correspond to the sites of articular cartilage and growth plate formation. They further postulate that the entire internal structure of long bones including the medullary cavity and trabecular morphology are governed primarily by the loading histories to which the bones are exposed during their growth and development. Endochondral ossification within the cartilaginous anlagen is accelerated by shear stresses and slowed by cyclic compressive dilatational stresses.

Their finite element studies suggest that (a) the ossific nucleus appears in an area of high shear (deviatoric) stresses, (b) the edge of the advancing ossification front of the periosteum (zone of Ranvier) also experiences high shear stresses, and (c) the joint surface, where articular cartilage forms, is exposed to high magnitude hydrostatic compression. These findings support the theory that intermittently applied shear stresses promote endochondral ossification whereas intermittently applied hydrostatic compression inhibits or prevents cartilage degeneration or ossification.

Frost and Jee [462, 463] have presented a theoretical model correlating biomechanical effects on endochondral ossification.

1.18.4 Experimental Studies on the Mechanical Behavior of the Growth Plate

The ranges of forces or strains across physes generated by the growth process in humans and animals have been calculated. Bylski-Austrow et al. [464] consider that the static equivalent loads exerted by the proximal growth plate of the tibia and the distal growth plate of the femur in adolescents are approximately 500 N, or 100 % of the weight of the individual, and that the stress exercised by each growth plate is around 1 MPa. However, according to Safran et al. in proximal tibial growth plates in growing patients with malignant tumors, the mean stress exerted by the growth plate was 5.8 MPa. In a study of finite elements, Cook et al. [465] pointed out that the physeal compression in the medial part of a varus tibia (30°) in children aged 2–5 years was seven times greater than that in a healthy tibia and that the stress necessary to halt growth was 4 MPa.

In quadruped models, experiments have been based on the use of an external fixator. The results indicate that the forces of the growth plate arc approximately 10 N or 1/2 of the weight in dog; 1.5 kN or somewhat lower than the weight in calves; between 30 and 40 N in rabbits, or between 1.5 and 2 times the body weight, although Wilson-McDonald [466] found the slightly lower figure of 10 N or 40–60 % of body weight in rabbits. The results vary greatly from one study to another because these experiments are limited by the small size of the growth plate, the system of measurement used, the surgical technique, and the fact that quadruped animals are used.

The greatest values of strain to failure and energy absorbed to failure were found in the hypertrophic cell layer

of the physes, and the amount of collagen was greater in the proliferating cell zone of the growth plate in rabbits. The older bovine growth plate was 25 % thinner, 34 % stronger, and strain at failure was 65 % greater. There is a greater collagen content in the areas of the growth plate that are more resistant.

Hert and others have applied experimental study to quantitate pressure effects on growth cartilage [467]. Within a normal range (or just above/below it), increases or decreases in compression both seem to accelerate cartilage growth. The increase in growth is particularly true with intermittent dynamic loading. With compression well below physiologic limits, growth can be reduced or even halted whereas massive increases in compression beyond normal severely retard growth. Robling et al. showed that longitudinal growth suppression resulting from compressible end-loads is proportional to load magnitude [468]. They also assessed appositional periosteal bone formation showing that dynamic loading increases osteogenesis whereas static loading suppresses it.

Villemure and Stokes have summarized work on growth plate mechanics and mechanobiology [469]. They concentrated on the question as to how bone growth is regulated in response to mechanical loading at the physeal regions. Much of their study assessed the histologic responses of the various regions of growth plate in the presence of sustained or cyclic mechanical load. Reference is made to longitudinal physeal growth by the combination of chondrocyte proliferation, matrix synthesis, and hypertrophy. While mechanical influences are extensive, each of genetic controls, systemic hormone levels, local growth and signaling factors, nutritional status, and blood supply play major roles. Mechanical factors are both intrinsic relating to expansion within the plate and extrinsic relating to the surrounding periosteum and musculotendinous tissues. The normal growth plate is generally under compression. A growth plate under compression demonstrates viscoelastic behavior. The compressive mechanical properties are non-uniform at varying regions and ages of the growth plates. Tensile rigidity also varies at different regions and levels. The Hueter–Volkmann "law" of increased compression of the growth plate reducing the growth rate, and vice versa, is a qualitative observation. The growth plates are affected by static, sustained loads and is not much affected by physiologic dynamic loading. In vivo loading experiments by Stokes and colleagues [470, 471] show that the relationship between sustained stress (tensile and compressive) and change in growth rate is linear. Very large compressive stresses arrest growth. It is calculated that a sustained compressive stress of 0.6 MPa would result in a 100 % reduction in growth rate (=no growth) [469]. Stokes et al. demonstrated that the numbers of proliferative chondrocytes, their rate of proliferation, and the amount of chondrocyte enlargement in the hypertrophic zone varied based on the stresses applied. Reduced growth rate with compression and increased growth rate with distraction were associated with corresponding changes in each of the parameters but chondrocyte enlargement played the greatest role [470, 471]. Stress leading to physeal growth arrest has been similarly estimated by others: Bylski-Austrow et al. 0.51 and 1 MPa [464], more than 0.3 MPa (Bonnel et al. [472]), and more than 0.5 MPa (Safran et al. [473]). The results on physeal growth dynamic activity are unclear. At the histologic level, static loading affects both proliferative and hypertrophic tissue and cellular shape. The number of proliferating cells and the size of hypertrophic cells are decreased. Thinning occurs in both zones. The zones are thickened and more active with pressure reduction with distraction. Sustained compressive loading decreases expression of type II and X collagen. The hypertrophic zone is the least rigid growth plate region and experiences the greatest deformation under growth loading and is the most sensitive mechanotransductive zone. There is also loss of columnar arrangement.

1.18.5 Normal Relationship of Epiphyseal Plates to Compressive and Tensile Stresses

It has long been accepted that the external shape of a bone and the disposition of the trabeculae within it are related to the stresses experienced during normal activity. Thomson [474] noted a correlation between the structure of the distal femur and the shape of the distal femoral physis. Smith [475] (1962) was one of the first to study biomechanical relationships to underlying structure of the epiphyseal plate feeling that physeal structure and orientation might also bear a similar relationship to stress (Fig. 1.24a–e). He defined the three stresses which can occur within any object: a compressive stress which causes a diminution of the dimension along which it acts; a tensile stress which increases the dimension along which it acts; and a shear stress which causes relative displacement along the intervening parallel planes. At any chosen point the compressive and tensile stresses were maximal in two orthogonal directions which are designated as the principal stresses at that point. At that same point shear stress is 0 in the direction of the principal stresses and maximal in a direction angled 45° to them. In an immature bone, stability of any epiphysis in relation to the diaphysis depended on the relationship of the plate to the internal stress patterns to which it was subjected. If the growth plate conformed through its extent to direction of one of the principal stresses, no shear stress would develop between the epiphysis and the diaphysis and the relationship would be stable. If that relationship did not exist then forces exerted on a bone during activity would cause shear stress

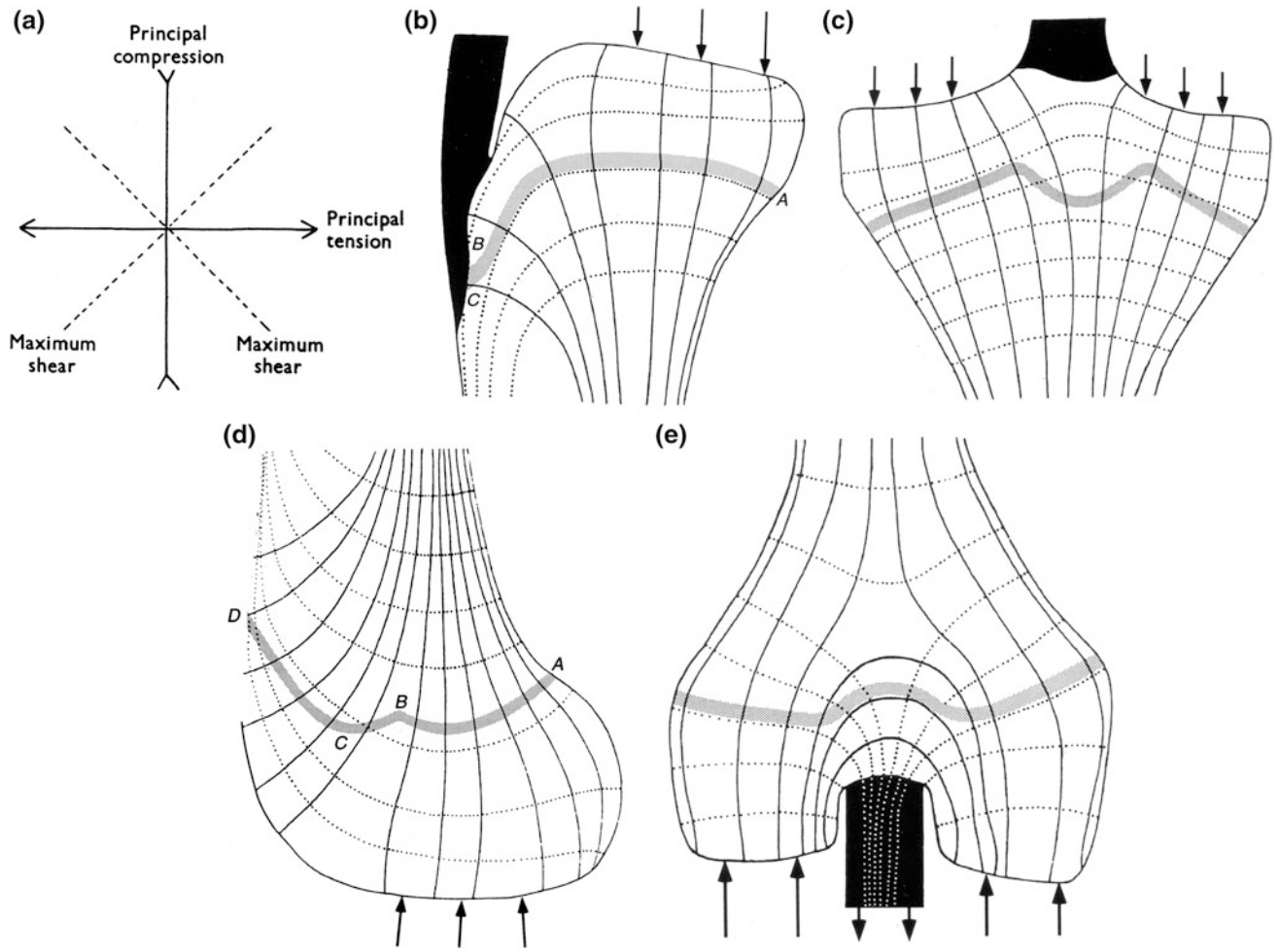


Fig. 1.24 Compressive and tensile stresses in relation to the physes of developing bones as shown by Smith [475]. **a** The disposition of the tensile and compressive stresses and the maximal shear stresses. (Reprinted with permission from Smith JW, The relationship of epiphyseal plates to stress in some bones of the lower limb. J Anat. 1962;96:58–78. Copyright 1962 Cambridge University Press). **b** Stress analysis of proximal tibia in standing position, sagittal plane. In the illustration the patellar ligament is in black, the stippled line is the growth plate, arrows denote applied forces, the main compressive stresses are the solid lines, and the main tensile stresses are the *dotted lines*. The same format is used in figures *below*. **c** Proximal tibial stress analysis, coronal plane. **d** Distal femoral stress analysis, standing state, sagittal plane. **e** Distal femoral stress analysis, standing coronal plane.

which would tend to lead to displacement of one part on the other. Shearing stress would be less the more the matrices are arranged along the pressure and tension lines of the system.

Smith performed studies in the proximal tibia and proximal and distal femur using the photo-elastic method which allowed him to construct the directions of the principal tensile and compressive stresses throughout the whole bone.

1.18.5.1 Proximal Tibia

Stress analyses were performed at the proximal end of the immature tibia with assessments illustrated in both sagittal and coronal planes. The epiphyseal plate in the sagittal dimension demonstrates anterior and inferior displacement in relation to the developing tibial tubercle cartilage extension of the epiphysis. The axial compressive forces are at right angles to the growth plate and the tensile stresses are parallel to it. Smith noted that owing to the retroversion present in the upper end of the tibia, the bone is subjected during weight bearing to a combination of axial compression and forward bending. Diagrams from the Smith article demonstrate how compressive stresses are at right angles to the growth plate and how even the shape of the growth plate itself relates quite well to the orthogonal compressive and tensile stress lines.

1.18.5.2 Distal Femur

On a coronal section which demonstrates both the principal compressive and tensile stresses the epiphyseal plate itself shows a clear relationship to the principal stresses similar to

that observed in the proximal tibia. On both medial and lateral sides the growth plate lies parallel to the lines of tensile stress, centrally it conforms to the line of compressive stress, and only in the intervening regions is it subjected to shear stress. Similar patterns are seen on the sagittal sections.

1.18.5.3 Proximal Femur

Knowledge of the shape of the developing cartilage within the femur as well as that of the adjacent metaphysis is very important to understand stresses here. In the first few years of life there is a single curvilinear growth plate in relation to the adjacent developing trochanteric and head and neck cartilage masses. That part of the proximal surface of the metaphysis which is associated with the head and neck maintains a more or less constant form throughout development. From the junction between the trochanteric and head–neck parts of the cartilage, the proximal surface of the diaphysis runs medially and slightly downwards in a gentle curve convex upwards. The plate is thus really not straight as is indicated by plain radiographs. The common stress pattern indicative of both compressive and tensile stresses is markedly similar to the analysis from over 100 years ago of the adult bone. The principal compressive stresses are seen medially and the tensile stresses laterally. In its most medial area the growth plate rather than persisting in a transverse plane turns sharply downwards to reach the articular margin. Here the physis is parallel to the compressive stress and again shear is minimal. Shear stress is present at the line of angulation of the physis which tends to lead to displacement of the femoral head downwards and medially on the neck in predisposed individuals.

Smith's analyses showed the greater part of the epiphyseal plates to be oriented parallel to one or the other of the principal stresses which affect the region during normal activity. Within the proliferating columns of growth plate chondrocytes, however, there are no direct relationships to the stress pattern but these are rather oriented in the direction of bone growth. Quite often the stress patterns have an orthogonal relationship to the direction of bone growth so that the cell columns lie at right angles to the plane of the epiphyseal plate. On occasion, however, the cell columns occupy an oblique position. If an epiphyseal plate therefore is oblique to the direction of bone growth there is a zone of cartilage cells in which these structural elements are not aligned to the stress pattern of the part and are thus exposed to shear stress tending to displacement. In general these studies show that the orientation of epiphyseal plates is in harmony with stress patterns of normal activity. This is because each plate tends to lie parallel to one or other principal stresses so that shear stress between the epiphysis and diaphysis is minimal. At both proximal and distal ends of the femur in particular the epiphyseal plate tends to lie at right angles to the compressive stresses within the bone.

Murray [476] points out that stresses within the epiphysis itself are multiplanar and that trabeculae of the secondary center develop a specific orientation only after growth plate closure and continuity has been established between the bone of the epiphysis and that of the adjacent metaphysis and diaphysis. The mechanical structure of the cartilage has been much less studied than that of bone and most of those studies are performed relative to articular cartilage rather than to physeal cartilage. Cartilage is less resistant than bone but is more elastic and is much better able to withstand pressure than tension. Much of the ability to withstand tension is due to its surrounding periosteal/perichondrial sheath. The surrounding perichondrium is essential for the structural integrity of the physeal cartilage. The perichondrial sheath runs parallel to the long axis of the bone and as such its fibrils are tension-resistant and not pressure-resistant structures. The fibrillar peripheral tissues thus responsible for resisting tension and the non-fibrillar components are pressure resistant.

1.18.6 Responses of Physes to Abnormal Pressures. Pathogenesis of Creation and Correction of Deformity in Developing Bones

Many clinical and experimental observations have been made concerning the response of various epiphyses and physes to pressure. Studies have been done more recently pertaining to the mechanisms by which the responses occur and to quantitation of the specific intrinsic and extrinsic epiphyseal pressures in normal and abnormal states. The presumed relationship between epiphyses and pressure phenomena has been ingrained in assessments for a very long time.

Delpech [477] (1828), in his early orthopedic classic De L'Orthomorphie, commented on developmental malformations of the bones during the growth period caused by abnormal pressure on the growth cartilages. During the growth period, unequal pressure on the growth cartilages led to a slowing of growth at areas of increased pressure and an exaggeration of growth where pressure was diminished. Stated otherwise, bone growth increases in regions of diminished pressure and decreases in regions of high pressure. In relation to growth cartilages, growth and development occur in inverse relationship to the pressures exerted on the cartilage.

The separate works of Hueter [428] (1862) and Volkmann [429] (1862) related the pathogenesis of deformity to abnormal pressure on the growth cartilages. What has become known in the English literature as the Hueter–Volkmann law postulates that pressure beyond the normal on growth cartilage leads to growth retardation. Stated another way, they noted an inverse relationship between

compressive forces along the long axis of epiphyseal growth and the rate of epiphyseal growth. Increased pressure on the concave side interfered with and slowed normal bone growth while on the convex side less than normal pressure led to overgrowth. Neither worker ever stated the premise as a specific law or performed any experimental investigation. The observation is evident in a clinical sense, for example, in relation to infantile and adolescent tibia vara which are felt to be caused by increased weight in relation to physes which are placed in a disadvantageous varus position. Although this concept is widely accepted very little work has been performed documenting the extent of the pressures which are normal on the one hand and sufficiently great on the other to cause damage. The absence of normal pressure is also known to alter epiphyseal development. A clinical example of this relates to dysplastic hips in particular those which are completely dislocated. In these the femoral head is smaller and misshapen in relation to the normal side and there is a delayed appearance of the secondary ossification center. It is unclear whether the delayed appearance of the secondary center is due to the lack of appropriate pressure on the head which would normally come from the acetabulum or to a relative hypo-vascularity owing to stretching of the femoral vessels with the head in an inappropriate position.

The work of Wolff [430] has played a major role in revealing how extrinsic forces on bone modify both the internal (by which is meant trabecular) architecture and the external shape of the bone (Fig. 1.25a). His law has been translated as: "Every change in the form and function of the bones, or of their function alone, is followed by certain definite changes in their internal architecture, and equally definite secondary alterations of their external conformation in accordance with mathematical laws." Wolff refers however to lamellar bone deposition and not to bone development; indeed, he felt that early bone formation from cartilage models was independent of mechanical stress.

Remodeling of a long bone following an acquired angular deformity is a function of three features. An excellent experimental model showing this was described by Ryoppy and Karaharju [478] following hind leg fractures in

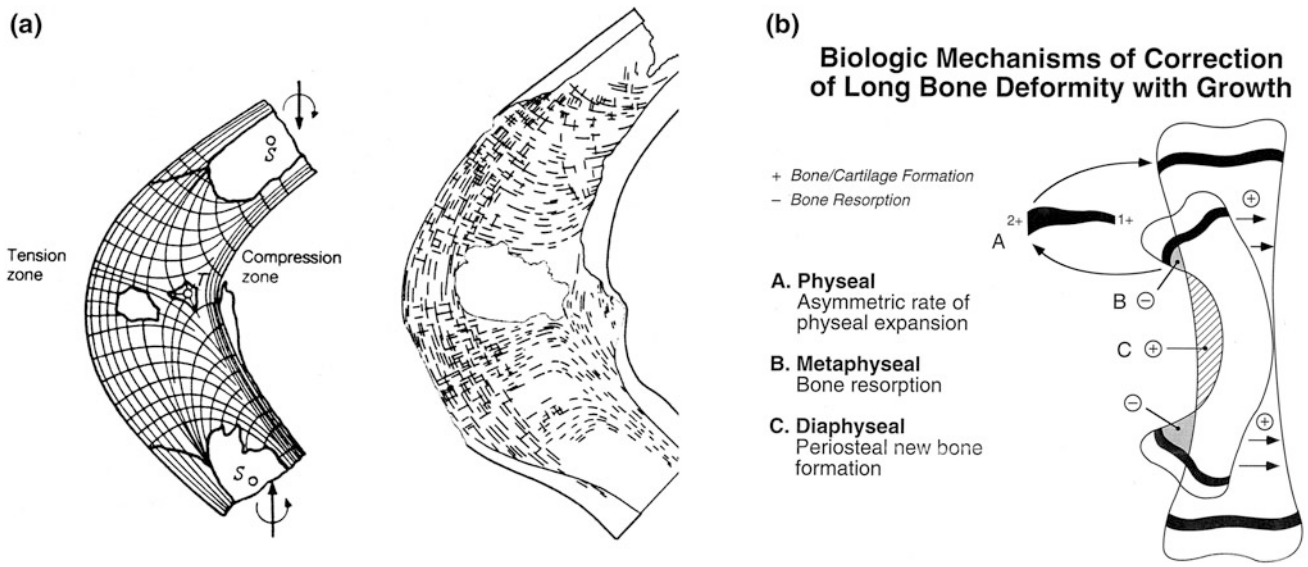


Fig. 1.25 **a** Illustrations of the trabecular orientations and cortical bone thickness based on Wolff's Law are shown (from Pauwels [438]). With angular deformation the concavity in both (*Left*) and (*Right*) is at *right* and compression predominates. Note the thicker cortex (*Right*) on the concave compression side. (Reprinted with permission from Pauwels F, Critical examination of the work of Roux: "description and explanation of a bony ankylosis of the knee" in *Biomechanics of the Locomotor Apparatus,* p. 242 and 230, 1980. Copyright 1980 Springer Science + Business Media). **b** There are three mechanisms by which a growing long bone can correct an angular deformity. Remodeling can occur by three different mechanisms at epiphyseal, metaphyseal, and diaphyseal regions. The first involves new bone synthesis on the concave side of the deformity in the metaphyseal and diaphyseal regions. This is mediated exclusively by the intramembranous mechanism, acts primarily at the diaphyseal level, and does not correct epiphyseal deformity. Bone is synthesized preferentially along the concave aspect with minimal amounts only on the convexity. As the overall bone increases in length and width, however, bone synthesis is along appropriate lines and the smaller deformed model becomes incorporated into a straighter, larger model. Second, the metaphyseal regions are remodeled by sequential resorption in particular on the concave side by tissues at the periphery of the metaphysis which normally perform that role. The greater the deformity in any concavity on the metaphyseal side, the greater the activation of the osteoclast metaphyseal remodeling mechanism. Three, the epiphyses themselves correct for angular growth by asymmetric physeal function. There is a 2 + growth function of the physis on the concave side of the deformity and a slower 1 + on the convex side. It is still not clear whether this increase in activity is manifested by an increased thickness of the physis or simply by an increased activity on the concave side which does not lead to any change in thickness of the physis owing to the symmetry of synthetic and resorptive phenomena

3-week-old rats. They demonstrated correction of angular deformity documenting not only metaphyseal and diaphyseal corrective mechanisms, but also asymmetric epiphyseal growth as a corrective mechanism. With mild to moderate increased pressure on the concave side of a deformity, there was actually a positive effect on the concave side physis leading to stimulation of growth compared to the opposite side of the physis and correction of deformity. These principles are outlined in Fig. 1.25b. (i) There is increased new bone formation by the inner layer of the periosteum on the concave side by the intramembranous mechanism of bone formation. This serves to decrease the concavity but has no effect on the angulation or obliquity of the epiphyseal growth plates or articular surfaces at either end. (ii) Asymmetric growth of the epiphyseal plate. The physis on the concave side has an increased rate of growth compared to the physis on the convex side. This serves to correct the obliquity both of the epiphyseal growth plate and of the joint surface. (iii) Metaphyseal remodeling occurs with resorption more extensive on the concave side than on the convex side. Three mechanisms are thus operative in correcting angular deformity in a growing long bone involving altered patterns of cell function in each of diaphyseal, metaphyseal, and epiphyseal regions.

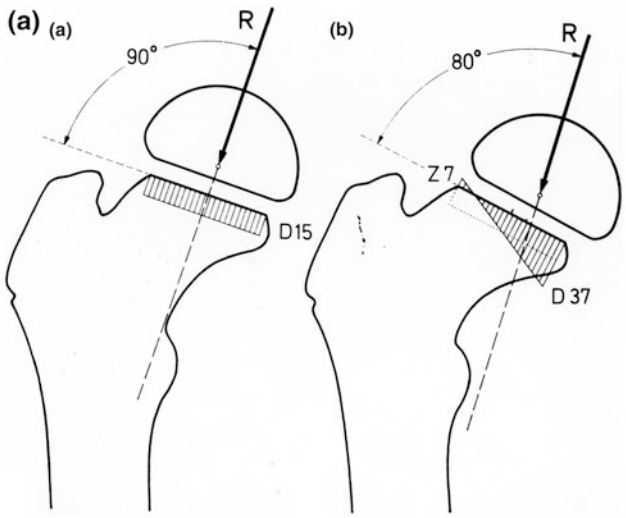
The question of the ability of a growing bone to correct rotational or torsional deformities has also long been of clinical interest but both clinical and experimental evidence of its occurrence has been less than definitive. There is little question that rotational changes in long bones occur with growth, and this phenomenon is well documented with the decrease in femoral anteversion at the proximal femur. It appears that a major reason many clinicians doubted the effective correction of malrotation came from assessments of long bone fractures with relatively severe rotational deformity which did not correct with time. There thus appears to be the potential ability of long bones to correct rotational malalignment which would be limited, however, by the extent of the rotational deformity and the age in relation to the developmental sequence at which it occurred. A study by Husby et al. [479] indicated, however, that even in the postnatal period acquired rotational abnormalities could be corrected with growth. They produced inward or outward rotation of approximately 25° in the right femur of kittens by midshaft osteotomy and plate fixation. The left femur served as the control and the angle of anteversion (AV) of the femoral necks was measured in axial radiographs from preoperative time to 58 weeks postoperatively. They noted that the AV angle of the unoperated left femurs did not change with growth in length over a 58 week period beginning at 13 weeks of age when operation was performed. The immediate postoperative mean torsional difference in the externally rotated group was −20° and in the inward rotated group +27°. Most of the torsional deformities regressed during the first 12 weeks postoperatively and by 1 year postoperatively, the mean torsional difference between matched right and left femurs was only −1° in the externally rotated group and +4° in the internally rotated group. They demonstrated that in all animals the rotational deformities of the operated femurs regressed concurrently with longitudinal femoral growth. They concluded that the regression took place in the femoral growth plates primarily due to helical growth in length in the distal physis to account for the correction, although proximal femoral growth plate growth in a dorsal direction might also contribute to the physiologic regression of the AV angle of the femoral neck.

The growth effects of one bone on the other in two bone segments are also shown in particular in pathologic conditions such as hereditary multiple exostoses. In this disorder there is a marked tendency for the ulna to be more deformed and shortened than the radius in the upper limb and for the fibula to be more deformed and shortened than the tibia in the lower limb. The shortness of the ulna and the fibula combined with their continuing close approximation and ligamentous binding to the radius and tibia, respectively, lead to the deformities of the adjacent bones caused by asymmetric physeal tethering. The physes and metaphyses of the relatively uninvolved longer side develop angular deformities with their curvature concave toward the shorter bone.

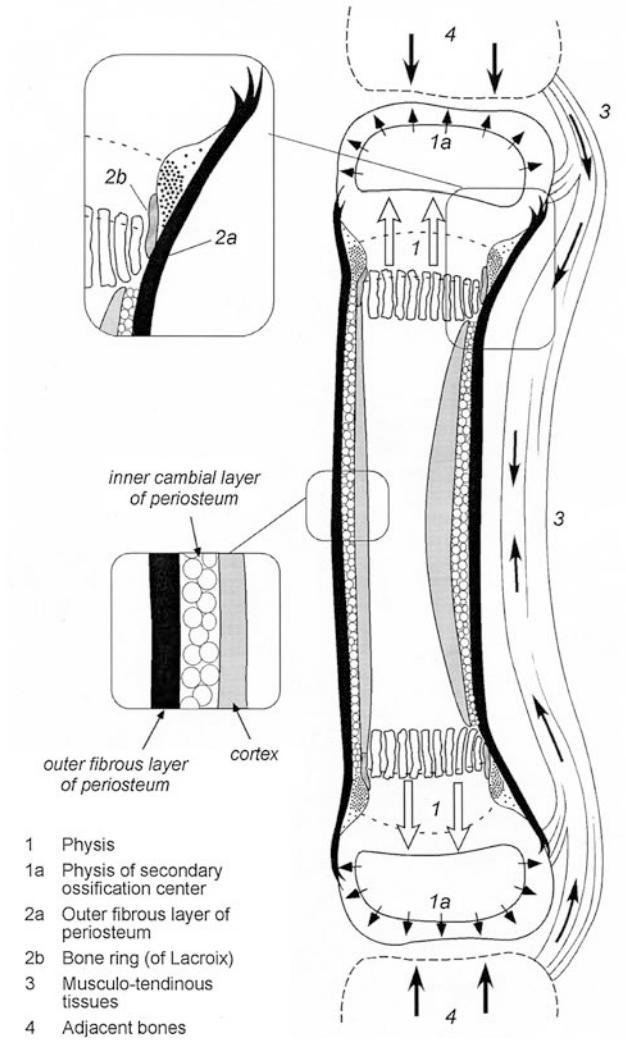
1.18.7 The Effects of Pressure on Epiphyseal Growth

Deformity in the epiphyseal and metaphyseal region of a growing long bone can be either improved with time which implies a corrective and regulatory response by the open physis or worsened with time which implies negative or inhibitory effects on physeal growth. There is little quantitative data indicating how much altered physeal pressure has a positive or stimulatory effect and how much has a negative or inhibitory effect. It is evident, however, both from clinical observations and investigational studies, that mild to moderate increases in pressure actually serve to stimulate the physeal growth asymmetrically and thus lead to correction whereas markedly increased pressure inhibits the growth of the physis and worsens deformity. The latter phenomenon was recognized throughout the nineteenth century and led to the principles of growing bone deformation articulated by Delpech, King, and Hueter and Volkmann.

Increasing study of bone deformity patterns over the past few decades, however, has led to the recognition of asymmetric stimulation of physeal growth leading to a corrective mode if the abnormal increased pressures are mild to moderate. Pauwels pointed out this corrective mechanism [437] (Fig. 1.26a). One of his examples illustrates straightening of the femoral neck to a normal range after an adduction or



(b) Biophysical/Biomechanical Forces on Long Bone Growth

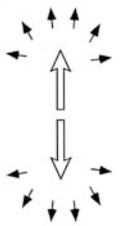


(c) Biophysical/Biomechanical Forces on Long Bone Growth

A. Intrinsic Outward Expansion

1 Physeal Growth
- chondrocyte proliferation
- matrix synthesis
- chondrocyte hypertrophy

1a Physis of Secondary Ossification Center Growth



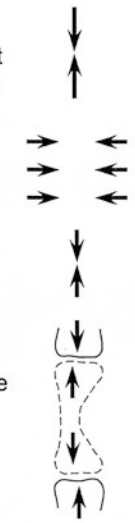
B. Extrinsic Constraints

2a Outer fibrous layer of periosteum (continuous from epiphyseal cartilage at one end of bone to epiphyseal cartilage at other end)

2b Periphyseal bone ring of Lacroix/ osteoid of groove of Ranvier (terminal extensions of cortex/cambial layer of periosteum)

3 Adjacent muscles and tendons

4 Adjacent bones (with own outward growth in opposite direction)



(d) Intrinsic-Extrinsic (Systemic) Molecular Controls on Epiphyseal-Metaphyseal Growth

Intrinsic
- Indian hedgehog (Ihh)
- Parathyroid hormone related protein (PTHrP)

} *signaling loop*

- Bone morphogenetic proteins (BMP)
- Fibroblast growth factors (FGF)
- Vascular endothelial growth factor (VEGF)
- Matrix metalloproteinases (MMP)
- Cell cycle proteins
  cyclins, cyclin dependent kinases, CD kinase inhibitors, activating transcription factor 2 (ATF-2)

Extrinsic (Systemic)
- Growth hormone (GH)
- Insulin-like growth factor I/II (IGF I/II)
- Thyroid hormone (T_3, T_4)
- Vitamin D3
- Glucocorticoids
- Estrogen

varus osteotomy early in childhood. In the normal anatomic alignment, uniform distribution of compressive stresses in epiphyseal cartilage leads to uniform increases in growth across the proximal femoral physis. Varus osteotomy diminishes the neck-shaft angle and tilts the epiphyseal cartilage such that the compressive stresses are now graded to the medial border of the femoral neck. Clinical examples show that after a varus osteotomy in a young child, the femoral neck straightens. Pauwels indicates that "this straightening results from stronger growth in length of the medial part of the epiphyseal cartilage." He thus articulates the effect of stimulation indicating that "unequal distribution of pressure in the epiphyseal cartilage, provided it is not above a certain threshold, leads to an unequal growth in length. This causes an alteration in the shape of the bone which in turn leads to a reduction in the bending stressing of the latter. Reduction in the bending stressing means an economy of material. This is the essence of functional adaptation." Pauwels further comments on pressure phenomena and their relation to physeal function. He presents in detail a case of coxa vara secondary to untreated subtrochanteric fracture of infancy in which the varus deformity gradually straightens following several years of growth. His analysis indicated that stresses on the epiphyseal cartilage of the femoral head and neck were such that "physiologically the resultant compressive force is perpendicular to its center …it is stressed throughout purely in compression". In the hip with coxa vara, the resultant compressive force under load was no longer perpendicular to the center of the epiphyseal cartilage but formed with it an angle of 70° open laterally. Bending was thus added to the normal pure compressive stressing of the epiphyseal cartilage, and in the lateral half of the physis, the pure compressive stresses were decreased with the addition of tensile stresses. In the medial half, the compressive stresses were more than doubled due to the additional bending. This pathologic distribution of the stresses is illustrated by Pauwels in the accompanying diagram. The metaphyseal bone density is uniformly distributed in the normal hip but markedly denser to the medial side in the coxa vara and abnormally stressed side. This deformity corrected with time because of "fundamental and progressive alterations which have developed because of stronger longitudinal growth on the compression side as a consequence of the additional bending stressing of the epiphyseal cartilage." Pauwels reached three conclusions: (1) In bending stressing combined with compression, the stresses on the compression side are always greater than on the tension side. On the compression side, it is the sum of the two types of stresses which act together, while on the tension side it is their difference. (2) Bone formation and resorption are controlled by the magnitude of the stresses. (3) The epiphyseal cartilage is normally stressed in pure compression. The addition of bending stressing causes more growth on the compression side where the stress is greatest. This serves to eliminate the additional bending stress.

Gelbke [480] addressed the issue of the influence of pressure and tension on physeal growth. He pointed out that the epiphyseal cartilage plates can bear, without any damage, a much higher degree of pressure than is effected under normal physiological conditions. He demonstrated that pressure on the physeal regions along the long axis of the bone led to retardation of physeal growth and ultimately, if retained, to full fusion. Negative effects were more marked with continuous pressure. His work concluded that "only an extreme increase in pressure leads to an inhibition of longitudinal growth and to a narrowing of the epiphyseal plate." This has also been borne out by the work of Blount. Both Blount and Gelbke show instances where a metal staple and circumferential metal wire, respectively, can both be broken by the forces of growth without growth inhibition occurring. Where pressure is great and growth inhibition occurs, the epiphyseal plate is narrowed. Maas [481] (1924) demonstrated that where the pressure was uniform and parallel to the long axis of growth, a shortening without angular deformity was seen. Where the pressure was asymmetric, angular deformity occurred concave to the side of increased pressure. With relatively milder pressures, the physis would actually widen in response. Not only must pressure be extremely high to have negative effects, but it must also be continuous. Similar experiments were performed by Haas who demonstrated that a circumferential wire loop encompassing epiphyseal and diaphyseal bone also led to growth retardation. He subsequently used staples which also led to growth diminution and angular deformity.

◀ **Fig. 1.26** **a** Proximal femoral angular correction is illustrated after varus osteotomy of childhood or after subtrochanteric fracture which healed with extensive varus. The medial physis comes under increased pressure but responds to this by increasing its rate of synthesis in relation to the more lateral aspect of the physis, thus correcting deformity. (From Pauwels [437]). (Reprinted with permission from Pauwels F, The significance of the medullary cavity for the mechanical stressing of the tubular bone in Biomechanics of the Locomotor Apparatus, p. 509, 1980. Copyright 1980 Springer Science + Business Media). **b** Biophysical/biomechanical forces on long bone growth are illustrated. The outwardly expanding growth forces generated by the physes (*1 open arrows*) and the hemispheric physes of the secondary ossification centers (*2 short black arrows*) are partially counterbalanced and channeled by the outer fibrous layer of the periosteum (*2a*), the bone ring of Lacroix (*2b*), the musculotendiuous tissues (*3*), and the adjacent bones (*4*). **c** The intrinsic outward expansion and extrinsic constraints in relation to long bone growth are outlined in more detail. **d** The intrinsic/extrinsic molecular controls on epiphyseal–metaphyseal growth are outlined

Arkin and Katz [482] studied the effects of pressure on epiphyseal growth and noted that pressures applied to epiphyses could be classified into two main types, one parallel to the direction of epiphyseal growth and the other at right angles to this direction. The forces applied in any direction intermediate between these two could subsequently be resolved into components or vectors parallel to one or the other.

The extreme forces generated by physeal growth have received some documentation. Blount and Zeier found that the forces of growth in a child could break staples which themselves were able to withstand 900 pounds of distraction in mechanical testing [483]. Franz [484] reviewed early results on physeal inhibition in a clinical setting using the epiphyseal stapling technique of Blount. Strobino et al. [485] assessed growth forces in a calf in which a transphyseal spring mechanism was inserted. They found no inhibition of growth in the upper tibial epiphysis, even when the restraining forces were as high as 400 pounds.

Arkin and Katz [482] also assessed the effects of pressure perpendicular to the axis of epiphyseal growth. This pressure served to change the direction of growth and the amount of change of direction varied with the degree of pressure. They felt that pressures applied in any direction between the perpendicular and the parallel could be broken down into vector components and the proportion effect of each component on rate and direction of growth could be determined. When forces were applied parallel to the direction of growth and were the same throughout the epiphyseal plate, growth was inhibited uniformly. It was inhibited asymmetrically if the pressure was greater on one side than on the other. Pressure thus serves, to modify both the rate and direction of epiphyseal growth. Torsional stress applied to developing femurs led to deviation which demonstrated no deformation of the shafts of the bone, but rather, deformation at the epiphyseal and adjacent metaphyseal regions. That portion of bone laid down by the epiphyseal plate while it was under torsional stress was the region that was deviated.

The torsional effect was greater the less the thickness of the bone. Any force exerted on the epiphyseal plate in a direction not parallel to the direction of growth will deflect growth away from the deforming force. The amount of deflection produced is a function of the direction of the force being directly proportional to the angle formed by the direction of growth and the direction of the deforming force up to 90°. They also concluded that pressure does not inhibit growth by an all or none law. While enormous forces are required to fully inhibit growth, much milder forces, in particular if they are applied asymmetrically, can inhibit or otherwise modify epiphyseal growth. They reached four conclusions which remain notable today. (1) When a growing epiphysis is subjected to a stress, the rate or direction of the growth of that epiphysis or both are modified so as to yield to that stress. (2) Pressures applied in directions parallel to the direction of epiphyseal growth inhibit the rate of such growth. While considerable pressures are necessary to stop cartilaginous growth completely, slight or even intermittent pressures can slow or hinder it. (3) Pressures applied in directions perpendicular to the direction of epiphyseal growth deflect the direction of such growth resulting in lateral or torsional displacement of the newly laid down bone. (4) The ease with which angular or torsional deformities may be produced in a growing bone varies inversely with its diameter.

Tschantz et al. [486] induced mechanical overload of the distal ulna in the dog by resecting a segment of the adjacent radius leading to a lysis of the ulnar physis and chronic tilting of the epiphysis. The model allowed for assessment of the effects of asymmetric loading on physes by histologic and radiologic criteria. Histologic study showed development of a large transverse intraphyseal fissure starting on the convex side and traveling various distances toward the convex side. In most cases the fissure was within the columnar, hypertrophic, or adjacent metaphyseal regions but on occasion it passed within the germinal cell zone. Epiphyseal tilt of 5° to 15° developed between the 4th and 10th postoperative days. In those instances where the germinal zone was involved, early transphyseal bone bridge formation occurred. Repair along with correction of the tilt followed in most dogs when fracture was below the germinal zone. Overload stopped when the radius healed thus allowing the ulnar physeal cartilage to heal and resume normal growth.

The effects on long bone growh are illustrated in Fig. 1.26b–d [443].

1.18.8 Mechanosensitive Genes During Skeletal Development

Efforts are being made to assess mechanotransduction in skeletal development and regeneration using gene and molecular assessments [487]. Nowlan et al. [488] have assessed how biophysical stimuli are integrated with genetic regulatory mechanisms in the embryonic chick. They assessed expression of type X collagen (specific to hypertrophic chondrocytes) and Indian hedgehog (Ihh, in bands of pre-hypertrophic chondrocytes) in normal embryos where muscle development was unimpeded and in embryos where muscle development was impaired by induced neuromuscular blockade. Expression was more prominent in the active embryos indicating co-localization with biophysical stimuli induced by muscle contractions [488]. In a later more detailed

study comparing normal mice embryos to mutant splotch-delayed (Spd) mouse embryos (a muscle-less mutant) mechanical stimuli effects on the developing skeleton were studied. Microarray and RNA sequencing analysis were used. The most strongly disturbed gene signaling group in the Spd group was the Wnt with 34 genes affected indicating their primary role in integrating mechanical and molecular signaling for skeletal development [489].

Ingber [490] and Leucht et al. [491] reasoned that integrin molecules were likely candidates for enhancing mechanotransduction in skeletal regeneration since they spanned the cell membrane from cytoskeleton at one end to the extracellular matrix at the other. Leucht et al. induced transcortical defects in mouse tibas and studied adjacent marrow repair following sox 9 and runx2 expression. The marker for integrin was a focal adhesion kinase (FAK), an intracellular component of the integrin signaling pathway. On activating FAK the osteogenic repair response was abolished leading to the interpretation that FAK served as an integral part for mechanotransduction in skeletal regeneration [491].

- A specific mechanosensitive glycoprotein is sclerostin which inhibits bone formation by interfering with Wnt signaling [492, 493]. Sclerostin is produced in osteoblasts and osteocytes and is effectively a negative regulator of bone formation. Sclerostin is a negative regulator of Wnt signaling in osteoblasts, antagonizing canonical Wnt signaling by binding to the Wnt co-receptors low-density lipoprotein receptor-related proteins 5 and 6 (LRP 5/6). Sclerostin, a product of the SOST gene, contains a signaling peptide for secretion. The cysteine-knot glycoproteins are a family that antagonizes BMPs and includes noggin and chordin and the DAN family (gremlin, cerberus, DAN, and sclerostin). Sclerostin is a negative regulator of osteoblast development and bone formation acting primarily as a Wnt antagonist. In vivo mechanical loading of bone (which increases bone formation) has been shown to reduce sclerostin expression [494] while mechanical unloading (reducing mechanical stress) suppresses osteoblast activity (decreasing bone synthesis) by increasing sclerostin expression further inhibiting the Wnt/ß-catenin function [493]. Mechanical stimulation of bone in vivo reduces the osteocyte expression of sclerostin, thus allowing new bone formation to proceed [494]. Reduced mechanical stress in bones serves to upregulate SOST (sclerostin) which inhibits the Wnt/beta-catenin signaling, suppressing osteoblast and osteocyte activity and leading to bone mass reduction [493]. Efforts are being made to intervene pharmacologically regarding sclerostin, primarily to block it to enhance bone formation and help overcome osteoporosis syndromes.

1.19 Radiographic Characteristics in Development of Major Long Bone Epiphyses

1.19.1 General Information

The time of appearance of the primary and secondary ossification centers has been an important point for study in long bone development [222, 495–498] (Fig. 1.27a–f). The variable times of appearance were well established in textbooks of anatomy and osteology in the nineteenth and early twentieth centuries before the discovery and widespread use of x-rays. With the widespread use of the radiographs, however, more accurate delineation of the time of appearance of the various secondary ossification centers was possible since larger numbers of individuals could be studied, sequential studies of the same individual were possible, and assessments were done in normal individuals [499–501]. Despite the advantages of the radiographic technique, the hope that there would be more precise timing of secondary ossification center development with a narrower range of variability for each epiphysis has been realized only partially. The reasons for this are clear since the times of appearance of ossification centers vary considerably not only in the two sexes but even within the same sex. The time of fusion of epiphyses to metaphyses has been even more difficult to document reproducibly because of the above-mentioned variability plus the differing criteria used in different studies to determine when fusion has occurred. Two of the most detailed radiographic longitudinal studies of the time of appearance of ossification centers are those by the Cleveland, Ohio group assembled by T. Wingate Todd at Case Western Reserve University and the Brush Foundation [436, 502, 503] and by Flecker [500]. The latter also assessed the time of fusion. Unfortunately, the data of Flecker are presented in such a way that they are difficult to interpret. Three papers from the Cleveland group were published in 1939 and 1940 detailing the fetal age assessment of centers of ossification by Hill [503], the appearance of centers of ossification from birth to 5 years by Francis and Werle [436], and the appearance of centers of ossification from 6 to 15 years by Francis [502]. These papers are particularly valuable because of their careful attention to detail relating to both primary and secondary ossification centers, and inclusion of all long bone epiphyses, as well as carpal and tarsal bone centers. They published their detailed database documenting the entire range of appearance of the secondary center at each site from the age at first documented appearance of any secondary center to the age at which 100 % of the study population had shown that appearance. These figures not only show the ranges of time of appearance of the centers, but also allow for detailed

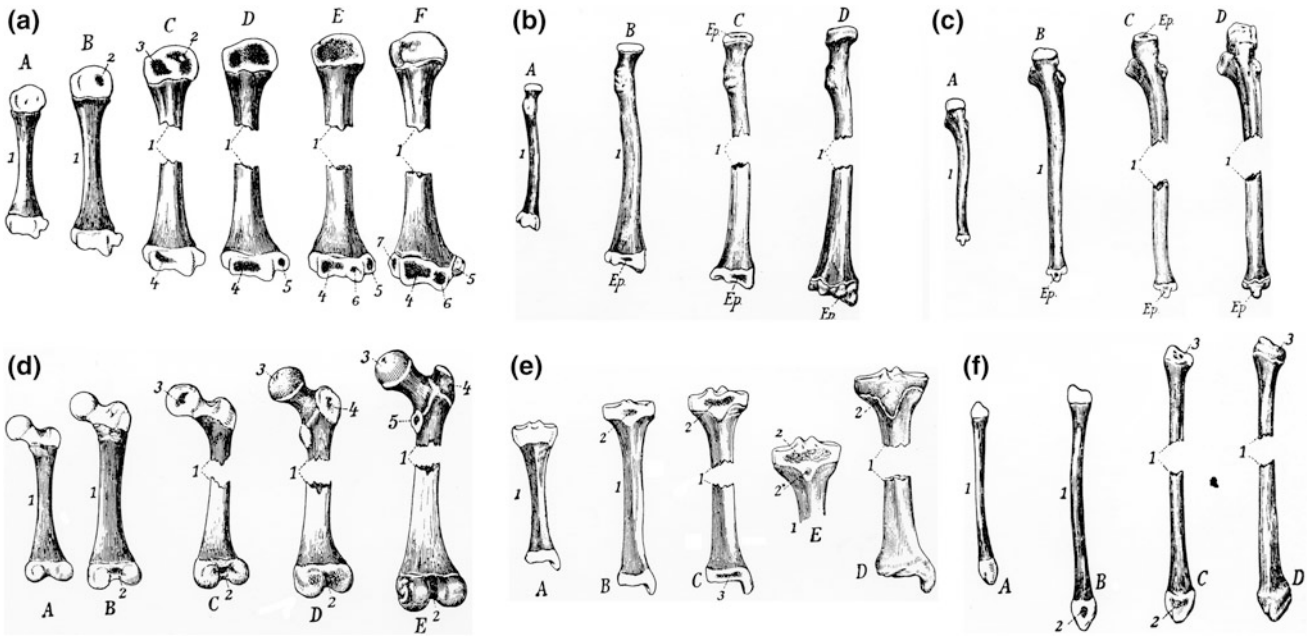


Fig. 1.27 Illustrations of developing long bones showing secondary ossification center development. (Illustrations from Quain's Anatomy as reproduced from an article on bone development by Bardeen in Keibel and Mall [495]). The times of occurrence of bone formation are listed in the text and in Tables 1.16 and 1.17. **a** Humerus. **b** Radius. **c** Ulna. **d** Femur. **e** Tibia. **f** Fibula

assessment of the progression of appearance of the centers with time. The studies were performed at 3, 6, 9, and 12 months of age; then every 6 months to the 5th birthday; and then annually to 15 years of age. Another study assessing large numbers of patients and presenting data clearly is that of Hansman (1962) [504], showing both time of appearance and fusion of ossification centers. The data of Hansman are reproduced in Tables 1.16 and 1.17. The method of data presentation varies from paper to paper such that close study is needed to make comparative assessments. Hansman provided the range of ages for appearance of each particular center plus the median age at time of appearance. Important radiographic features of development of each of the major long bone epiphyses follow.

1.19.1.1 Proximal Humerus

Two secondary ossification centers form in the proximal humeral epiphysis [505]. The medial center forms first and is generally present in all at 2 months of age. Hill notes that 26 % of individuals have presence of the medial secondary ossification center of the proximal humerus at birth with the earliest fetal appearance between the 28th and 31st week. Studies indicate its presence within 2 days after birth in 45 % of individuals; 78/81 % by 2 months of age; 86/86 % by 3 months and 100 % by 6 months. The lateral center appears later at a median age of 9 months in girls (range 2 months to 2½ years) and 1 years 2 months in boys (range 4 months to 4½ years; 96 % by 2 years). The two centers fuse into one between the ages of 5 and 7 years. The external shape of the proximal humeral epiphysis is retained with little change from birth until skeletal maturation. The radiographs indicate, however, that the internal shape of the epiphyseal growth plate as indicated by the epiphyseal–metaphyseal junction changes from an initial transverse or curvilinear orientation to that of an inverted V. The lateral secondary center is frequently referred to as that of the greater tubercle but it appears to be a true secondary center of the epiphysis and should not be considered as an apophysis. The medial center relates to the inclined plane of the medial aspect of the physis and the lateral center to the inclined plane on the lateral side of the physis. Radiographic definition of the time of appearance of the two centers shows a fairly wide range because of the superimposition of one on the other depending on the rotation of the arm at the time of radiograph. This also applies to accurate definition of the time of fusion of the two secondary centers. From birth to 3 years of age, the plate is slightly curved, concave toward the metaphysis. Once the two ossification centers of the proximal humerus have fused, antero-posterior radiographs demonstrate an inverted V shape to the plate. The epiphysis interdigitates with the metaphysis in a trough-like fashion along the antero-posterior axis.

Table 1.16 Median ages in years and months and ranges in age at which certain ossification centers appear

Center	Median	Girls range	No. of cases	Median	Boys' range	No. of cases
Metacarpal I	1-11	0-6 to 3-0	72	3-1	1-6 to 6-0	51
II	1-4	0-6 to 2-0	71	1-10	0-6 to 3-0	53
III	1-4.5	0-6 to 2-6	74	2-0	0-6 to 3-6	53
IV	1-6	0-6 to 2-6	74	2-1.5	1-0 to 4-0	54
V	1-7	0-6 to 3-0	73	2-5	1-0 to 4-0	54
Proximal Phalanx I	2-1.5	1-0 to 3-0	69	3-4.5	1-6 to 6-0	49
II	1-2	0-4 to 2-0	70	1-7.5	0-6 to 3-0	55
III	1-1.5	0-4 to 2-0	72	1-7	0-6 to 3-6	55
IV	1-2	0-4 to 2-0	71	1-8	0-6 to 3-0	54
V	1-5.5	0-6 to 2-6	73	2-1.5	1-0 to 4-0	54
Middle Phalanx II	1-8	0-6 to 3-0	64	2-6	1-0 to 4-0	49
III	1-7.5	0-6 to 2-6	69	2-4	0-6 to 4-0	49
IV	1-7.5	0-6 to 2-6	69	2-5	1-0 to 4-0	52
V	2-3	0-6 to 4-0	65	3-7	1-6 to 5-6	50
Distal Phalanx I	1-5	0-4 to 2-6	63	1-10.5	0-6 to 4-0	50
II	2-5	0-6 to 3-0	58	3-7	1-0 to 6-0	45
III	1-11	0-6 to 3-0	65	2-7	1-0 to 4-0	48
IV	2-0	0-6 to 4-0	66	2-8	1-0 to 4-0	48
V	2-4	0-6 to 3-6	63	3-7	1-6 to 5-0	48
Humerus-head	81 % by 0-2	0 to 0-4	58	78 % by 0-2	0 to 0-6	45
Greater tuberosity	0-9	0-2 to 2-6	68	1-2	0-4 to 4-6	53
Capitellum	0-7	0 to 1-6	69	0-10	0 to 2-6	56
Lateral epicondyle	9-10	7-6 to 12-0	70	12-5	9-6 to 15-6	61
Trochlea	9-5	5-6 to 12-6	70	10-7	7-0 to 14-0	58
Medial epicondyle	3-10	2-0 to 6-6	64	7-1	4-6 to 10-0	60
Radius-head	4-10	2-0 to 8-0	70	6-3	2-6 to 9-6	57
Olecranon	8-8	6-0 to 11-6	69	11-3	7-6 to 14-0	54
Distal radius	1-15	0-4 to 3-0	69	1-4	0-4 to 3-6	53
Distal ulna	6-0	3-6 to 9-0	75	7-5	5-0 to 10-0	62
Femur-head	0-5	0 to 1-0	67	0-6	0-2 to 1-0	55
Greater trochanter	2-10	1-6 to 4-0	68	4-0	2-0 to 6-0	60
Distal femur	100 % by 0-2	0 to 0-2	58	100 % by 0-2	0 to 0-2	47
Proximal tibia	100 % by 0-2	0 to 0-2	58	98 % by 0-2	0 to 0-2	47
Proximal fibula	3-1.5	1-0 to 6-6	60	4-5	2-0 to 6-6	57
Distal tibia	0-5	0 to 1-0	68	0-5.5	0-2 to 1-0	56
Distal fibula	1-0.5	0-4 to 3-0	69	1-4	0-4 to 2-6	50

From Hansman (Ref. [504])

1.19.1.2 Distal Humerus

The newborn has a completely cartilaginous epiphysis [227]. The physis is mildly curvilinear but approaches the transverse plane in the antero-posterior projection. It is somewhat more curved in its lateral projection. In both projections, the physeal concavity is toward the metaphysis. The metaphysis relates to the epiphysis as a cylinder with its long axis in the coronal plane. The lateral capitellar ossification center appears at a median age of 7 months in girls (range birth to 1½ years; 100 % by 2 years) and at a median age of 10 months in boys (birth to 2½ years; 100 % by 2 years). The trochlea ossification center appears much later at a median age of 9 years 5 months in girls (5½–12½ years; 100 % by 12 years) and 10 years 7 months in boys (7–

Table 1.17 Median ages in years and months and ranges in age at which certain epiphyseal ossification centers fuse with their metaphyses

Center	Median	Girls range	No. of cases	Median	Boys' range	No. of cases
Metacarpal I	14-1	11-6 to 16-0	31	16-4	14-0 to 18-6	32
II	14-6	11-6 to 17-0	31	16-6	14-6 to 18-6	31
III	14-6	11-6 to 17-0	31	16-6	14-6 to 18-6	31
IV	14-5	11-6 to 17-0	31	16-5	14-6 to 19-6	31
V	14-5	11-6 to 16-9	31	16-6	14-6 to 19-6	31
Proximal Phalanx I	14-2	11-0 to 17-0	33	16-3	14-6 to 18-6	33
II	14-2	11-0 - 16-6	31	16-4.5	14-6 to 18-6	32
III	14-2	11-0 to 16-6	32	16-4	14-0 to 18-6	32
IV	14-3	11-0 to 16-6	33	16-6	14-6 to 18-6	32
V	14-2	11-0 to 16-0	32	16-3	14-6 to 18-6	33
Middle Phalanx II	14-4.5	11-0 to 17-0	33	16-5	14-6 to 19-6	30
III	14-4.5	11-0 to 17-0	31	16-6	14-6 to 19-6	31
IV	14-4	11-0 to 17-0	31	16-5	14-6 to 18-6	31
V	14-3	11-0 to 17-0	33	16-4	14-6 to 19-6	30
Distal Phalanx I	13-8	10-6 to 15-6	36	15-11	13-6 to 18-0	35
II	13-7	10-6 to 16-0	37	15-10	13-6 to 19-6	35
III	13-7	10-6 to 16-0	37	16-0	13-6 to 18-0	34
IV	13-8	10-6 to 16-0	35	15-10.5	13-6 to 18-0	34
V	13-7	10-6 to 15-6	37	15-11	13-6 to 18-0	33
Humerus-head	15-7	13-0 to 17-0	27	18-2	16-6 to 20-0	19
Greater tuberosity	4-1	2-0 to 7-6	71	5-6	3-0 to 8-6	63
Capitellum	12-5	9-6 to 14-0	62	15-2	13-6 to 17-6	58
Lateral epicondyle	12-8	9-6 to 15-0	57	15-4	13-6 to 18-0	56
Trochlea	12-4	9-6 to 14-0	58	15-1.5	13-0 to 18-0	58
Medial epicondyle	14-1	11-0 to 16-0	51	16-4	14-0 to 19-0	45
Radius-head	13-6	10-6 to 16-0	57	16-2	14-0 to 19-0	47
Olecranon	12-8	10-0 to 14-6	58	15-4.5	13-6 to 18-0	56
Distal radius	15-10.5	13-0 to 17-0	28	18-0	16-0 to 20-0	21
Distal ulna	15-11	12-6 to 17-0	30	17-10.5	16-0 to 20-0	20
Femur-head	14-2	11-0 to 16-6	52	16-3	14-0 to 19-0	49
Greater trochanter	13-11	11-6 to 16-0	50	15-11	14-0 to 19-0	47
Distal femur	14-9	12-0 to 17-0	46	16-7.5	14-0 to 19-0	47
Proximal tibia	14-10	12-0 to 17-0	44	16-11	14-6 to 19-6	42
Proximal fibula	15-2	12-0 to 17-0	38	17-2	15-0 to 20-0	37
Distal tibia	14-10	12-0 to 17-0	44	16-10.5	14-0 to 20-0	46
Distal fibula	14-10.5	12-0 to 17-0	42	16-10.5	15-0 to 20-0	45

From Hansman (Ref. [504])

14 years; 100 % by 15 years). The trochlea usually ossifies from multiple foci which fuse gradually with time. The medial epicondyle ossification occurs at a median age 3 years 10 months in girls (range 2–6½ years; 95 % by 5 years) and 7 years 1 month in boys (range 4½–10 years; 95 % by 9 years); and the lateral epicondyle at a median age 9 years 10 months in girls (range 7½–12 years; 100 % by age 12) and 12 years 5 months in boys (range 9½–15½ years; 100 % by 15 years).

1.19.1.3 Proximal Radius

The proximal radial epiphysis is completely intra-articular [506]. The physis approaches the transverse plane in all projections. There is a slight concavity to the plate which

relates to the gentle dome-shaped metaphysis. The ossification center of the radial head appears at a median age of 4 years, 10 months in girls (range 2–8 years; 89 % by 5 years) and 6 years, 3 months in boys (range 2½–9½ years).

1.19.1.4 Distal Radius

The plate closely approaches the transverse plane in all projections with slight concavity relating to a dome-shaped distal radial metaphysis [507]. The median age of appearance of the distal radial secondary center in girls is 1 year, 2 months of age (range 4 months to 3 years; 99 % by 2 years of age) and 1 year, 4 months of age in boys (range 4 months to 3½ years; 91 % by 2½ years). The secondary center appears centrally initially but tends to expand or ossify laterally toward the styloid giving it a more lateral position during much of the growth period.

1.19.1.5 Proximal Ulna

The proximal ulnar secondary ossification center resides within the olecranon [506]. This appears relatively late at a median age of 8 years, 8 months of age in girls (range 6–11½ years; 97 % by 10 years of age) and at a median age of 11 years, 3 months in boys (range 7½– 14 years; 99 % by age 13).

1.19.1.6 Distal Ulna

The distal ulnar physis lies along the transverse plain in all radiographic projections [507]. The secondary center appears at a median age of 6 years in girls (range 3½–9 years of age) and at a median age of 7 years, 5 months in boys (range 5–10 years; 100 % by 10 years of age). The ossification center is central in the epiphysis in all radiographic projections and expands equally in all directions.

1.19.1.7 Proximal Femur

The shape of the proximal femur undergoes the greatest degree of change during development of any epiphyseal region both in external contours and internal bone–cartilage relationships [508–512]. Two major epiphyseal ossification centers develop at the proximal end of the femur: one in the femoral head and the other in the greater trochanter along with an apophyseal center of the lesser trochanter (1). The median time of appearance of the proximal femoral capital secondary ossification center is 5 months of age in females (range birth to 1 year; 100 % by 1 year) and 6 months of age in males (range 2 months to 1 year). It is interesting to observe the specific time of appearance of the proximal femoral capital femoral epiphysis secondary center appearance. In the study by Francis and Werle [436], in girls the femoral head center is present in 40 % at 3 months age, 89 % at 6 months of age, and 100 % by 12 months. In boys, 24 % have appeared at 3 months, 91 % by 6 months, and 100 % by one year of age.

The median time of initial appearance of the greater trochanter secondary center is 2 years 10 months of age in girls and 4 years in boys (range 2–6 years; 94 % by 4½ years). The lesser trochanter begins to ossify as an apophysis at an approximate median age of 8½ years (range 6–12 years) in girls and a median of 11½ years in boys (range 7–15 years).

The upper end of the femur is composed initially of a solid mass of cartilage. The proximal femoral growth plate has a curvilinear shape and underlies the cartilage of the head, the cartilage of the greater trochanter, and the cartilage of the intervening notch region. Toward the end of the first year this curvilinear shape is changed as there is a relative overgrowth of the head–neck region in relation to that of the greater trochanter. The appearance of the metaphyseal bone thus assumes an inverted V shape with the medial limb approximately one-third of the length compared to two–third length of the lateral limb underlying the notch region and the greater trochanter. At approximately 3–4 years of age the notch region is transformed from cartilage to fibrous tissue thus setting up two separate epiphyseal regions. From 6 years onward, there is a gentle dome shape to the femoral neck metaphysis, with the concavity of the epiphyseal plate toward the neck.

A study of trabecular orientation is particularly helpful in assessing the growth patterns of the proximal femur. At birth the metaphyseal trabeculae are splayed with no specific preferential orientation underneath the curvilinear aspect of the single growth plate from medial to lateral sides. By 14 months when there is deepening of the notch between the medial femoral head and lateral greater trochanter regions, the orientation of the trabeculae is seen. By 5 years the adult type pattern is demonstrated.

Additional changes in shape during development relate to the external structure of the bone. These are frequently combined with use of the term anteversion but are really comprised of changes in two planes. One involves a rotation of the entire proximal end of the femur in relation to the diaphysis in a direction such that the head–neck mid-line axis in relation to the coronal plain of the distal femoral condylar region is increased. The second angle, which can be appreciated by considering a lateral projection of the proximal end of the femur with the diaphysis, places the head–neck–trochanter region in a flexed position relative to the diaphysis. It is possible to conceive of an absence of rotation of the proximal end with a flexed posture as well as anteversion of the head and neck without true flexion.

The internal architecture of the bone trabeculae of the proximal end of the femur is appreciated better in the adult but is quite clearly shown in the child and provides many clues in relation both to normal and abnormal development.

1.19.1.8 Distal Femur

The first secondary ossification center to appear in human development is that of the distal femur. This is invariably present normally at birth in 100 % of girls and boys. It is always a single ossification center which widens in both coronal and sagittal planes with growth. This secondary center has been noted as early as 28 weeks of gestation and is generally described as being present in all fetuses after 33 weeks [513]. Sonographic identification of the distal femoral center increases between its earliest appearance at the 28th gestational week. Its normal diameter at birth has been listed at 5 mm.

The peripheral regions of the secondary ossification center of the distal femur are frequently irregular in shape on post-natal radiographs, a finding which must not be considered as pathologic. This rough fringe-like margin is especially common between the 2nd and 6th years. Serial antero-posterior and lateral radiographic projections document distal femoral epiphyseal development. The configuration of the epiphyseal region changes little from the fetal period to that at skeletal maturity. The growth plate of the distal femur has an irregular shape. From birth to skeletal maturity in the antero-posterior projection, there is a double concave shape toward the metaphysis. From 8 years onward, the depth of the concavity is relatively greater. On the lateral projection from birth to approximately 7 years of age, the epiphyseal growth plate projects in a transverse plane; during the next few years a slight double concave curve can be noted; and over the final few years, a U-shaped growth plate concave to the metaphysis is seen.

1.19.1.9 Proximal Tibia

The proximal tibial epiphyseal ossification center is also present in virtually 100 % of individuals at birth [514]. This secondary ossification center is second in order of appearance only to that of the distal femur. It develops during the fetal period somewhat later than the distal femur and occasionally is absent for a couple of months in the human at birth. Even with slow development, it should be present in 100 % regardless of sex by 3 months of age. The initial secondary ossification center is centrally placed and spherical.

At the anterior, mid-line, and inferior part of the developing tibial epiphysis the cartilage is continuous toward the area that will become the tibial tubercle. From birth to approximately 2 years of age in the antero-posterior projection, the plate is slightly curved, concave toward the metaphysis. Over the next several years, the plate approaches the true transverse plane, but again toward the end of growth a slight double concavity is seen. In the lateral projection from birth to approximately 13 years in the male and approximately 10 years in the female, the plate appears level although it is continuous with the apophyseal plate anteriorly and curves inferiorly at a sharp angle. This becomes readily apparent when anterior ossification commences. The secondary ossification center in the tibial tuberosity forms late towards the end of the first decade [515]. It forms initially in girls between 8 and 14 years of age with 64 % present by age 10 years and in boys between 9 and 15 years of age with 59 % present by age 12 years. The tibial tubercle ossification center initially forms distally. With time, the two centers approach each other; the anterior and inferior portion of the initial primary ossification center is extended distally and the secondary ossification center of the tibial tubercle is extended proximally. The tuberosity physis closes from proximal to distal.

1.19.1.10 Distal Tibia

The secondary ossification center of the distal tibia appears in both girls and boys around 5 months of age with that in girls seen only a few weeks before that in boys [516–518]. The median age of appearance in girls is 5 months (range birth to 1 year; 93 % by 6 months) and in boys 5½ months (range 2 months to 1 year; 85 % by 6 months). Several developmental points are of interest. By 3 years of age the distal fibula physis is at the same level as the distal tibial articular surface, a relationship which is then maintained until skeletal maturity. The distal tibial growth plate is horizontal on radiographic projections until around 3 years of age. At this time the medial third of the growth line is characterized by an undulation in which a focal area of the physeal region is indented superiorly into the metaphyseal region before regaining its linear orientation. This conformation is maintained until skeletal maturity. By 5 years of age the medial part of the distal tibial secondary ossification center begins to extend inferiorly into the medial malleolar cartilage mass. By 10 years of age approximately 50 % of the medial malleolar volume has ossified. In approximately 20 % of normal children there is an independent ossification center at the tip of the medial malleolus although most of these fuse to the main distal tibial ossification center during adolescence [519]. Some descriptions of these extra centers within the medial malleolus have noted their presence registered as high as 47 % in girls and 17 % in boys [520]. The average age of appearance of these accessory centers was 7.6 years in girls and 8.7 years in boys. It is important not to diagnose these as fractures as they are almost always brought to light in association with radiographs for foot and ankle injuries.

The plate is transverse in the antero-posterior projection, except for the slight focal proximal displacement in the medial third. The lateral projection shows a gentle curvature of the plate convex toward the metaphysis. The distal tibial epiphysis relates to the metaphysis as a cylinder with the long axis in the coronal plane. Closure of the distal tibial physis is unique passing from the medial side which closes earliest to the lateral side. Ogden indicates that this closure

pattern can occur over a period as long as one and a half years.

1.19.1.11 Proximal Fibula

The median age at appearance of the proximal fibular secondary ossification center in girls is at 3 years 1 month of age (range 1–6½ years; 97 % by 4½ years) and in boys at 4 years 5 months of age (range 2–6½ years; 92 % by 5 years). The plate lies in a transverse plane in all projections.

1.19.1.12 Distal Fibula

The plate lies in the transverse plane in all projections [517]. The median age at appearance of the secondary ossification center in girls is 1½ years (range 4 months to 3 years; 100 % by 18 months) and in boys is 1 year 4 months (range 4 months to 2½ years; 10 % by 2 years). The distal fibular epiphysis may exhibit irregular ossification although accessory centers are found in only 1 %.

1.19.2 Relationship of Proximal and Distal Tibial and Fibular Physes

The proximal tibial physis is always more proximal to the physis of the fibula. The proximal tibial–fibular physeal difference was determined to be 0.4 cm prior to the first year with a gradual increase to approximately 2.0 cm at age 12 years [521]. The distal fibular physis is always more distal in position than the distal tibial physis. The distal fibular growth plate lies at the level of the tibiotalar articular surface. The distal tibial–fibular physis difference was also 0.4 cm prior to the first year of age and increased to approximately 1.0 cm at the age of 12 years.

1.19.3 Time and Pattern of Physeal Closure

The time of physeal closure at each epiphyseal region has also been a matter of study since the nineteenth century owing to its clinical importance and the fact that it seemingly could be defined relatively easily. While it is true that no further growth will occur once the physeal cartilage has been obliterated, physeal growth has invariably diminished to negligible amounts and then terminated long before there is radiologic evidence of complete physeal disappearance. It is important to make the distinction between physeal function and physeal presence since the former invariably diminishes before actual physeal obliteration occurs.

The sequence of union of epiphyses in the human from first to last as defined by Stevenson is distal humerus, proximal radius, proximal ulna, proximal fibula, distal tibia, distal fibula, proximal tibia, distal radius, distal ulna, and proximal humerus [522]. Humphrey and Ollier noted that the end of the shaft where growth was greatest united last. Payton [68] demonstrated, in the pig, that some epiphyseal growth occurred at the side nearest the joint, by which is meant the area under the articular cartilage. The epiphyseal growth is greater at the end of the bone where diaphyseal growth is greater but the proportionate difference is less. In Tables 1.8 and 1.9, the times of growth plate closure are listed.

Of increasing importance in a clinical sense is recognition of the pattern of closure in each of the specific physes. There can be considerable variation in the time of physeal closure of the various epiphyses in the body, epiphyses at the proximal and distal ends of any particular bone, and even within any epiphysis itself.

1.19.4 Distal Tibial Growth Plate Closure

An example of asymmetric physeal closure with important clinical implications is that of the distal tibia. This invariably closes not uniformly but over a several month period from the medial side to the lateral side [516]. At a certain stage, therefore, the medial one-third to one-half of the physis is closed whereas the lateral segment is open. This leads to a characteristic type of fracture, the Tillaux fracture, in which the Salter–Harris type III conformation is seen with the physeal transverse component along the lateral aspect and the fracture then cracking into the secondary ossification center and out through the articular cartilage. The variable pattern of closure also contributes to the characteristic triplane fracture of the distal tibial epiphysis in the latter few years of growth.

1.19.5 Proximal Femoral, Proximal Tibial, Metatarsal and Phalangeal, Growth Plate Closure

Dvonch and Bunch [523] have studied closure of 25 proximal femoral and 10 proximal tibial growth plates. They felt that the proximal femur physis initiated closure superiorly with closure proceeding inferiorly in all instances. Haines et al. [524] also identified closure of the proximal femoral epiphysis beginning peripherally at its superolateral margin. In the proximal tibia, closure occurred initially along the anteromedial aspect of the tibia and tibial tubercle and then proceeded posteriorly. Union of the larger epiphyses of bones other than those of the hands and feet begins at or near the periphery of the cartilaginous physes. The union of the phalangeal physes is different from the major long bones as it occurs initially centrally and then proceeds centrifugally toward the periphery.

Haines has also outlined the histology of growth plate closure [525].

1.20 Why Epiphyses Form. Evolution of Epiphyses

An important feature underlying consideration of the epiphyseal regions concerns the basic question of why epiphyses form the way they do. The contribution of the end of the bones to longitudinal growth was apparent as early as the mid-1700s beginning with the classic experiments of Hales [35] and Duhamel [30–34] (Table 1.1). The reasons for occurrence of the secondary ossification centers have been unclear.

Two mechanisms have been proposed for their presence although experimental verification of these mechanisms is lacking. The two theories advanced for the formation of secondary ossification centers are (i) mechanical, in the sense that they are required for the appropriate distribution of support for the developing ends of the bone and (ii) nutritional–vascular, wherein the central regions of the epiphysis, furthest from the peripheral vasculature, are considered to be prone to calcification of the matrix and subsequent ossification. Observations were frequently made that the secondary ossification centers formed in the central regions of the epiphyses and in particular in those of larger animals. Those animals which are relatively large at birth and which walk in the first few hours to days after birth are characterized by far more advanced development of the secondary ossification centers, in particular of the hips and knees, than is seen in the human where walking does not begin until the second year of life. In ungulates including ox, bovine, and lamb epiphyses, the secondary ossification centers of the proximal femur, distal femur, and proximal tibia are far more extensively developed at birth than those in the human.

These features were felt to be consistent with the interpretation that the secondary ossification centers formed in regions of relatively poor or diminished nutrition since the epiphyseal cartilage received its nutrition either by diffusion of nutrients through the articular surface or via penetration of vascular canals which had their origin in the perichondrium. It was felt that the chondrocytes in the most central regions of the larger epiphyses tended to degenerate because of relatively diminished nutrition which provided a signal for calcification of the adjacent matrix. The mineralization then provided a signal which allowed for vascular invasion by way of the cartilage canals at which time the endochondral ossification mechanism was activated.

Parsons addressed the pressure or articular epiphyses at the ends of the developing long bones in 1905 and focused on the questions of "1. How these epiphyses come, 2. What use they are, 3. Why they come [224]." His use of the term epiphysis refers to the secondary ossification centers. He noted that they were not essential for growth since birds did not develop epiphyses with secondary ossification centers except at the anterior part of the proximal tibio-tarsus which was really a traction epiphysis at the site of attachment of the patellar tendon. In terrestrial vertebrates other than birds the epiphyseal cartilage sometimes just remained cartilaginous sometimes calcified only and sometimes progressed to a true bony secondary center. He observed that "the larger the cartilaginous mass at the end of a long bone, the earlier will an epiphysis appear in it," and "that the first ossific deposit occurs in the very center of the cartilage, and nowhere near the perichondrium."

Parsons indicated that the secondary ossification centers did not help in growth which occurred almost exclusively on the diaphyseal side of the growth plate, did not serve as protection for the physeal region, and did not contribute meaningfully to the shaping of the articular end of the bone. Although admitting "that I have heard no satisfactory explanation of the good which these epiphyses do" he pointed out that in certain ungulates such as ox, sheep, and lambs, the secondary ossification centers appeared long before birth and that a lamb 2 days old shows them as well developed as a human of 12 or 13 years. He hypothesized that since these animals are able to walk almost as soon as they are born the secondary ossification centers might have represented an adaptation from "some mechanical need." He felt that "some mechanical cause will be found for the early appearance of these ungulate epiphyses as the subject comes to be further inquired into". He speculated that it would eventually come down to some answer which had both chemical and mechanical components. The triggering formative mechanism was not pressure per se which he felt would be least in the center of cartilage region but rather one of the nutrition. The secondary centers begin "as a degenerative process in the least vascular part of the cartilaginous end of the bone, that is to say the center of it, and one would expect that the larger the mass of cartilage the less well-nourished would the center of it be, and so the more liable to the deposit of lime salts." This observation was consistent with the initial presence of secondary centers in the central part of the epiphyseal cartilage and earlier in the larger epiphyses.

Haines stressed that epiphyses in general are a compromise arrangement to allow for the simultaneous growth and function of bones [526]. The concept of appositional growth is clearly established for bone tissue and necessitates the epiphyseal cartilage mechanism to allow for interstitial growth at both ends. The development of a flattened growth plate is as much a reflection of the entire long bone biophysical environment as it is of any mechanism of orientation. One can think of the bulky cartilage epiphyses at each end as being under pressure being attached to each other by

the continuous outer fibrous layer of the periosteum and essentially separated by a strut of cortical bone holding them apart in between. Thus the epiphysis takes the pull not only of the muscles directly inserted into it but also of those usually described as being inserted into the shaft of the bone. It is argued that if the articular cartilage and the growth cartilages can be separated, then each can be arranged in the most advantageous structural position, the former for giving a joint surface of appropriate shape and orientation even if the articular surface is offset from the main axis of the shaft and the growth plate for directing the arrangement of trabeculae along the long axis. In land-living stress-bearing animals the weakness of this large mass of undifferentiated cartilage between the two layers would be apparent, a weakness overcome by the introduction of the secondary ossification centers of calcification or ossification.

Haines wrote a detailed review of the evolution of epiphyses stressing the structural changes in the various groups [526]. Cartilaginous epiphyses are present in bony fish and there is a clear arrangement of periosteal and endochondral bone in the long bones. The structure in fish indicates that the mechanism of growth is the same as in land animals and that fish have epiphyses. They differ in that they have no secondary centers of calcification or ossification and no physeal ordering of flattened or hypertrophic chondrocytes. Haines defines the most primitive tetrapod with secondary centers as sphendon where there is central cartilage calcification and outlines development of formal bony centers in lizards and mammals. The evolutionary changes of cartilage canals for vascularity of epiphyseal cartilage and secondary centers of calcification and ossification are concerned with better nutrition, strengthening, and better functional positioning of component parts of the epiphyses.

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Overview of Deformities

2

2.1 Deformity

Deformity is a deviation in structure or position from normal.

2.2 Orthopedics and Pediatric Orthopedics

The term orthopedics was initially defined by Nicolas Andry, a French physician, in his book Orthopaedia [1]. In his words, "As to the title, I have formed it of two Greek words viz "*orthos*" which signifies straight, free from deformity and "*paideia*" a child. Out of these two words I have compounded that of "*Orthopaedia*", to express in one term the design I propose, which is to teach the different method of preventing and correcting the deformities of children." When one considers its origin, the word "orthopedics" (American English spelling) or "orthopaedics" (British English spelling) has been employed in a semantically challenged fashion. It came to refer to the diagnosis and treatment of musculoskeletal problems in adults as well as children, evolved into the surgically oriented specialty "orthopedic surgery", and more recently the term "pediatric orthopedics" has come into use as groups of orthopedic surgeons began restricting their practices to childhood and adolescent age groups.

2.3 Founders of the Discipline of Pediatric Orthopedics

Overviews of the historical development of orthopaedics and orthopaedic surgery have been written in journal articles by Buckwalter [2, 3] and in more detailed books by Keith [4], Valentin [5], and Peltier [6]. A few noteworthy individuals concentrated however on the description, treatment, and study of childhood deformities.

2.3.1 Nicolas Andry (1658–1742)

Andry was a prominent professor of medicine in Paris who published his famous book when he was over 80 years of age. The book "L'Orthopedie, ou l'art de prevenir et de corriger dans les enfants, les difformities du Corps" was published in Paris in 1741, in English translation in London in 1743 as "Orthopaedia, or the Art of Correcting and Preventing Deformities in Children", and in German in Berlin in 1744 [1]. Ironically, he campaigned forcefully throughout his career against the practice of surgery and wrote on the pre-eminence of medicine over surgery. His book was addressed to parents describing external deformities of childhood and the means they could employ themselves to limit deformity and occasionally straighten the body. The book contained few anatomic descriptions of deformity or detailed treatments of the musculoskeletal system. The work remains noteworthy for its introduction of the term "orthopedics" and for its illustration of a crooked tree being corrected to a straighter position by splinting (Fig. 2.1). In referring to the now classic illustration, Andry explains "if… the leg is already crooked, you must apply, as soon as possible, a small plate or iron upon the hollow side of the leg, and fasten it about the leg with a linen roller. This roller must be made tighter and tighter everyday, 'till it compresses sufficiently the part that bunches out; and that this compression may not hurt it, you must put a large compress under the bandage, on that part of the leg. In a word, the same method must be used in this case, for recovering the shape of the leg, as is used for making straight the crooked trunk of a young tree." Volume 1 (of 2) which describes deformities of the back and extremities however does refer to the proportionality of the human body, basic anatomy, neck and spine deformity, deformities of the upper and lower extremities including limb length discrepancies, extra fingers (usually 2 thumbs), ankle equinus contractures, dislocations, and in-toeing and out-toeing. It describes the still valid concepts

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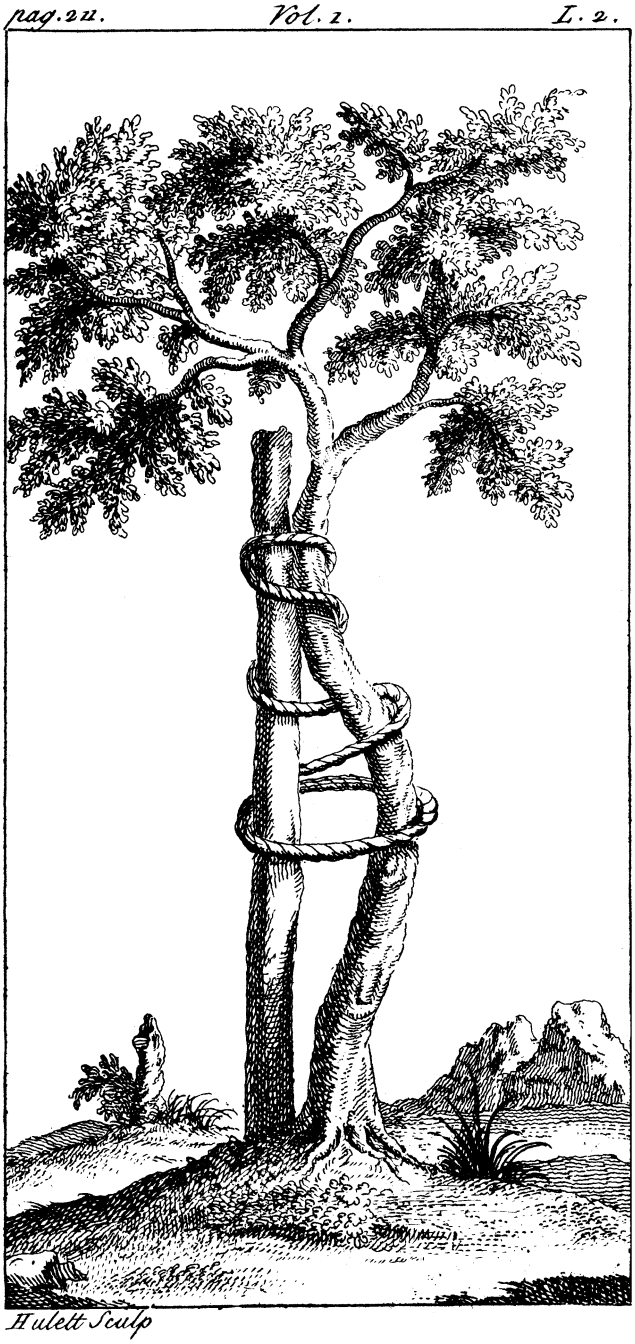


Fig. 2.1 Illustration used by Andry [1] to point out the similarity between the pressures applied by splints and bandages to straighten the deformed legs of children and the method used to straighten the crooked trunk of a young tree. ["In a word, the same Method must be used in this case, for recovering the Shape of the Leg, as is used for making straight the crooked Trunk of a young Tree." Andry, Orthopaedia, London 1743.]

of the plasticity of the child, the value of gymnastics in enhancing structural development, and treatments with active mobilization or splinting where needed to overcome deformity. The book was never intended as a medical text directed to physicians but it was the first book to discuss childhood deformity in a specific region-by-region fashion.

2.3.2 Jean-Andre Venel (1740–1791)

Venel was a physician from Geneva, Switzerland who established in 1780 the first orthopedic hospital designed specifically for the treatment of skeletal deformities [7, 8]. The institute at Orbe, a few miles north of Geneva, made and applied numerous braces and apparatuses to treat deformity in children such as scoliosis and club foot. Many of the children being treated lived there for extended periods of time, also undergoing vocational training. Massage and manipulation were used to achieve deformity correction, along with traction apparatuses and orthoses, and much effort was subsequently placed on maintaining correction to prevent relapse. Venel developed a clubfoot brace (the "sabot de Venel") which was used for well over a century in some regions. It featured a boot, lateral strut to evert and abduct the foot, and a hinged foot piece to bring about gradual heel cord stretching and dorsiflexion. He wrote on the treatment of lateral curvatures and torsion of the spine using mechanical devices. Venel's brace applied both axial extension along the spine and transverse forces at the region of deviation thus treating both lateral deviation and rotation (torsion) at the same time. He recognized that up to four different deviations of the trunk could occur in a single patient in the sagittal, frontal (coronal) and oblique planes along with torsion. It was necessary to treat both lateral deviation and rotation in scoliosis. Building on the principles of axial extension along the spine used in previous braces, Venel kept the pelvis as a point of support below and both the axilla (used by Antoine Portal 1742–1832) and the head (used by Francois-Guillaume Le Vacher 1732–1816) above. He then added the application of forces in the transverse planes at regions of deviation applying the principle of derotation by using a rotatory pad in the transverse plane, being the first to simultaneously correct lateral deviation and torsion. He felt that treatment for scoliosis needed to be continuous, without interruption. The brace was used during the day ("appareil du jour") and he developed an orthopedic traction-extension bed for night-time use ("appareil du nuit"). This unique contribution served to continue correction in the supine position with gentle stretching force applied to head and axilla in one direction and each of pelvis, supracondylar (above knee) and supramalleolar (above ankle) regions in the other direction. He felt that treatment would be successful only for patients younger than 12 years of age.

2.3.3 Johann Georg Heine (1771–1838)

Heine was originally a craftsman making medical instruments, artificial limbs, orthopedic beds, wheelchairs and

orthopedic appliances. He eventually became a physician and opened the Karolinen-Institut, the first orthopedic institution in Germany, in 1816 in Wurzburg [5, 9].

2.3.4 Jacques Delpech (1777–1832)

Delpech was the professor of surgery at the University of Montpellier, France. He played a prominent role in describing and treating childhood orthopedic deformities of the spine and club feet. He established an orthopedic clinic in Montpellier with facilities for both inpatient and outpatient therapy. He also authored the first major text of orthopedic deformities with extensive discussion of pediatric disorders, published in 1828. The book, De L'Orthomorphie, was subtitled "with regard to humans: anatomic-pathologic researches on the causes, the means of preventing, the principles of curing deformity and on the true fundamentals of the art called Orthopedics" [10]. The 2 volume book included an atlas of drawings of deformities (both of the clinical appearance and of the skeletal deformities) with commentary for each case. There were examples of various spinal deformities followed by illustrations demonstrating the architecture of his institute and the various apparatuses and exercises used to correct deformity. Spinal and lower extremity braces were illustrated in detail and clearly showed application of principles of deformity correction still in use. Delpech also played a prominent role in early efforts at surgical correction of musculoskeletal deformities. He performed an Achilles tenotomy for correction of clubfoot deformity but an early case suffered infection so he did not pursue this treatment.

The book was remarkably well organized, detailed and insightful. Volume I had 3 chapters: I—Some anatomic considerations; II—General introduction to the causes of deformities; and III—Effects of deformities. Amongst the causes of deformities were: muscle weakness; growth in childhood associated with abnormal positionings such as with hemiplegia, paraplegia, joint displacements, underlying lung problems; effects of paralysis and contracture of certain muscles; lower limb asymmetries and length inequalities; club feet; bone deformity being primary or secondary; intervertebral fibrocartilaginous disorders leading to spinal deformities; effects of rheumatism on joints and on the spine specifically due to effects of muscle contracture, fibrous tissue inflammation, and damage to the fibro-cartilages; (pathologic) softening of the bones; tuberculosis of the bones; and combinations of causes. The effects of deformities were extensive involving those on the joints, on involved bones, on muscles, and on adjacent or contained organs such as lungs and heart. In volume II Delpech continued his description of deformities with 3 more chapters: IV—Differential diagnosis of deformities; V—Prognosis; and VI—Treatments of deformities. Diagnosis required a systemic appreciation of the health or illness of the child followed by assessment for signs of deformities dependent on specific causes. These included deformities caused by: muscular weakness; paralysis or contracture of muscles; other organ diseases such as empyema (of the chest) or external scarring; asymmetric development particularly of the extremities; various foot deformities; congenital or acquired deformities of the pelvis including dislocation of the (proximal) femur (at the hip joint); spinal deformity secondary to problems of the fibro-cartilages (intervertebral discs); rheumatism, rickets or tuberculosis.

Prognosis was dependent on several factors such as: spontaneous improvement with time (growth) or worsening with time. An overview of treatments then practiced was provided. This section is least relevant to today but does show both use of and conflicting opinions of effectiveness of methods still in use today. He comments extensively on spinal support corsets (braces) stressing their need to have an element of elasticity since rigid braces lead to further weakening of the components of the spine. Elastic supports allow for beneficial movement of the spinal joints. Effects of bracing on control of lateral and rotational deformity were discussed as were the practical issues of prolonged immobilization. The primary treatments involved exercises and positioning devices designed to favor certain body positions. A few illustrations from the atlas serve to show the complexity of these and the recommended need for residential facilities to carry out the programs. Figure 2.2a, b show the accurate presentations of deformities.

2.3.5 William John Little (1810–1894)

Little was a British physician and surgeon prominent for introducing subcutaneous tenotomy to England, writing landmark articles and books establishing the principles of orthopaedics based on his extensive experiences, and establishing the first hospital in England devoted to the study and treatment of disabilities of the limbs and spine [11]. Little himself suffered from an acquired equinus deformity due to infantile paralysis when he was 4 years old which left him with an equinovarus deformity. He visited several centers in Germany for additional training in 1835 and 1836 and eventually travelled to Hanover, Germany in 1836 for treatment of his deformity by Achilles tenotomy performed by Stromeyer. The procedure was very successful, as were the results of other cases operated by Stromeyer that he observed during his visit. On his return to London, Little began performing the subcutaneous tenotomy procedure in regular fashion starting in 1837. These events in the treatment of club foot launched the surgical era of pediatric orthopedics. Little wrote a series of articles and books

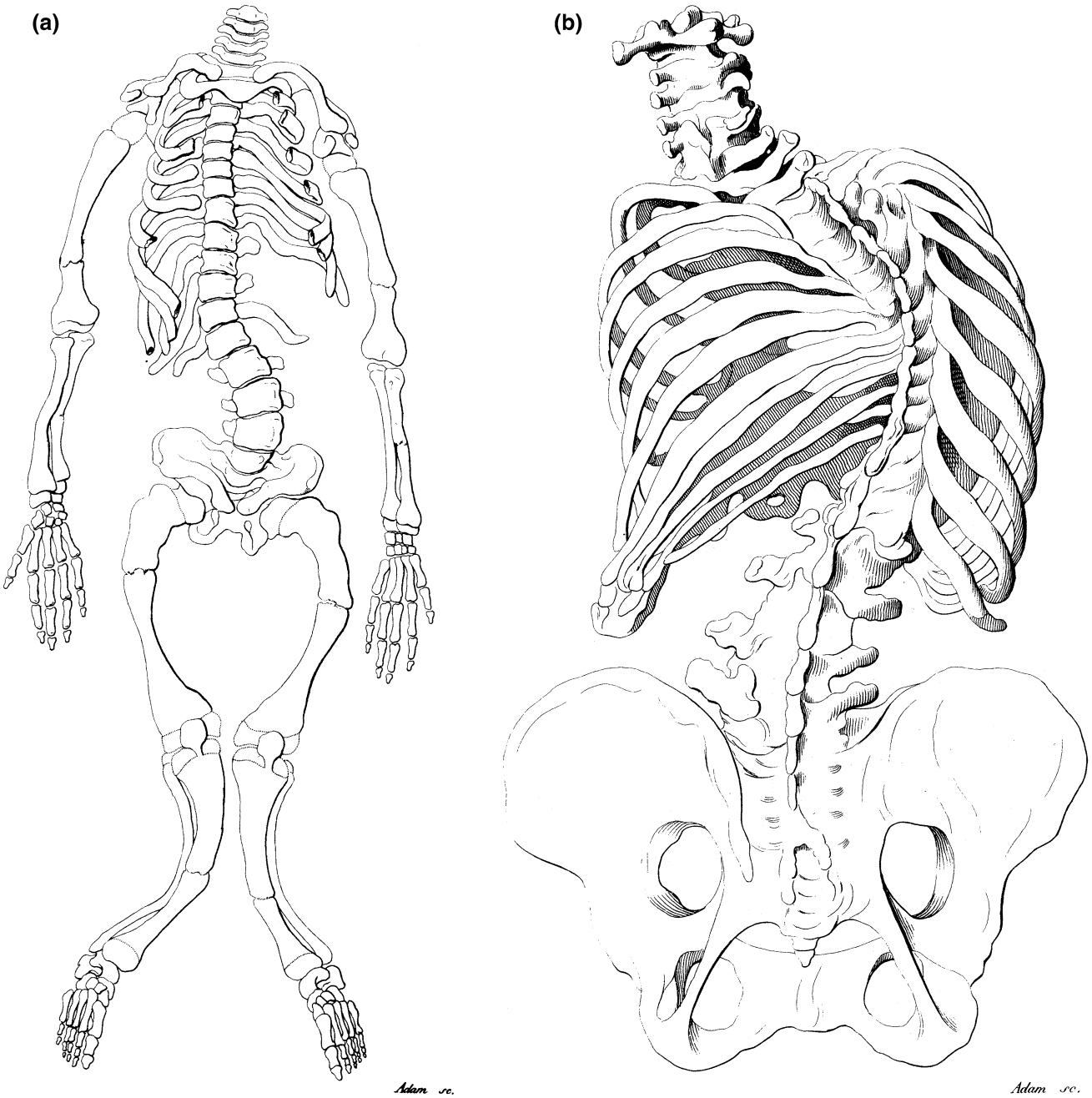


Fig. 2.2 Two images from the atlas by Jacques Delpech published with his text de l'Orthomorphie [10] in 1828 show an early appreciation of the pathoanatomy of complex orthopedic deformities. **a** Scoliosis, rib deformities, pelvic obliquity, long bone diaphyseal bowing and many undisplaced transverse defects consistent with partially healed or pseudofractures; and **b** thoracolumbar scoliosis with thoracic rotation and rib deformity

outlining childhood deformity that helped establish the principles for the discipline still valid today. In 1839 he published his book on "Club-foot and Analogous Distortions" [12]. Little further outlined his experiences observing and treating childhood deformity in a series of articles in Lancet in 1841 and subsequently published these in book form in 1853 with the title "On the Nature and Treatment of Deformities of the Human Frame" [13]. Little was particularly observant of deformities in children with spasticity providing detailed descriptions and management approaches. In 1862 he summarized several years of observations, describing 63 patients in an article in Transactions of the Obstetrical Society of London titled "On the influence of abnormal parturition, difficult labours, premature birth, and

asphyxia neonatorum, on the mental and physical condition of the child, especially in relation to deformities" [14]. The disorder subsequently known as cerebral palsy came to be known in England and elsewhere as Little's Disease. He established the Orthopaedic Infirmary in London in 1840, the first institute in England specifically for the treatment of limb and spine deformities. This subsequently became the Royal Orthopaedic Hospital and eventually the Royal National Orthopaedic Hospital.

2.3.6 William Adams (1820–1900)

Adams followed his teacher Little as the chief at the Royal Orthopaedic Hospital, also concentrating on childhood deformities and their correction. He spent several years training in anatomy and pathology before training in surgery with Little. Adams also performed studies on the gross and histologic repair of human and animal tendons after tenotomy. He published "On the Reparative Process in Human Tendons after Subcutaneous Division for the Cure of Deformities" in 1860, a book which included post mortem human studies, his experiments in rabbits, and a complete resume of the English and foreign literature on the subject [15]. He published a study on club foot, "Club-Foot: Its Causes, Pathology, and Treatment", which served as the classic reference in its era [16]. Adams further solidified his status as an early founder of pediatric orthopedics with his book on scoliosis published in 1882, "Lectures on the Pathology and Treatment of Lateral and other forms of Curvature of the Spine" [17]. He was also prominent surgically, performing tenotomies and osteotomies for correction of deformity.

2.3.7 Léopold Ollier (1830–1900)

Louis Xavier Édouard Léopold Ollier of Lyon, France performed extensive investigations on bone growth and repair in several animal species, concentrating on the role of the periosteum in bone formation and the mechanisms of long bone growth. He defined the role of the periosteum in the rabbit using transplants into muscle and noting bone formation. Ollier's experimental work on the periosteum was recognized as very significant as soon as it was published. In 1860, when he was only 30 years old, the British Medical Journal published a detailed 2½ page review of his animal periosteal experiments "on the function of the periosteum as a producer and regenerator of osseous tissue" recognizing that "the subject is of some importance in a surgical as well as a physiological point of view" [18]. He continued to apply his experimental findings to his patient population. He played a leading role in the development of bone and joint surgery clinically establishing it as a separate discipline. He worked on bone transplantation; joint arthrotomy and debridement in children; maintenance of growth plates when doing surgery on growing limbs; joint excision in adults to treat ankylosis and sepsis (minimizing amputations) especially in the upper extremity at elbow and shoulder; osteotomy and osteoclasis to correct deformity; and the use of Lister's principles of asepsis. Ollier performed bone resections leaving the periosteum and its subperiosteal bone forming layer intact to encourage post-resection repair. At joints he also performed excision in the sub-capsular, sub-periosteal plane keeping tendons, ligaments and muscles in place to enhance repair and provide some post-surgical range of motion. He developed an elevator to detach a continuous sheet of periosteum, the sub-periosteal layer and the joint capsule. Ollier not only performed experimental work in animals but also adapted his finding to human surgery (in both children and adults). He did 827 joint excisions (a progressive operation in his time) and also documented all his surgical cases with follow-up over several decades. He later improved upon arthrotomy for diseased joints, especially in children and for major lower extremity joints, saving excision for major upper extremity problems in adults where mobility was essential. He published two major treatises: "Traité expérimental et clinique de la régénération des os et da la production artificielle du tissu osseux" in 2 volumes in 1867 (V. Masson) [19] and "Traité des Résections et des Opérations Conservatrices qu'on peut pratiquer sur le système osseux", Paris in 3 volumes from 1885–1891 [20].

2.4 General Principles Regarding Pediatric Orthopedic Deformity

Several general principles regarding deformity must be considered in the pediatric age group:

- The shape within individual bones and the alignment between adjacent bones or regions often change with growth especially in the first few years after birth. It is important to be aware of developmental patterns which are normal physiologic variants and not pathologic deformities. For example, anteversion of the femoral head and neck can be 40° at birth but will decrease with normal growth to 12°–15° in late adolescence but 40° anteversion in an adolescent regardless of cause will not correct spontaneously and is problematic for the future. Also, a bow leg positioning (genu varum) of 30° is almost always a normal, self-correcting physiological position in a 14 month old but is highly likely to be pathologic in the adolescent.

- There is a range of normal angles and rotations within individual bones and between adjacent bones and regions. The range may be narrow but is rarely exactly the same from person to person. Variations within these normal ranges should not be interpreted as deformities.
- Deformity may be evident by clinical observation alone (such as moderate to severe scoliosis or club foot deformity), by plain radiography (such as coxa vara of the hip or varus of the distal femur and valgus of the proximal tibia causing knee joint obliquity), or by more sensitive imaging modalities such as ultrasound, magnetic resonance imaging (MRI) or computerized tomographic (CT) scanning.
- Gene mutations can cause intramolecular and intermolecular mal-alignments (molecular deformation) leading to abnormal tissue development and eventual musculoskeletal deformation. Examples include skeletal dysplasias, osteogenesis imperfecta, peripheral neuropathies (Charcot-Marie-Tooth disease) and muscle disorders (Duchenne muscular dystrophy) all of which can lead to significant clinical deformation. In children with deformities it is necessary to consider abnormalities of chromosomes, such as Down syndrome with an extra copy of chromosome 21 (Trisomy 21) or genetic point mutations, deletions or insertions on specific molecules, such as collagen abnormalities in osteogenesis imperfecta, dystrophin abnormalities in Duchenne and Becker muscular dystrophy, and PMP22 abnormalities in Charcot-Marie-Tooth peripheral neuropathy.
- A pathologic deformity during the growing years may proceed along one of three pathways: it may correct spontaneously with growth, it may remain unchanged with growth, or it may worsen with growth.
- Each of the main mechanisms of spontaneous correction of a bone deformity in a growing child can be seen with remodeling following a physeal, metaphyseal or diaphyseal fracture which heals with angulation or malrotation but an intact functional physis. The repair mechanisms involve (i) differential physeal growth tilting and rotating the physis to the normal plane, (ii) periosteal new bone formation on the concavity and (iii) bone resorption on the convexity. These mechanisms are more effective the greater the number of years of growth remaining, the closer the angular deformity is to the physis, the more the physis involved contributes to the growth of the bone, and the presence of deformity in the plane of motion of the adjacent joint.
- If persistence of a deformity or its worsening with growth is likely, the deformity must be assessed as problematic or non-problematic over the short, intermediate and long (adult years) time frames. Problems resulting from deformity include some or all of pain, abnormal function such as gait disturbance, associated organ impingement (cardiac, pulmonary), or appearance. Also to be considered for any deformity is what degree of deformity is associated with what amount of clinical problem.
- Some deformities are sufficiently mild that no treatment is warranted since they cause no current problem and there is little convincing evidence that they will cause problems in the future.
- Treatments for some childhood deformities may not be warranted even if they are moderate to severe in view of the severity and progressive nature of the primary underlying pathologic process such as a neurodegenerative disorder even though treatment of the same deformity in an otherwise normal or only mildly involved child would be warranted.
- Deformity even if marked may be a secondary compensatory deformity necessary to maintain function such that its correction to a normal anatomic position may significantly decrease function. Marked lumbar lordosis in a patient with neuromuscular disease with gluteus maximus muscle weakness can allow a person to continue walking whereas spinal bracing or fusion straightening the spine can make the patient anatomically normal but unable to walk.
- Treatment in childhood is warranted for deformities that will not correct on their own if they are already symptomatic, causing discomfort or altered function, or if they are asymptomatic but there is scientific evidence that they will become symptomatic with time, even if that will be during the adult years.
- Once a deformity is considered treatable, two general approaches follow. The first is to treat any existing primary underlying disorder by medical means, for example, infection with antibiotics, hemophilic arthropathy with factor replacement, rickets with vitamin D, and spastic cerebral palsy with muscle relaxant therapy. The second is to treat the deformity itself by orthopedic means.
- There is a constant interplay of forces during the growing years between the soft tissues [muscle, tendon, ligament, intervertebral disc] and the developing bones [composed of cartilage and bone tissue]. Any abnormality in either the soft tissue or the developing bones due to imperfect structure or function can lead to deformity.
  - For any deformity it is essential to determine whether it is flexible or rigid. If it is flexible there is need to know if it fully straightens, or at a joint fully reduces, with change of position or passive manipulation or if it only partially corrects. Conversely, if rigid there is need to determine whether it is completely rigid or if manipulation partially straightens or reduces the deformity. The more rigid the deformity, the more

extensive the surgery needed to correct it and, in the case of the spine, the less correction attainable.

- *Primary soft tissue deformity*: Deformities due to soft tissue abnormalities, including neuromuscular disorders, are initially associated with normal cartilage model/bone model development. The longer the deformity persists and the more severe the deformity the greater the likelihood that asymmetric pressure on the skeletal elements involved will lead to structural deformity of the cartilage and bone.
  (a) Excess muscle pull leads to malposition of joints and distal structures. The malposition may correct with muscle relaxation or muscle-tendon transfer to balance strength across a joint but will recur with continuing asymmetric activity and eventually lead to cartilage and bone deformity with growth.
  (b) Ligamentous laxity leads to malpositioned joints which are initially present only with weight-bearing but correct to a normal anatomic position with non-weight-bearing. If left uncorrected in the presence of continuing growth the malposition can progressively become rigid, not actively or passively correctable, and even associated with misshapen bones.
  (c) Asymmetric soft tissue tightness can lead to rigid joints (contractures) and distal structure deformation which with continuing malposition eventually leads to developing bone deformity with growth over years.

- *Bone/cartilage deformity and its relation to the orientation of adjacent cartilage surfaces*:
  (a) Angular bone deformity centered at metaphyseal or diaphyseal regions leads to asymmetric joint alignment (obliquity) at one or both ends of an individual bone with a predisposition to abnormal intra-articular pressure and articular cartilage osteoarthritis.
  (b) Asymmetric growth plate function due to focal physeal abnormality leads to angular growth of the bone and joint obliquity distal and sometimes proximal to the involved physis which predisposes to abnormal intra-articular stresses.
  (c) In rare instances there is bi-directional angular deformity of a bone owing to curvature within the metaphyseal-diaphyseal regions. This can occur in patients with osteogenesis imperfecta or rickets. For example, a valgus angulation of the tibia centered at the proximal metaphysis can reverse direction by curvature in the mid-diaphysis leading to varus angulation centered at the distal metaphysis. In some instances there can be normal articular surface alignment persisting at both ends while in others the angular deformity also tilts the physis, epiphysis and articular surfaces into an oblique plane.

- Correction of deformity due to soft tissue abnormalities will often allow for spontaneous growth related correction of mild to moderate cartilage model/bone deformities.
- Neuromuscular deformities with both soft tissue and cartilage model/bone deformities usually require soft tissue correction (balancing of muscle groups) and might need bone correction by osteotomy or asymmetric physeal stapling.
- Repositioning of dislocated or partially dislocated (subluxed) joints by non-operative or operative means often allows mild to moderate cartilage model/bone deformities to correct with growth.
- Normal function or improved function post-treatment allows the normal stresses on immature tissues to further correct remaining deformity by differential growth towards a normal position.
- Deformities of intra-articular soft tissue structures, such as knee menisci or cruciate ligaments, if allowed to persist, can damage articular cartilage. These deformities can be suspected by clinical history and examination but are diagnosed definitively by direct arthroscopic visualization or by MR imaging.

- *Trauma to a developing bone can lead to deformity in several ways*:
  - Acute diaphyseal or metaphyseal fractures which heal with angulation, malrotation, translation or length discrepancy represent deformities which, with growth, may correct partially or fully, persist unchanged, or (rarely) worsen and require surgical intervention for correction.
  - Acute physeal (growth plate) fractures (or fracture-separations) can heal with no subsequent growth sequela or with partial or complete growth plate fusion predisposing to angulation and/or shortening with growth.
  - Chronic repetitive stresses on growth plates can lead to growth damage and premature growth plate fusion. Chronic tendon insertion site stresses in growing bone can lead to non-displaced tendon-cartilage-bone interface avulsions with painful tendinitis and insertion site swelling.
  - Articular surface damage either by displaced osteochondral fractures or linear oblique intra-articular fractures with persisting surface irregularity or gaps predispose to arthritic changes.

- Bone deformities are not passively correctable. They may, however, spontaneously remodel with growth, be correctable with growth with use of serial casting or bracing, or eventually require surgical intervention by metaphyseal/diaphyseal osteotomy or asymmetric physeal stapling for correction.
- Once a deformity is identified, the presence of a specific disease or an underlying causative disorder must be considered. Treatment can differ significantly for the same deformity (i) in a patient who is otherwise normal and in one who has an underlying disorder and (ii) between patients with different specific diseases.
- It is important to distinguish between a primary deformity and a secondary or compensatory deformity. The primary (or initial) deformity is at the site of pathologic abnormality and tends to be at least partially fixed or rigid. The secondary deformity tends to be fully flexible initially and for a longer period of time since it represents a process designed to maintain stability, balance and alignment. A longstanding secondary deformity may become rigid with time.
- A static joint deformity is present at all times and in all positions (e.g. supine, standing) owing to its bone or soft tissue rigidity. A dynamic joint deformity is present only with muscle activity since it is due to muscle imbalance. A joint deformity due to ligamentous laxity is present (initially) only with weight-bearing.
- Orthopedic treatment can be non-operative or operative. The variety of non-operative therapies is great and includes rest, range of motion and stretching exercises, pharmacologic agents for pain relief and muscle relaxation, and serial casting or bracing to stretch tightened soft tissues and position the deformed part straight to allow normal cartilage and bone growth to occur. The ranges of operative therapy are also great. Some operations cure deformity permanently with one intervention. Other procedures correct one aspect of the deformity and then rely on spontaneous growth or repositioning for full correction of adjacent structures. Some deformities need a series of operations over a short or longer period of time in the growing years since (i) the underlying cause may persist; (ii) the damage done to the growing structure may itself lead to recurrence; or (iii) soft tissue and bone procedures may be needed for correction but are best done at different times in the growth period.
- Once a deformity in childhood has been corrected it may follow one of three pathways during the remaining years of growth. (i) The region involved may remain anatomically normal and no further management is ever needed. (ii) The deformity may recur due either to the fact that it had not been fully corrected or the underlying disorder that caused it persists. (iii) The deformity may overcorrect leading to deformation in the opposite direction due to such factors as: a new pattern of muscle imbalance, asymmetric growth plate function, or continuing growth correction resulting in overgrowth.

2.5 Terminology Describing Body Planes and Regions

Anatomic Position	description of planes and regions is based on the body as it rests in the anatomic position. This refers to the body in the standing position facing forward with the feet plantigrade (flat on the ground), the knees extended (straight), the upper extremities at the side of the body with the elbows extended (straight) and the palms pointing forward (forearms supinated).
Proximal	that part of a bone or region closer to the central body.
Distal	that part of a bone or region further away from the central body.
Median	along the midline of the body.
Medial	that part closer to the midline of the body.
Lateral	that part further away from the midline of the body.
Coronal or Frontal plane	along an axis parallel to the middle of the body in the right to left longitudinal vertical direction. [In the same plane as the coronal suture of the skull between the frontal and parietal bones.]
Sagittal plane	along an axis parallel to the midline of the body in the antero-posterior longitudinal vertical direction. [In the same plane as the sagittal suture of the skull between the two parietal bones.]
Longitudinal plane	along a vertical plane perpendicular to the ground with the body in the standing position.
Transverse plane	along a horizontal plane across the width of a body part from right to left and at right angles to the longitudinal axis.
Superior	towards the top of the body.
Inferior	towards the bottom of the body.
Cranial	towards the head.
Caudal	towards the coccyx.
Dorsal	towards or situated on the back surface, or the corresponding part of an extremity in the anatomic position.
Posterior	towards the back.

Ventral	towards or situated on the anterior part of the abdomen, or the corresponding part of an extremity in the anatomic position.
Anterior	towards the front.
Cubitus	referring to the elbow; referring to the forearm distal to the humerus.
Coxa	referring to the hip.
Genu	referring to the knee.
Hallux	referring to the big toe.

2.6 Terminology Describing Extremity Deformities

2.6.1 Angular Deformity

An angular deformity exists when there is an angle beyond the normal between a distal and a proximal part along the longitudinal limb axis. The point of reference can be within a long bone or at a joint. An angular deformity tends to place the distal articular surface in an oblique plane rather than its normal transverse plane. The angle can be greater or lesser than the normal range.

Valgus	tending to a more lateral position distal to any point of reference [positioned outward away from the midline of the body].
Varus	tending to a more medial position distal to any point of reference [positioned inward towards the midline of the body].
Flexion	tending to a maximal extended position less than the normal 180° (or fully straight) distal to any point of reference.
Extension	tending to a maximal extended position beyond the normal 180° distal to any point of reference [hyper-extended].

When angular deformity is within a single long bone the direction where the apex or convexity of the deformity points can be used as a reference point to describe the angulation. The terms anterior angulation, posterior angulation, medial angulation or lateral angulation are used to describe the deformity as are intermediate positional deformities such as anteromedial, posteromedial, etc. In the upper extremity anterior angulation is often referred to as volar angulation and posterior angulation as dorsal angulation. A unique variant of a bowing deformity within a single bone may leave both articular surfaces in the transverse plane when the bending occurs gradually over a period of time in pathologically softened bone (such as osteogenesis imperfecta or rickets).

2.6.2 Rotational Deformity

Rotational deformity refers to a rotation, torsion or twisting of a part around its own longitudinal axis to a greater than normal amount

Internal Rotation	Excessive internal rotation or torsion beyond the normal with the distal part oriented toward the midline.
External Rotation	Excessive external rotation or torsion beyond the normal with the distal part oriented away from the midline.

2.6.3 Translational Deformity

Translational deformity refers to displacement in a transverse plane of a distal part in relation to a proximal part without angular or rotational changes. The translation of the distal part relative to the proximal can be medial, lateral, anterior or posterior (or intermediate positions).

2.6.4 Length Deformity

2.6.4.1 Limb Length Discrepancy

A length deformity exists when a bone on one side is longer or shorter than the same bone on the opposite side. That side which is normal or closer to normal is the reference point with the contralateral side having either a shortening deformity or a lengthening deformity. The deformity can involve either the upper or lower extremity. The term "leg length discrepancy" (LLD) is commonly used to refer to lower extremity discrepancies, even though in an anatomic sense leg refers to the region between the knee and ankle. The anatomically correct terms are either lower extremity length discrepancy (LELD) or lower limb length discrepancy (LLLD).

2.6.4.2 Short Stature

A short stature syndrome is present when the patient's total height is less than 2 standard deviations below the mean for age. A clinical gauge of normal proportionate development places the outstretched fingers at mid-thigh in the anatomic, standing or supine, position. Patients with short stature have either **proportionate short stature** where the outstretched fingers are at mid-thigh level in the anatomic standing or supine position or **disproportionate short stature** where the outstretched fingers reach either to the hip region (greater trochanter), **short limb variant**, or to the knee region, **short trunk variant.** Disproportionate short stature is usually due to an underlying skeletal dysplasia. If a person with short stature has proportionate development the growth problem is likely to have a chronic medical cause such as a pulmonary, cardiac, renal, endocrine or hepatic disorder rather than being due to a primary skeletal dysplasia.

2.6.4.3 Shortening Within Regions of an Extremity

(a) **Rhizomelic**. Rhizomelic shortening is concentrated in the proximal parts of an extremity (e.g. upper arms and thighs).
(b) **Mesomelic**. Mesomelic shortening is concentrated in the middle segments of a limb (e.g. shortening of forearms and legs).
(c) **Acromelic**. Acromelic shortening is concentrated in the distal portions of the limbs (e.g. short hands and feet with stubby digits).

2.6.5 Gigantism

An abnormal total body overgrowth syndrome is present when the patient's total height is greater than 2 standard deviations above the mean for age.

2.6.6 Multiplanar Deformity

Many deformities involve more than one plane and are referred to as multiplanar. Examples include a genu varum (bowleg) which is often associated with internal tibial torsion and a posteromedial angular deformity of the tibia.

2.6.7 Primary Site of Limb Deformity

Deformity can be centered (i) within a bone such that the angulation, rotation or translation places the bone, the adjacent joint and the rest of the limb distal to that point of deformation in an abnormal position or (ii) at the level of a joint placing all structures distal to the joint in an abnormal position.

2.6.8 Joint Deformities

A distinction needs to be made in describing a joint deformity as to whether it is due to an acute abnormality or a chronic disturbance. If chronic, the problem can be due to (i) an intra-articular, capsular, or pericapsular process, (ii) bone deformity of the adjacent epiphyseal-metaphyseal regions (such as a distal femoral fracture healed with 45° anterior angulation), or (iii) musculo-skeletal tendinous tightness in units crossing the joint (such as hamstring tightness in cerebral palsy as demonstrated with the hip flexed as the knee is extended). In acute abnormalities the decreased ranges of motion are due primarily to pain with motion and/or intra-articular limitations such as interposed torn menisci due to trauma or fluid accumulation with septic arthritis or hemophilic hemarthrosis. In acute disorders the limited range of motion can be described in general terms with position and any range of motion measured accurately by goniometer. In acute abnormalities (with intra-articular fluid accumulation and synovial hypertrophy) the involved joint is usually positioned by the patient for maximum comfort; the hip in a flexed, abducted and externally rotated position, the knee joint in flexion, the ankle in equinus (plantar flexion), the elbow in flexion, the shoulder in adduction and slight flexion, the finger joints in flexion, and the wrist in neutral to slight palmar flexion.

In chronic disorders the decreased ranges of motion are not associated with acute pain. Examples include chronic synovitis with longstanding rheumatoid arthritis or hemophilic arthropathy. The more specific terminology used to describe chronic or non-acute joint deformities is defined below. The terms ankylosis and contracture are used in reference to fixed chronic deformities, not limited motion due to acute pain.

2.6.8.1 No Joint Motion

Ankylosis. If there is no motion at all at a joint, that joint is referred to as being ankylosed or fused. The ankylosis can be bony (with firm bone union between the two adjacent bones), fibrous (with complete obliteration of a joint cavity by fibrous tissue interposition), or fibro-osseous (where non-continuous bone and fibrous tissue interposition prevent any motion). The position of fusion is usually added to the description, for example "fixed at 20° flexion and 40° external rotation".

2.6.8.2 Decreased Range of Motion

Contracture. A contracture refers to a decreased range of motion at a joint as determined by passive manipulation on clinical examination. Contractures are painless. They are generally due to soft tissue tightness which can be extrinsic to the joint, as with heel cord tightness limiting ankle dorsiflexion in cerebral palsy or intrinsic within the joint, as with capsular and synovial thickening and hypertrophy following recurrent hemarthroses of hemophilia. Capsular tightening and fibrosis can occur over time with growth in the presence of the persisting contractures. With persisting equinus due to heel cord contracture the ankle joint capsule tightens posteriorly and, conversely, with persisting knee flexion due to intrinsic hemophilic arthropathy the hamstring muscles posteriorly tighten in relation to the relatively overstretched quadriceps mechanism anteriorly.

A joint would not be considered as having a contracture if lack of full motion is due to weakness, for example where active motion is limited in a particular direction due to a neuromuscular disorder but an examiner can move the joint through a full range of motion by passive manipulation. An example of this is a knee lacking full active extension due to

quadriceps muscle weakness but passively able to be fully extended by an examiner. The extent of angle of decreased active extension is referred to as being due to a quadriceps lag.

General terminology for common contractures follows:

Flexion contracture	The joint lacks full extension but otherwise flexes fully
Extension contracture	The joint lacks full flexion but otherwise extends fully
Abduction contracture	A joint can be placed in a fully abducted position but cannot be moved toward or beyond the neutral plane to a position of full adduction
Adduction contracture	A joint can be placed in a fully adducted position but cannot be moved toward or beyond the neutral plane to a position of full abduction
Internal rotation contracture	A joint can undergo full internal rotation but cannot be rotated to a position of full external rotation
External rotation contracture	A joint can undergo full external rotation but cannot be rotated to a position of full internal rotation
Pronation contracture	The wrist and forearm can be placed in full pronation but cannot be moved toward or beyond the neutral plane to a position of full supination
Supination contracture	The wrist and forearm can be placed in full supination but cannot be moved toward or beyond the neutral plane to a position of full pronation
Mid-range contracture	There is no widely accepted term for a contracture where the normal full range of motion is not obtainable at both ends of the spectrum. We describe this as a mid-range contracture and list the limited range of motion [e.g. for a knee from 20° (lacking full extension) to 110° (lacking full flexion)]

Limitations in terminology exist when describing decreased ranges of motion in certain joints. Current descriptive terminology is clear for those joints that are positioned anatomically in full extension at 180° such as the elbow, knee and finger joints and subsequently move into flexion or that have well defined ranges of motion on either side of the neutral plane such as the hip and, to a lesser extent, the shoulder. Difficulties in description occur at the wrist and ankle where there are considerable ranges of motion on either side of the neutral anatomic plane which is 180° for the relation of the long axis of the forearm to the long axis of the hand and 90° for the long axis of the leg to that of the foot. Current terminology uses dorsiflexion and palmarflexion at the wrist and dorsiflexion and plantarflexion at the ankle without use of the term extension which was used extensively in the early orthopaedic literature. At these joints it is advisable to describe the range of motion in degrees as well as referring to a particular descriptive contracture. If an individual with hemiparesis can dorsiflex one ankle 10° above neutral and the other 25° above neutral, he or she technically has a 15° contracture but since the restricted motion is still beyond the neutral plane the limitation is generally described as "lacking 15° of full dorsiflexion". Contractures at some joints have their own unique descriptive terms. Heel cord tightness leading to ankle dorsiflexion only to −15° of neutral is referred to as an equinus contracture. If the ankle dorsiflexors are tight in relation to the plantarflexor tendo Achilles, leaving the foot dorsiflexed +15° to +30° above neutral with plantarward motion limited to 15° above neutral, the person is said to have a calcaneus deformity (although the term calcaneus contracture is rarely used).

2.6.8.3 Malalignment of Articular Surfaces

Dislocation	A joint is dislocated when there is no contact between the articular surface of the two bones comprising the articulation at all times.
Subluxation	A joint is subluxed when there is partial contact between the articular surfaces of the two bones comprising the articulation at all times.
Dislocatable	When the articular surfaces of the two bones comprising the articulation lack complete contact in certain positions but resume a normal relationship in other positions the joint is referred to as being dislocatable.
Subluxatable	When the articular surfaces of the two bones comprising the articulation have partial contact in certain positions but resume a normal relationship in other positions the joint is referred to as being subluxatable.
Incongruent joint	A step-off, gap, or segmental collapse of an articular surface is present disturbing the normal arc of motion.
Obliquity	A slanting of the characteristic angle, usually greater but sometimes lesser than normal, that each joint has in relation to the longitudinal axis of the limb.
Collinear	points lying in the same straight line.

2.6.8.4 Ligamentous Laxity

Ligamentous laxity predisposes to excess ranges of motion for joints, generally appearing as (i) hyperextension (beyond the normal anatomic 180° range), (ii) hyperflexion (as with ankle dorsiflexion greater than 30°), (iii) increased varus-valgus tilt (as at knee and ankle), (iv) a predisposition to subluxation (as at hip, shoulder and patello-femoral joints), and (v) increased displacement at multiple smaller joints as with flat feet.

2.6.9 Lower Extremity Mechanical Axis Deformities

The normal anatomy of the pelvis, femur, tibia and fibula, and talus and calcaneus individually and in their relationship to each other establishes the frontal plane mechanical axis of the lower extremity. The normal alignment of the hip, knee and ankle joint centers is collinear. Deformities lead to mechanical axis deviation (MAD) which primarily affects the knee but also the hip, ankle and subtalar joints. The normal longitudinal weight bearing axis from the center of the femoral head (hip joint) to the mid part of the ankle joint passes just to the medial side of the center of the knee joint near the medial tibial spine. This alignment serves to distribute weight symmetrically across each joint which enhances normal joint and articular cartilage maintenance. Deformities of the femur or tibia or both create a mechanical axis deviation with the line of weight bearing force passing either medial or lateral to the center of the knee. With the weight bearing force passing medial to the center of the knee along or even medial to the medial condyle of the femur, genu varum is present, the lateral collateral ligament is stressed, and deterioration of the medial meniscus and medial femoro-tibial articular surfaces develop with time. When the weight bearing axis is lateral to the mid-knee, close to the head of the fibula, a state of genu valgum exists, the medial collateral ligament is under tension, and the lateral meniscus and lateral femoro-tibial articular surfaces deteriorate with time.

Paley points out that each joint has a normal anatomic inclination to the mechanical and anatomic (structural) axis of a limb segment [21, 22]. The femur shows a slight deviation of these axes since the mechanical axis is from the middle of the femoral head to the center of the knee while the anatomic longitudinal position of the shaft is 5°–7° off the midline, angling towards the mid-knee. In the tibia both axes are the same. The ankle joints are parallel to the floor. The knee joint line is 3° off the horizontal or off a perpendicular to the longitudinal mechanical axis with the distal femur in slight valgus and the tibial diaphysis in slight varus to the knee joint line.

Coronal plane anatomic axis. A line from the center of the femoral head to the tip of the greater trochanter subtends an angle of 84° to the long axis of the femoral shaft [21, 23]. A line along the articular surface of the femoral condyles subtends an angle of 81° to the femoral shaft (into valgus) while a line along the tibial plateau joint intersects the tibial shaft at an angle of 87° (into varus). The tibial shaft is perpendicular (90°) to the distal tibial articular surface. *Sagittal plane anatomic axis.* The normal sagittal axis from the center of the femoral head to the center of the ankle joint (tibiotalar) with the knee fully extended passes through the knee joint approximately at the junction of the anterior and middle thirds of the joint surface. On lateral radiographs the longitudinal shaft axis line intersects the distal femoral joint line at an angle of 83°. The articular surface of proximal and distal tibia intersects the sagittal axis at approximately 80° [21, 23].

Another way of expressing the anatomic lower extremity axis is to indicate that the tibial shaft axis is in 6° of valgus relative to the femoral shaft axis.

The lower extremity mechanical and anatomic axes to assess alignment should be measured from standing full length antero-posterior femoral and tibial radiographs which include clear views of the hip and ankle joints. Other ways of defining measurement of the mechanical axis include a line drawn from the center of the femoral head to the center of the talus or the center of the tibial plafond. Most define it as passing through the midpoint between the tibial spines although some refine the definition placing it nearer to the medial tibial spine. A series of measurements have come to define deformity analysis and the extent of mechanical axis deviation [21, 22, 24–26]. Gorman et al. have recently considered the middle 2 quadrants as zone 1, the more medial varus zones as −2 and −3 and the more lateral valgus zones as +2 and +3 [24]. The zone of the mechanical axis at the level of the knee joint is the designated standard. The mechanical axis deviation is measured from the center of the tibial spines. The anatomic lateral distal femoral angle and the medial proximal tibial angle are measured as well [22, 24]. While radiographic imaging allows for accurate measurement of the various axes, lower limb alignment was understood by surgeons before the radiographic era. Macewen, one of the developers of the osteotomy technique, commented in 1880 that “in the normal limb, a line drawn from the head of the femur to the middle of the ankle joint passes through the center of the knee-joint” [27]. Figure 2.3a–d illustrate mechanical axis measurements.

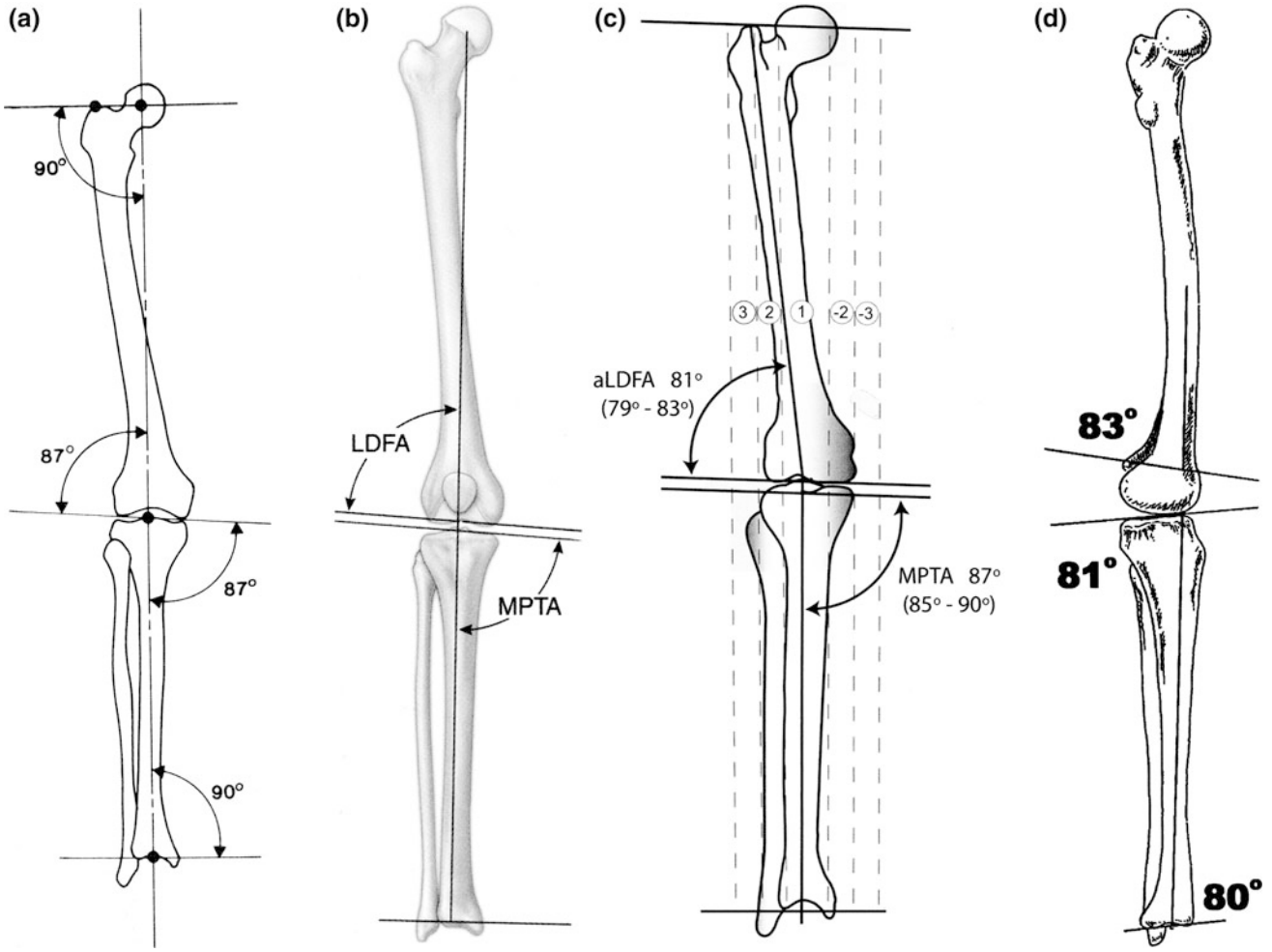


Fig. 2.3 The normal ranges of the frontal and sagittal alignment of the lower extremity (the mechanical axes) have been outlined. Measurements are based on standing full-length antero-posterior radiographs of both femurs and tibias which must include clear views of hips, knees, and ankles. **a** The frontal plane mechanical axis of the lower extremity consists of 2 components, collinear centers and an almost perpendicular relationship of the hip, knee, and ankle joint orientation lines to the mechanical axis [41]. The slight obliquity of the horizontal knee axis approximately 3° off the perpendicular, with the distal femur in slight valgus laterally and the tibial diaphysis in slight varus medially, leads to a relationship of the horizontal axis of 87° to the femur laterally and 87° to the tibia medially. Hip (tip greater trochanter and center femoral head) and ankle axes are perpendicular to the longitudinal head-mid-knee-tibia (ankle) axis. (Reprinted with permission from Paley and Tetsworth, Mechanical axis deviation of the lower limbs. Clin Orthop Rel Res. 1992;280:48–64. Copyright 1992 Wolters Kluwer Health). **b** The knee angles are illustrated in relation to the mechanical axis. *LDFA* lateral distal femoral angle; *MPTA* medial proximal tibial angle. [Saran and Rathgen, J Am Acad Orthop Surg 2010;18:528–536.] (Reprinted with permission from Saran and Rathjen, Guided growth for the correction of pediatric lower limb angular deformity. J Am Acad Orthop Surg 2010;18:528–536. Copyright 2010 by the American Academy of Orthopaedic Surgeons). **c** The long axis of the femur (tip of greater trochanter to knee center) lies at 81° and is referred to as the aLDFA where a is anatomic. The MPTA is the same in both measurements. Gorman et al. [24] have outlined a method of defining zones of the mechanical axis to quantitate states of deformation. (Reprinted with permission from Gorman et al. Mechanical axis following staple epiphysiodesis for limb-length inequality. J Bone Joint Surg Am 2009;91A:2430–2439). **d** Normal sagittal alignment is illustrated. [Price and Izuka, Orthopedics 2005; 28:20–25.] (Reprinted with permission from Price and Izuka, Osteotomy planning using the anatomic method: A simple method for lower extremity deformity analysis. Orthopedics 2005;28:20–25. Copyright 2005 SLACK Incorporated)

2.7 Deformities of the Spine

The spine is straight in the anteroposterior plane at all stages. In the anatomic standing or erect sitting position the head is centered normally over the middle of each vertebra including the sacrum. There are normally no angular, rotational or translational positionings between the vertebrae. In a lateral view of the spine after the first years of life the normal alignment involves a cervical lordosis, thoracic kyphosis and lumbo-sacral lordosis.

2.8 Spontaneous Correction of Deformities by Growth

Certain deformities in the growing child can correct spontaneously with growth. These are of two types.

- Physiologic Correction. Some limb positionings in the growing child are referred to as deformities but are in reality normal developmental patterns that correct, or more accurately change on their own, to the normal adolescent and adult orientation with growth. These changes occur in the very young and most commonly involve bow legs (physiologic genu varum) which become straight and then align into a few degrees of genu valgum and intoeing due to internal tibial torsion or proximal femoral anteversion which becomes positioned into neutral or slight out-toeing.
- Correction of pathologic deformity. Some pathologic deformities due to trauma, disease, or surgery can correct spontaneously with growth even though they are initially extensive. Common examples of this involve remodeling after certain long bone fractures, correction of bowing deformities in rickets once medical treatment is given, and remodeling after proximal femoral varus osteotomies to a physiologic head-neck/shaft angle.

2.9 Correction of Deformities by Non-operative Treatment

There are many ways to correct deformities of the growing skeleton without resorting to surgery. A brief overview is provided.

2.9.1 Stretching Exercises to Correct Deformities

Stretching exercises can play a role in correcting musculoskeletal deformities. They are a time-honored intervention used for hundreds of years but there are very few controlled studies to validate these efforts. They appear to be effective and very few orthopedic surgeons would be comfortable totally eliminating this approach to childhood deformity. For maximal effectiveness careful adherence to specific technique and continuing management and assessment after correction is achieved are needed. Many of these treatments are demonstrated and performed by physical therapists but active involvement by family and caretakers in the home environment and, at a certain age, by the patient are essential. They are particularly valuable for some newborn deformities which are essentially positional in nature, for neuromuscular disorders, and after long periods of immobilization after fractures or surgical corrections. Stretching can be done by passive, passive- assisted, active-assisted, or active mechanisms.

Passive manipulation: This refers to the situation where the corrective force is gently applied to the deformed part by another person. Examples include repetitive gentle stretching of a foot with metatarsus adductus into abduction to hasten correction.

Passive-assisted exercises: This refers to the situation where the corrective force is gently applied to the deformed part by another person but the affected child or adolescent cooperates by trying to move the part on their own at the same time.

Active-assisted exercises: This refers to the situation where the affected child or adolescent moves the deformed part towards the corrected position with gentle manual assistance from another.

Active exercises This refers to the situation where the affected individual moves the deformed part in repetitive fashion on their own to release tightness and strengthen muscles.

2.9.2 Casting/Splinting/Bracing

Some deformities can be permanently corrected by casting, splinting or bracing. The mechanism of correction involves stretching of the tightened soft tissues at the concavity of the deformity with associated relaxation and shortening of lengthened structures at the convexity. With repetitive or continuous use over several weeks to months the straightened position also channels normal cartilage and bone growth. This treatment is most effective when the adjacent bones are not deformed or only minimally deformed and it cannot correct moderate or severe bone deformation. The corrective cast, splint or brace can be used full-time or part-time. Part-time use at night can be effective if tolerated by the child.

2.9.2.1 Bi-valved Night Casts

The corrective cast is applied with the patient awake and the limb held in a position of maximal comfortable correction. It is then removed (bi-valved), scraped to remove any prominent internal ridges of fiberglass or plaster, and lined with webril, stockinette and adhesive tape or moleskin. It is re-made at appropriate intervals to incorporate progressive improvement in position towards normal. When a cast intended to become a bi-valved cast is applied slightly more webril padding than would be used normally is placed. The maximal comfortable position towards full correction is applied as the fiberglass cast hardens. The bi-valved cast was made for several decades with plaster of Paris but fiberglass

is now used in most centers. Once the cast hardens it is removed (bi-valved) in such a way that each half (anterior and posterior) can be easily re-applied. The two halves are held together with 1 inch strips of linen-tape fastened with self-locking buckles or with a series of adhesive Velcro straps. For part-time use, which is the most common application, a bi-valved cast is preferred in some centers. It provides continuous but static stretch.

2.9.2.2 Dynamic Splints

Manufactured splints with continuous and adjustable stretch applied to the involved joints at hinged articulations are often used, especially for stretching spastic muscles. The tension and range of motion at each joint can be changed as further correction is achieved. Bi-valved casts and braces are often used in the weeks and months after surgery to help maintain corrections achieved.

2.9.3 Correction by Inducing Muscle Relaxation

Muscle relaxation in spasticity disorders can be treated with oral baclofen, an internal baclofen pump delivering the medication by catheter into the spinal canal or intramuscular Botox injections each of which can be helpful in obtaining correction of deformity. Botox effectiveness wears off in 3–4 months and usually needs to be repeated. When relaxation of spasticity is induced, active exercises to strengthen anti-deformity muscles and splinting/night casting/bracing to stretch previously tight structures must be done to take advantage of the muscle relaxation.

2.9.4 Traction

Traction is used much less frequently now than several decades ago. A common use is to induce muscle relaxation in traumatic disorders by continuous gentle pressure. It can be used in cervical subluxation or in joint region fracture displacements. It is more often used now in conjunction with skeletal fixation, again usually in traumatic treatments for reduction of displacement. For deformity correction it still plays a role with use of a skeletal halo for gradual correction of severe scoliosis.

2.9.5 Immobilization

For deformity created or worsened by discomfort, simple immobilization remains a primary principle of treatment. Rest allows tissues to heal and inflammation including synovitis to resolve. Rest can span the spectrum from non-ambulation to crutches or canes, wheelchair use or any of the various immobilization casts or splints.

2.9.6 Closed Reduction with Immobilization

An important non-operative treatment involves closed reduction of dislocated or dislocatable joints (primarily the hip) followed by full time immobilization by harness, splint, or cast until capsular tightening allows for maintenance of full correction.

2.10 Brief Overview of Correction of Deformities by Operative Treatment

2.10.1 Discoveries Greatly Enhancing Development of Surgical Procedures for Correction of Deformities

In the nineteenth century three major scientific breakthroughs greatly enhanced the development of surgical procedures for childhood musculoskeletal deformities. These were: the discovery of anesthesia (1846); the development of subcutaneous surgery for tenotomy (1830s) or osteotomy (1870s) to minimize the risks of infection; and the principle of antiseptic surgery (1867) to decrease the likelihood of infection for longer and more complicated surgeries.

2.10.2 Subcutaneous Surgery

Subcutaneous surgery referred to the use of limited puncture incisions 1/8 to 1/4 of an inch wide at a slight distance from the structure to be cut to effectively eliminate the admission of air which was recognized as predisposing to inflammation and suppuration (infection) [12, 27–29]. Description of the technique stressed an indirect track from skin to the structure to be divided in the procedure, minimal damage to adjacent tissues and immediate closure of the wound with pressure and bandaging applied to minimize bleeding and prevent air entry. The principle was most effective for subcutaneous tenotomy (initially used for clubfeet and other foot deformities) by Stromeyer in Germany, Little in England, and Guerin in France in the 1830s. It also allowed for the development of subcutaneous osteotomy although it was less effective with bone surgery in terms of limiting infection since osteotomy generally required longer incisions, more time, more direct exposure of bone to the external atmosphere, and led to more bleeding. The principle of subcutaneous surgery (or percutaneous in current terminology) has been attributed to Hunter (1784) who distinguished between the effects of open wound and subcutaneous approaches based on their different exposures to air. He maintained that subcutaneous procedures tended to heal uneventfully while open procedures undergo inflammation and suppuration. He

did not use the approach in patients but based his theory on his animal tenotomy experiments (see Adams, Ref. [28]).

2.10.3 Antiseptic Surgery

While tendon release surgery (tenotomy) was established as safe and effective from the 1830s it was antiseptic surgery using the principles established by Lister and others (Semmelweis, Pasteur, Koch) that allowed bone surgery to be conducted much more safely. Lister's initial papers on the effectiveness of antisepsis in bone surgery using carbolic acid were published in 5 articles in 1867 in Lancet [30] and in 4 articles in 1868 in the British Medical Journal (the antiseptic system of treatment in surgery) [31]. Lister was a surgeon and worked extensively in the orthopedic area [32]. The earliest successes with the antiseptic approach were in preventing sepsis in compound fractures. The principles of antisepsis and asepsis were accepted relatively slowly in the surgical world across several countries. The technique gradually evolved to include hand scrubbing with soap and water, immersion of instruments and wound site towels in carbolic acid pre-surgery, and operative site skin scrubbing with soap, water and carbolic acid pre-incision. The antiseptic technique of Lister gradually came to include a more complete aseptic technique. Wangensteen et al. [33] wrote a detailed review of the development of antiseptic and aseptic practices beginning from ancient times. Ignaz Semmelweis of Vienna introduced the features of chemical preventative antisepsis by stressing the importance of hypochlorite as a material for washing hands for those involved with obstetrical deliveries and their assistants and chemical sterilization of all materials likely to come in contact with the parturient vaginal canal with a striking effect upon the mortality rate of puerperal fever in childbirth several years before Lister's work. The works of Louis Pasteur on the existence of microorganisms and their medical and surgical implications (1878) and of Robert Koch identifying specific bacteria and implicating them in the causation of infection in 1878 were vital in advancing acceptance of the need for measures to limit and ideally prevent wound and surgical infections. Both antisepsis and asepsis play major roles today in dealing with surgical infection. Antisepsis (against sepsis) refers to prevention of sepsis by inhibiting or destroying the causative organism while asepsis (without sepsis) is a broader concept implying prevention of wound contact with microorganisms.

2.11 Surgery on Tendons

2.11.1 Tenotomy

Tenotomy refers to cutting of a tendon for the purpose of correcting a fixed deformity at a joint. Tenotomy of the Achilles tendon was the procedure that effectively launched operative orthopedics [10–13, 29]. Initial effective use of Achilles tenotomy for equinus deformity is attributed to Thilenius of Frankfort (Germany) and his surgeon colleague Lorenz in 1784, correcting a case of talipes varus in a 17 year old with open Achilles tenotomy which healed well. Tenotomy was described and performed by Delpech of Montpellier, France in 1816 using a relatively long open incision which was followed by severe suppuration although it was described as eventually healing. The high incidence of infection caused the procedure to be abandoned for several years. It was first done effectively in several patients by Stromeyer in Hanover, Germany in 1831 using a subcutaneous approach for correction of equinus due to a tight tendo Achilles. Little began performing Achilles tenotomy for club feet in London in 1837 and the procedure was soon adopted widely. Guerin of France described the subcutaneous method of tendon release at many sites as a prime principle of surgery [28, 29]. With tenotomy, the tendon is not repaired surgically after its release but the cut ends are eventually reunited by collagenous repair in the gap guided by the tendon sheaths.

2.11.2 Tendon Lengthening

The tendon is cut in such a way that it is lengthened, leaving the cut tendon segments in contact with each other to enhance repair. The tendon is stabilized at its desired new length either by side-to-side suturing (as with a Z-lengthening) or by maintaining muscle tissue continuity while the tendon segments separate to their desired position (Vulpius procedure). Repair occurs in both instances with the joint held in its neutral or corrected position with cast immobilization.

2.11.3 Tendon Shortening

The tendon is cut, shortened by overlapping the cut ends and repaired by suturing the two segments. This procedure is infrequently done (compared to tenotomy alone or tenotomy with lengthening) owing to its unpredictable effect in improving muscle strength and active function.

2.11.4 Tendon Transfer

The tendon is released from its normal point of insertion and reattached at a different position to change the direction of muscle pull. If the muscle function is maintained, the procedure changes a deforming musculotendinous action into a corrective action. If muscle function is lost there are still partial benefits from tendon transfer as it removes a deforming force and provides a passive stabilizing tenodesis effect in its new position. The tendon transfer may be

complete or partial/split where one half remains at the original site to prevent overcorrection and the other half is moved to a position correcting the deformity.

2.11.5 Lysis of Tendon Adhesions

If a tendon is bound down in scar tissue it can be surgically freed (tenolysis) with subsequent range of motion improved by application of the continuous passive motion principle during the healing phase or early remobilization post-operatively along with longer term passive and active range of motion exercises.

2.12 Surgery on Joints

2.12.1 Capsulotomy. Arthrotomy

When a joint is surgically opened, either for diagnostic inspection or reparative intervention, the joint capsule is cut, a procedure referred to as a **capsulotomy**—cutting the capsule—or an **arthrotomy**—surgically cutting into a joint.

2.12.2 Open Reduction. Capsulorrhaphy

When a joint is partially (subluxation) or fully (dislocation) displaced there is associated capsular enlargement and laxity. Surgical open reduction with capsular repair can restore normal articular relationships and correct the deformity. Capsular repair, to allow repositioning of the bony components, by release of tight or narrowed segments and suture repair by overlap of stretched/lax regions, is referred to as capsulorrhaphy.

2.12.3 Capsular Release

Where the capsule is contracted, limiting motion or preventing full reduction, a capsular release is done and either left open to repair itself or sutured in the correct lengthened position.

2.12.4 Synovectomy

A synovectomy refers to an extensive and if possible complete surgical excision of the thickened inflamed synovial lining of a joint. It can be done after open capsulotomy or by arthroscopy. It is done when recurrent synovial inflammation causes increasing articular cartilage, ligamentous, and meniscal damage by intra-articular fluid accumulation, release of lytic enzymes, hemarthrosis, and pannus overgrowth which cannot be controlled by medical means. It is currently done most commonly for rheumatoid arthritis and hemophilia and on occasion for rare disorders such as pigmented villonodular synovitis.

2.12.5 Intra-articular Repairs

Large numbers of intra-articular procedures are done to repair damaged structures. Lesions such as osteochondritis dissecans, congenital discoid meniscus, torn hip joint labrum, and femoral-acetabular impingement can be treated by intra-articular approaches.

2.12.6 Joint Arthrodesis

Deliberate fusion of a joint may be done to correct deformity, eliminate pain, and create stability. It is infrequently done in large joints today since arthoplasty is preferred to maintain motion in cases with severe joint damage. Arthrodesis is resorted to primarily in foot surgery with neurogenic disorders. Triple or mid-foot arthrodeses are done to correct deformity and provide stability. Interphalangeal joint fusions are common to straighten toe deformities usually in association with tendon transfers.

2.12.7 Joint Debridement

Debridement refers to a surgical approach to abnormal joints to remove debris involving (i) lavage (a therapeutic washout), (ii) removal of loose osteocartilaginous bodies and intra-articular osteophytes, (iii) shaving fibrillated cartilage and (iv) performing partial synovectomy to remove excess synovium. For many years, especially at the knee, this was the primary surgical treatment for abnormal joints although it was widely recognized to provide only symptomatic relatively short term relief. At present it is done as the preliminary approach in more specific or definitive interventions.

2.12.8 Arthroscopy. Arthroscopic Surgery

Much current diagnostic work on intra-articular disorders is done by arthroscopy rather than by open arthrotomy. Knee, hip, ankle, shoulder, elbow and wrist joints can be assessed with this technique. Many operative treatments can also be done via the arthroscope.

2.12.9 Arthroplasty

Any operation on a joint designed to repair a problem can be considered as an arthroplasty. Increasingly however the term is reserved for major interventions removing damaged articular cartilage and subchondral bone and replacing it with autologous cartilage cells or osteochondral plugs, large

osteochondral allografts or, increasingly, total or hemi-joint metal/plastic implants.

2.13 Surgery on Ligaments

Surgical repair of ligaments as a primary intervention is generally associated with traumatic ruptures or insertional tears and often needs to be supplemented, as with anterior cruciate ligament tears of the knee, with additional autograft or allograft tendinous, ligamentous, or biologic enhancement procedures. Surgery on ligaments is not indicated as a primary corrective mechanism in deformity surgery but ligament release, shortening, or repositioning may be needed secondarily as associated parts of major repair sequences.

2.14 Surgery on Bones. Osteotomy

2.14.1 Definition

Osteotomy refers to cutting of a bone for the purpose of repositioning it to correct a deformity

2.14.2 Historical Background

There are several reports of osteotomy in the first half of the 19th century but the lack of anesthesia and the high incidence of infection at this time greatly limited its performance. The relatively wide incisions used for the surgery were referred to as the "open wound" technique. Around the 1850s osteotomy was performed more often owing to the discovery of anesthesia (1846) and application of the principle of "subcutaneous surgery" which had been effective for limiting infection with tenotomy. The principle of subcutaneous surgery referred to using a very small incision to effectively exclude entrance of air, and its contents, which was recognized as being associated with infection. The first major practitioner of subcutaneous osteotomy was Langenbeck of Germany who in the period 1852–1854 performed the procedure for ankylosis of the hip and knee joints and rachitic deformity of the legs [28]. Through a small incision he drilled a 1/4 in. defect in the bone, introduced a pointed saw 1/8 in. wide at the tip, cut the bone almost completely, and then broke it manually in the process of manipulating it straight. The first subcutaneous osteotomy in Britain is attributed to Mr. L. Stromeyer Little in 1868 [28]. He was the son of William Little, who first performed subcutaneous Achilles tenotomy in Britain to correct equinus deformity. William Adams summarized subcutaneous surgery, including subcutaneous osteotomy, in an 1879 article from a symposium in the British Medical Journal [28].

Osteotomy was developed into a meaningful procedure in the 1870s soon after the introduction of antisepsis by Joseph Lister in 1867. The first detailed report of use of antisepsis with osteotomy was by Volkmann of Halle, Germany beginning in 1872 and reported in 1874 [34]. He published 13 successful cases correcting ankylosis of the hip and knee joint. Macewen of Glasgow rapidly adopted the procedure, performing the first antiseptic osteotomy in Britain in 1875 [27, 35] with the second performed by Lister himself. A detailed 2 part overview of lower limb antiseptic osteotomy by Macewen the main practitioner of the procedure was published in 1878 and 1879 [36]. His preferred time for the procedure was between 8 and 20 years of age. Over the next several years Macewen did over one thousand procedures. In his classic book "Osteotomy", which defined the procedure in a way still valuable today, he indicated that strict adherence to antiseptic principles rendered the procedure safe [27]. By 1884, 9 years after the 1st procedure, Macewen was reporting 1800 operations in 704 patients with no septicemia or fatal wound complications [37].

2.14.3 Uni-planar and Multi-planar Deformities

Assessment of any deformity needs to determine whether it is uni-planar or multi-planar and, if the latter, which dimensions are altered. Deformities of the limbs especially when being considered for correction by osteotomy need to be assessed in terms of varus-valgus, flexion-extension, rotation (internal-external), translation, and length (short-long).

2.14.4 Stabilization Post-Osteotomy

The methods used for stabilizing the fragments to maintain correction and enhance healing post-surgery have changed with time and varied with clinic and surgeon preferences.

(a) *Osteotomy with cast fixation*: When osteotomy was first developed, maintenance of the corrected position was by a cast or splint until healing occurred. The stabilization was effective to a considerable extent and was adapted from fracture care. Various osteotomy shapes were developed to provide for correction and a reasonably stable mechanical environment for repair such as dome-shaped osteotomies, closing wedge osteotomies and open wedge osteotomies with or without bone graft to hold the wedge open. It was difficult to fully control position of the fragments however and efforts at stabilization by metallic fixation were soon attempted.

(b) *Osteotomy with internal fixation*: Internal fixation refers to the use of metallic implants to hold the bone

fragments in position until healing occurs. The osteotomy is performed, the deformity is corrected and then stabilized at the same operation with an internal fixation device. This approach began in the late nineteenth century and since then a wide assortment of wires (straight and flexible), screws, screws and metal plates, blade-plate constructs and intramedullary rods have been developed. These are placed internally and are usually supplemented by cast fixation. Improvements have come from use of non-reactive metallic alloys with improved strength. Over the past 50 years the most widely used instrumentation for internal fixation of fractures and osteotomies has been that developed by the Swiss AO (Arbeitsgemeinschaft für Osteosynthesefragen) or Association for the Study of Internal Fixation (ASIF) group [38]. The principles of fracture and osteotomy treatment outlined both experimentally and clinically by the group initially stressed anatomic reduction of fractures or immediate intra-operative definitive positioning at osteotomy sites, rigid stabilization to the point of inducing compression to hasten healing between fragments with minimal to no external callus, and minimal to no need for casting to allow for early joint range of motion and early resumption of muscle activity. Some problems developed such as fractures after plate removal owing to avascular bone underneath the plates and stress risers at the screw holes. Modifications to the instrumentation have included less contact surface on the undersides of the plate against the cortices to minimize cortical avascularity, unicortical screws which limit compression of the plate against the cortex, and application of plates without wholesale periosteal stripping and with fewer screw insertions. These later changes served to slightly decrease osteotomy site stability, preserve vascularity and induce differing mechanisms of bone repair. The newer plates include the limited-contact dynamic compression plate (LC-DCP) [39] and the Less Invasive Stabilization System (LISS, Synthes) [40]. LISS is infrequently needed for pediatric age deformity correction, being more designed for adult fracture work, but the biological principles involved warrant understanding.

A limitation of internal fixation for deformity correction has been described as its inability to allow for multiplanar correction of complex deformities. This limitation is often referred to in the context of recommendations for external fixation. This is not completely accurate, however, and internal fixation is not solely applicable to correction of uni-dimensional deformities. For example, an osteotomy can be done on a single bone simultaneously incorporating valgus or varus correction, rotational correction, shortening, flexion or extension correction and even some translational correction. The advantage of internal fixation following corrective osteotomy is the immediate and definitive stabilization of the newly achieved position.

Internal fixation is slightly more limited in those with open growth plates since transphyseal bridging cannot be done. Once skeletal maturity is reached the AO system now supplies plates and blade-plates shaped to the specific contours of most long bone epiphyses/metaphyses. Modifications have been developed for intramedullary fixation, small bone fixation and pelvic fixation.

(c) *Osteotomy with external fixation*: Problems with internal fixation and limitations to the amount of correction obtainable at the time of surgery led to the development of external fixation for added stabilization and multiplanar deformity correction. External stabilization involves the use of screws or wires placed into or through the bone and protruding through the skin to which stabilization devices are applied externally outside the body. These devices can be circumferential and multiplanar such as the Ilizarov device [41] or Taylor spatial frame [42] or single unilateral. External fixation minimizes vascular and soft tissue damage to osteotomy or fracture sites and has been considerably improved by advances in metallurgy, design, and understanding of biomechanical principles. Pin-tract infection and metal-bone interface softening continue to be problematic in long term applications. With the addition of gradual distraction to allow for lengthening, deformities of greater magnitude, especially multiplanar deformities, can be corrected since the incremental lengthening over a several day period allows for stretching of the neurovascular structures not possible with single stage acute corrections. As with internal fixation, varus-valgus, flexion-extension, and rotation can be built into the final stabilization along with diaphyseal-metaphyseal lengthening or shortening and translation.

2.14.5 Osteotomy to Shorten or Lengthen Bones

Osteotomy to shorten or lengthen bones may correct length discrepancies alone or may simultaneously correct some other deformities as well. In some situations deformities other than length are corrected first with length discrepancy corrected as a separate procedure afterwards.

(a) *Osteotomy to shorten bones*: Metaphyseal or diaphyseal osteotomies can be done, generally at or after

skeletal maturity, to shorten major long bones at one stage by lengths up to 5 cm by removing (resecting) metaphyseal-diaphyseal segments of bone and then reducing and stabilizing the proximal and distal fragments usually by internal but occasionally by external fixation to allow healing to occur.

(b) *Osteotomy to lengthen bones*:
Osteotomy can be done for the purpose of lengthening bones.
   (i) **Immediate lengthening**. For relatively short lengthenings up to 3–4 cms., oblique osteotomies, one stage intraoperative lengthening, and immediate internal fixation can be done.
   (ii) **Gradual lengthening**. Most lengthenings greater than 4 cms. are currently done with diaphyseal/metaphyseal osteotomy followed by application of an external fixation device, circumferential or unilateral, and gradual distraction to allow lengthening and bone healing simultaneously by the process of distraction osteogenesis.
   (iii) **Gradual lengthening at 2 or more osteotomy sites with segmental transport**. In more complicated length deformities osteotomy may be done at 2 or more sites within a single bone, segments of poor quality bone may be resected, and distraction lengthening may be accompanied by transport of a segment more distally or proximally for more optimal quality bone healing.

2.15 Surgery on Growth Plates

Surgery specifically designed to alter growth plate function can allow for correction of deformity if sufficient growth remains.

2.15.1 Complete Epiphyseodesis

Complete growth plate fusion across an entire physis can be surgically induced at a specific physis of a longer limb to allow the shorter limb to equalize limb lengths in the remaining months and years of growth.

2.15.2 Partial Epiphyseodesis

Growth can be impaired at one part of a physis allowing the rest of the physis to continue growing to correct an angular deformity within the bone without the need for osteotomy. This principle has been used intermittently for several decades [43] and is currently popular again in many centers under the descriptive term "guided growth" [44] or hemiepiphysiodesis. There are 2 ways regarding timing of intervention to apply this principle. One is to retard growth at one part of a physis by staples or plates across the physis towards the end of skeletal growth with timing determined so that deformity correction is completed at the same time that physeal growth terminates across the remaining physis. The other approach applies the transphyseal plate with extensive growth still remaining, in a much younger child. Once deformity is corrected the plate is removed with the expectation that symmetric physeal growth will continue and deformity will not recur. Two theoretical dangers with this latter approach exist. First, the disorder causing deformation may still be active and lead to recurrent deformity once the unilateral plate is removed. Second, the physis may have been damaged during the period of time the plate was on and it may not function (i.e. grow) normally after plate removal causing deformity in the reverse direction. The first danger appears to be much more common than the second.

2.15.3 Growth Plate Transphyseal Bone Bridge Removal

A focal transphyseal bone bridge, if sufficiently small (less than 30 % of plate area), can be removed and replaced with an interposition tissue such as autologous fat that allows the remaining healthy physis to continue growth.

2.15.4 Transphyseal Lengthening

A bone can be lengthened through the physis by applying controlled distraction forces with an external fixator attached on the epiphyseal and metaphyseal-diaphyseal sides of the growth plate. Transphyseal lengthening is referred to as distraction epiphysiolysis when the distraction force is sufficiently great that a physeal fracture- separation occurs or chondrodiatasis when lesser distraction forces leave the physis intact with hyperplasia occurring in the proliferating and hypertrophic zones. (These distinctions arose from animal research studies and are rarely distinguishable in clinical cases.)

2.15.5 Growth Plate Transplantation

Efforts have been made both experimentally and clinically to transplant growth plates to enable growth to continue. Both partial and complete transplants have been studied. Effective clinical use of these approaches has not yet been developed. The approaches most effective in experimental studies have been autografts involving vascularized entire growth plates (with adjacent bone) and focal partial non-vascularized growth plate transplants relying on persisting epiphyseal and metaphyseal vasculature at the host transplant site to retain

viability. Another investigative approach has used instillation of undifferentiated cartilage or stem cells in an effort to induce differentiation to functional physeal cartilage.

2.16 Amputation

Amputation is occasionally warranted to treat some pediatric developmental deformities. It may be a primary treatment for severe congenital pseudarthrosis of the tibia to permit immediate prosthetic fitting or after multiple failed surgical attempts at correction. It is sometimes needed for severe deforming vascular lesions making the foot unable to bear weight, for lower extremity transverse myelitis or meningomelocoele where prosthetic use would allow more normal ambulation, or for supernumerary toes or fingers. Amputation is more frequently needed currently for severe tumor or post-traumatic complications.

2.17 Mechanisms of Bone Development and Repair. The Role of Mesenchymal Osteoblasts and Surface Osteoblasts in Bone Development and Their Relation to Fracture and Osteotomy Repair

This section is adapted and expanded from our article on the mechanisms of bone repair [45].

2.17.1 Bone Formation

Bone formation is complex but the three-dimensional positioning of cells and matrices is straightforward. As in any discussion of bone formation it is important to keep in mind the distinction between ***bone as a tissue*** (bone cells and the mineralized matrix) and ***bone as an organ*** (including several tissues such as bone, cartilage, fibrous tissue, marrow and blood vessels). Normal bone develops using only 2 mechanisms.

Intramembranous bone formation is mediated by the inner periosteal osteogenic layer with bone synthesized initially without the mediation of a cartilage phase.

Endochondral bone formation describes the synthesis of bone on a mineralized cartilage scaffold after epiphyseal and physeal cartilage have shaped and elongated the developing organ. These mechanisms are also used in fracture and osteotomy repair with the specific mechanism dependent on the mechanical environment provided for repair. With ***intramembranous bone repair***, mesenchymal cells differentiate along a pre-osteoblast to osteoblast line while ***endochondral bone repair*** is characterized by the initial synthesis of cartilage followed by the endochondral sequence of bone synthesis. The terms intramembranous and endochondral refer to the tissue being replaced, not to the eventual bone synthesized which is the same in both mechanisms.

2.17.2 Matrix Orientation

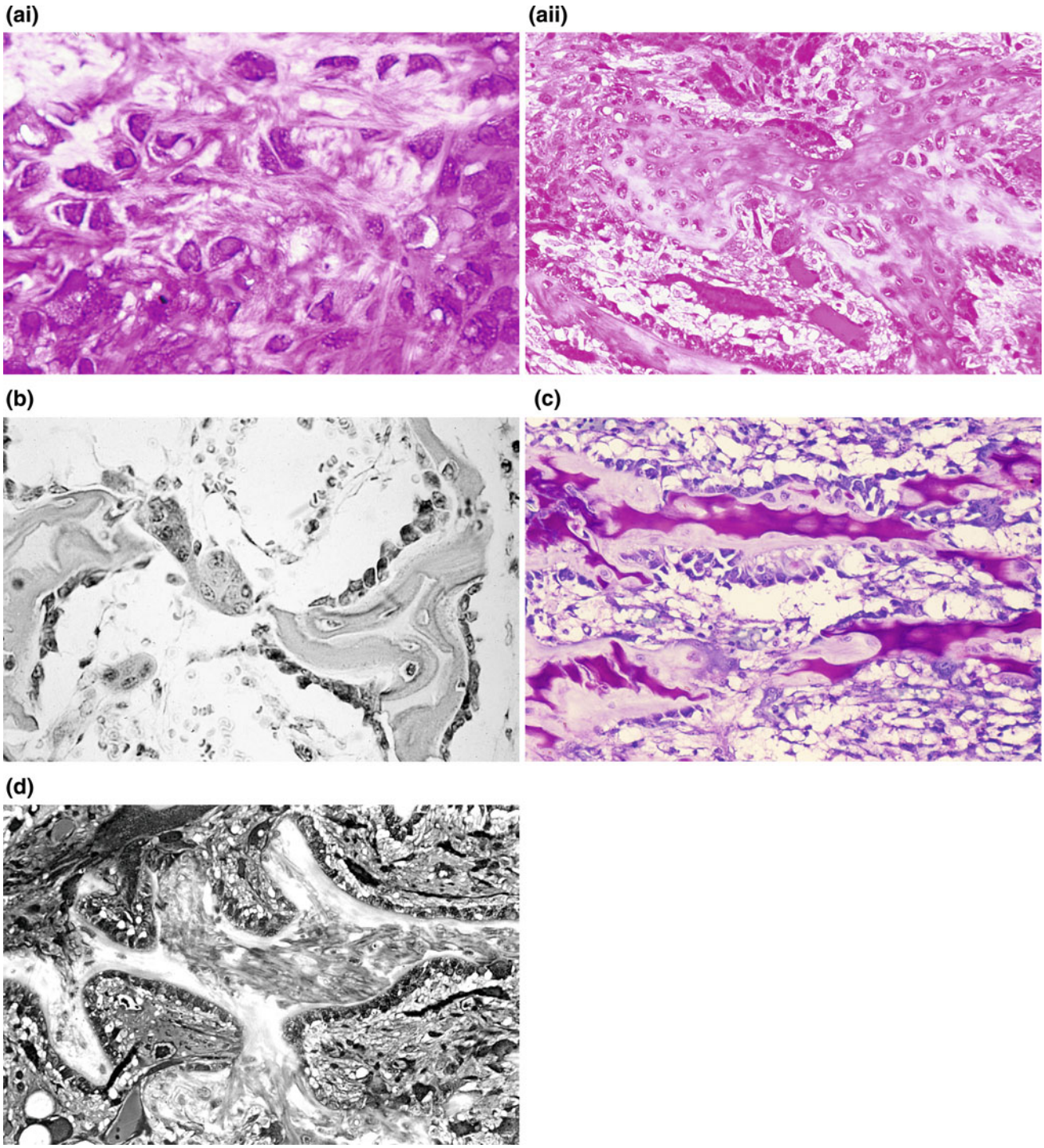
In bone tissue formation osteoblasts synthesize and deposit type I collagen, the main protein constituent of bone matrix, in only 2 basic conformations, ***woven*** and ***lamellar***. In woven bone the collagen fibrils are randomly oriented while in lamellar bone they are clustered in parallel arrays. These processes are repeated in normal bone development, in bone repair utilizing any of several mechanisms, and in several pathologic conditions.

2.17.3 Osteoblasts

We use a specific terminology for osteoblasts describing them as either ***mesenchymal osteoblasts*** (MOBL) or surface ***osteoblasts*** (SOBL) since these 2 variants only are seen to underlie essentially all bone tissue formation [46]. Matrix conformation shift from woven to lamellar is virtually always abrupt with infrequent tendency to shading of one pattern into the other via fibro-osseous or chondro-osseous accumulations. With the first stages of bone formation, in an environment where no pre-existing bone matrix is present, undifferentiated mesenchymal cells differentiate to pre-osteoblasts and then to osteoblasts which secrete collagen fibrils in a 360 degree direction in random pericellular array. We refer to these cells as ***mesenchymal osteoblasts*** and the bone matrix synthesized as ***woven*** [Fig. 2.4a(i, ii)]. When a sufficient amount of woven bone has been synthesized to serve as a ***structural scaffold***, osteoblasts which we refer to as ***surface osteoblasts***: (i) array themselves in well-polarized fashion only along the woven bone surface, (ii) secrete collagen fibrils only onto the bone surface (not circumferentially), and (iii) secrete fibrils in a parallel or ***lamellar*** orientation (Fig. 2.4b–d). An osteoblast completely surrounded by the mineralized collagen matrix is now an ***osteocyte***, although it can be in woven or lamellar bone.

2.17.4 The Molecular Biology of Developing Bone and of Fracture Repair

Since the histologic appearance of repair bone is the same as that associated with various phases of normal development it stands to reason that the molecular involvement [47, 48] is at least similar and in most ways probably the same. Several reports have outlined this similarity [49–52] with repair bone showing the same array of structural proteins (such as type II


(ai)
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and type X collagen in repair cartilage callus and hypertrophic chondrocytes respectively and the type I, type III and type V collagen in newly synthesized osteoid) the many regulators of chemotaxis, mitosis and differentiation are present such as wnt, Indian hedgehog (ihh), downstream genes responding to hedgehog proteins like Gli 1 and patched (Ptc), bone morphogenetic proteins (BMP 2, BMP 3 [osteogenin], BMP 4, and BMP 7 [osteogenetic protein, OP 1]), Smads 1-8 (a class of proteins that function as intracellular signaling effectors for the TGF-B superfamily, the BMP receptor kinases that phosphorylate intracellular cytoplasmic Smads, the transcription factor core binding factor 1 (cbfa 1), fibroblast growth factors (FGF1, 2 and 9), platelet derived growth factors (PDGF), transforming growth factor beta (TGF beta) superfamily including matrix metalloproteinases (MMPs) and the angiogenic molecules vascular endothelial growth factor (VEGF a → d). At the start of the repair cycle, inflammatory cells secrete cytokines including (interleukin) IL-1, IL-2, RANKL and tumor necrosis factor (TNF x and b).

The value of such studies lies: (i) in helping determine why bone is one of the few organs to fully repair itself to a normal pre-injury structure and function, (ii) how these molecules interrelate with one another and with the mechanical-biophysical environment to bring about bone tissue synthesis, and (iii) which molecules are the main determinants for repair such that their use as pharmacologic agents can enhance repair.

2.17.5 Bone Repair

Bone repair can occur by different specific mechanisms primarily dependent on the biophysical environment. Although the various types of repair use differing normal cells and tissues, the eventual bone synthesis is always mediated by the mesenchymal and/or surface osteoblasts (MOBL and SOBL) and via the woven and/or lamellar matrix conformations. The histologic patterns of bone repair are:

- *endochondral bone repair* (repair by callus formation), mediated by inner periosteal layer and marrow tissues, synthesizing cartilage and then woven and lamellar bone in an environment of interfragmentary space and mobility;
- *primary bone repair* (contact repair), mediated exclusively by intraosseous Haversian system osteoblasts (SOBL), without a cartilage phase, synthesizing lamellar bone initially parallel to the longitudinal axis of the bone such that no remodeling is needed, in an environment of no interfragmentary space and rigid stability;
- *direct bone repair* (gap repair, direct transformational bone repair) mediated without a cartilage phase by marrow derived vessels and mesenchymal cells, initially perpendicular to the long axis of the bone (woven and lamellar) and then remodelled along the long axis (lamellar), in an environment of interfragmentary space > 0.1 mm wide but with rigid stability; and
- *distraction osteogenesis* (callotasis) mediated by inner layer periosteal and marrow tissue, synthesizing woven and then lamellar bone in the slowly widening gap, parallel to the long axis of the bone in an environment of stability and slow distraction.

Bone repair can also be considered in relation to the regions of bone where repair is occurring, for example: cortical (diaphyseal) fractures in dense ***compact bone*** and metaphyseal or epiphyseal fractures occurring in the ***spongiosa*** where bone trabeculae are distributed within marrow spaces.

- The ***source of repair cells*** following a fracture or osteotomy of bone is either from (i) the periosteum,

◀ **Fig. 2.4** Mesenchymal osteoblasts (MOBL) and surface osteoblasts (SOBL) and their relationship to woven and lamellar bone respectively are illustrated. Tissue sections (**a**), (**c**) and (**d**) were prepared by the JB_4 plastic embedding technique and stained with 1 % toluidine blue. The section in (**b**) was prepared by paraffin embedding and hematoxylin and eosin staining. **a** Mesenchymal osteoblasts (MOBL) are illustrated. **a(i)** The earliest mesenchymal cells in a bone repair sequence lie within a scanty fibrinous matrix. a(**ii**) The mesenchymal osteoblasts are surrounded by newly formed bone matrix in the central part of a circular cortical femur defect in a rabbit at one week post-surgery. (Reprinted with permission from Shapiro F, Bone development and its relation to fracture repair. The role of mesenchymal osteoblasts and surface osteoblasts. Europ Cells Materials (eCM) 2008;15:53–76. Copyright 2008 European Cells and Materials; with kind permission of full reproduction from eCM journal). **b** Surface osteoblasts (SOBL) are aligned on metaphyseal trabeculae from newborn bovine bone. Remnants of cartilage are noted surrounded by bone containing osteocytes. An osteoclast is seen between 2 trabeculae. **c** Surface osteoblasts (SOBL) are seen in newborn rabbit metaphyseal bone aligned on the surface of bone trabeculae. The *dark purple* staining material is the persisting calcified cartilage from the endochondral sequence. **d** Surface osteoblasts (SOBL) line the surface of bone repair tissue from a circular cortical rabbit femur defect at 2 weeks. Initially synthesized woven bone has been surrounded by lamellar bone with surface osteoblasts on the lamellae clearly seen

(ii) the osteoprogenitor cells associated with the blood vessels of the Haversian systems within the cortex, (iii) the endosteum, (iv) the undifferentiated mesenchymal cells of the bone marrow, and (v) (according to some) the "soft tissue" undifferentiated cells of the surrounding muscle and connective tissue based on their ability to differentiate as needed. The environment provided for repair determines which source of cells serves as the primary repair agent. In endochondral bone repair with motion between the fragments the periosteum is the main source of repair cells. With rigid internal fixation and anatomic coaptation of fragments with a gap of less than 0.1 mm, the repair is exclusively from the intracortical vessel-associated osteoprogenitor cells and with direct bone repair with rigid fixation but a gap of greater than 0.1 mm the marrow stem cells are the primary repair source moving into the interfragmentary gap.

2.17.6 Woven Bone and Lamellar Bone

Bone formation is initiated with matrix deposition in a randomly oriented pattern referred to as woven or coarse fibered bone followed by its replacement with bone with a definitive lamellar structure (Fig. 2.5a, b). There are several patterns of lamellar bone deposition in vertebrates described as: (i) uniform lamellae encircling the entire diameter of the bone, (ii) a more complex pattern characterized by laminae separated from adjacent structures by vascular canals, or (iii) multiple Haversian systems or osteones such as occur in higher mammals including humans [53]. An ***Haversian system*** or ***osteon*** in cortical bone refers to a central canal containing longitudinally oriented vessels and associated osteoprogenitor cells surrounded by concentric lamellae of matrix. Longitudinally oriented lacunae containing osteocytes are embedded in the lamellae linking both adjacent

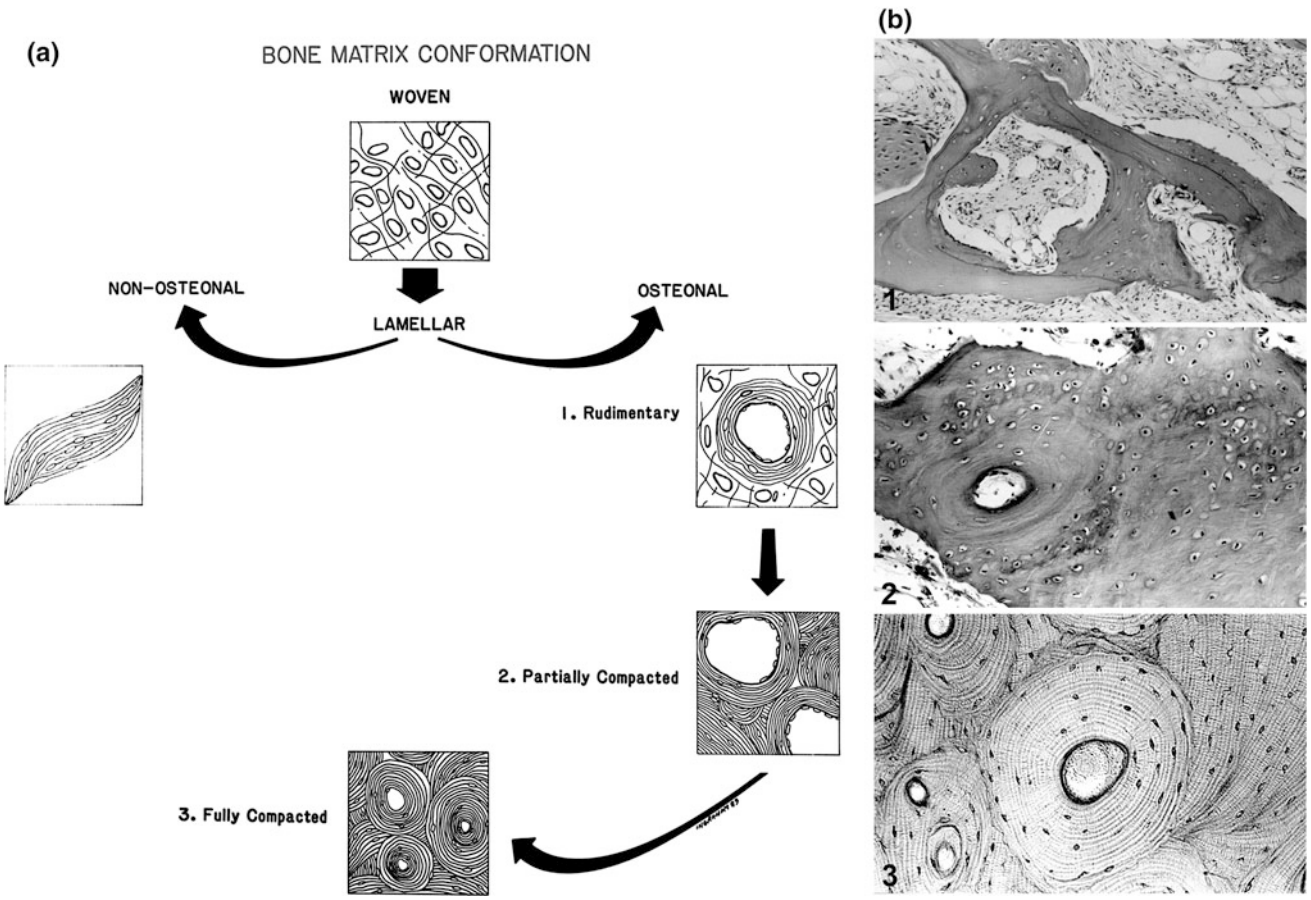


Fig. 2.5 Bone matrix synthesis, both in normal development and fracture or osteotomy repair, generally begins with woven bone synthesis followed by lamellar bone synthesis once the woven scaffold is in place. (Reprinted with permission from Shapiro F, Bone development and its relation to fracture repair. The role of mesenchymal osteoblasts and surface osteoblasts. Europ Cells Materials (eCM) 2008;15:53–76. Copyright 2008 European Cells and Materials; with kind permission of full reproduction from eCM journal). **a** Osteonal bone, forming around central Haversian blood vessels which are generally aligned along the long axis of the bone, begins as rudimentary and progresses to partially compacted and then fully compacted bone. This occurs as surface osteoblasts synthesize lamellar bone building up tissue deposition towards the central vessel. Lamellar bone forms in metaphyseal regions but is non-osteonal in nature. **b** Histologic sections of bone show *1* rudimentary, *2* partially compacted, and *3* fully compacted variants

cells and vessels by canaliculi containing the osteocyte cell processes. Many Haversian systems are present in a cross-section of bone.

The formation, structure and continuous remodeling of the bone matrices have been the subject of detailed investigation with various works defining: coarse fibered primary bone and fine-fibered lamellar bone [54]; woven-fibered bone, parallel-fibered bone and lamellar bone (Weidenreich) [55]; and woven-fibered bone, primary osteones, secondary osteones, surface bone, and interstitial bone [56, 57]. The mechanisms by which regions of woven bone are subsequently found to be composed of dense lamellar bone are of considerable biological and clinical importance. Woven bone in the human is seen characteristically in association with bone formation: (i) in the fetus and newborn, (ii) in initial early repair following fractures and osteotomies, and (iii) in pathologic states as diverse as osteogenesis imperfecta and osteopetrosis.

Woven bone is synthesized by mesenchymal cells, which we refer to as mesenchymal osteoblasts (MOBL), which have just differentiated along a pre-osteoblast to osteoblast line in a localized region where no bone is present. It has a matrix with randomly oriented collagen and is relatively hypercellular with round to oval cells linked by cell processes in canaliculi which are also randomly oriented. It is weak structurally and is synthesized primarily to serve as a scaffold upon which the better oriented and mechanically stronger lamellar bone is deposited. Once a sufficient amount of woven bone has been deposited to serve as a scaffold, osteoblasts, which we refer to as surface osteoblasts (SOBL), align in single array along the woven bone surface and deposit new matrix in a linear or lamellar orientation.

Lamellar bone is less cellular than woven bone, its osteocytes are flattened and aligned along the long axis of the matrix, and the canaliculi are more regularly patterned parallel and perpendicular to the osteocytes and adjacent blood vessels. The lamellae in secondary (remodeled) bone align in multilayered cylindrical osteons around a central blood vessel. The lamellae are not all in the same plane however. Thin and thick lamellae alternate and adjacent sheets are positioned at oblique angles to one another in what is referred to as a "***twisted plywood***" ***orientation*** for structural support [58]. The angles between adjacent arrays in lamellar bone have been studied and it was shown that most angles were 30° with a subset at 70° [59]. They proposed a structural model for collagen organization with an individual lamellar unit (thick and thin lamellae) composed of 5 arrays of parallel fibrils each offset by 30°. The spiral twisting of fiber orientation in bone lamellae has been assessed by others as well [60]. Another feature of collagen fibril formation in lamellae is that it is a ***self-assembly process*** in the extracellular environment determined to a large extent by the intrinsic chemical properties of the collagen molecules rather than being specifically cell-directed [61–63].

2.17.7 Endochondral Bone Repair

Endochondral bone repair describes bone repair which occurs in an initial environment of macromotion and then micromotion between the fragments such as with fractures treated in a cast or with traction (Fig. 2.6 i–vi). After injury there is extensive ***bleeding*** with tearing of the periosteum and adjacent soft tissues. A large ***hematoma*** contained by the surrounding tissues forms after which a ***fibrinous blood clot*** is formed to serve as a medium for repair cell ingrowth. The first few days post-fracture are characterized by an ***inflammatory phase***. It is now considered that molecules associated with the inflammatory phase and blood clot formation are essential for initiating the correct repair response. The outer fibrous layer of the periosteum eventually reconstitutes to contain the hematoma and clot while the inner

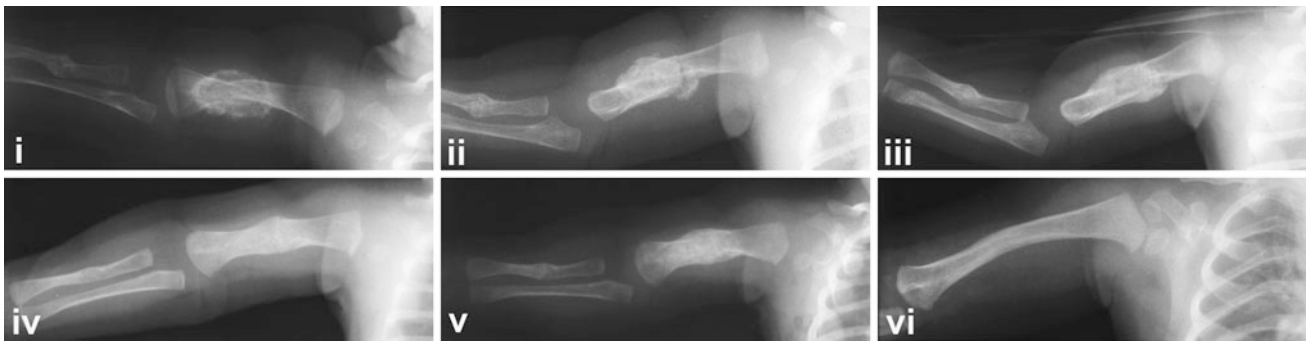


Fig. 2.6 Radiographic examples of the progression of long bone healing of the mid-shaft humerus by the endochondral mechanism are shown in a sequential study of one patient with osteogenesis imperfecta. Radiographs of mid-diaphyseal humeral fracture illustrate endochondral bone repair in: (**i**) at approximately 3.5 weeks post-injury; (**ii**) 4 weeks; (**iii**) 5.5 weeks; (**iv**) 7 weeks; (**v**) 9 weeks; and (**vi**) 1 year. Radiograph at one-year post injury shows complete repair with excellent remodeling. (Reprinted with permission from Shapiro F, Bone development and its relation to fracture repair. The role of mesenchymal osteoblasts and surface osteoblasts. Europ Cells Materials (eCM) 2008;15:53–76. Copyright 2008 European Cells and Materials; with kind permission of full reproduction from eCM journal)

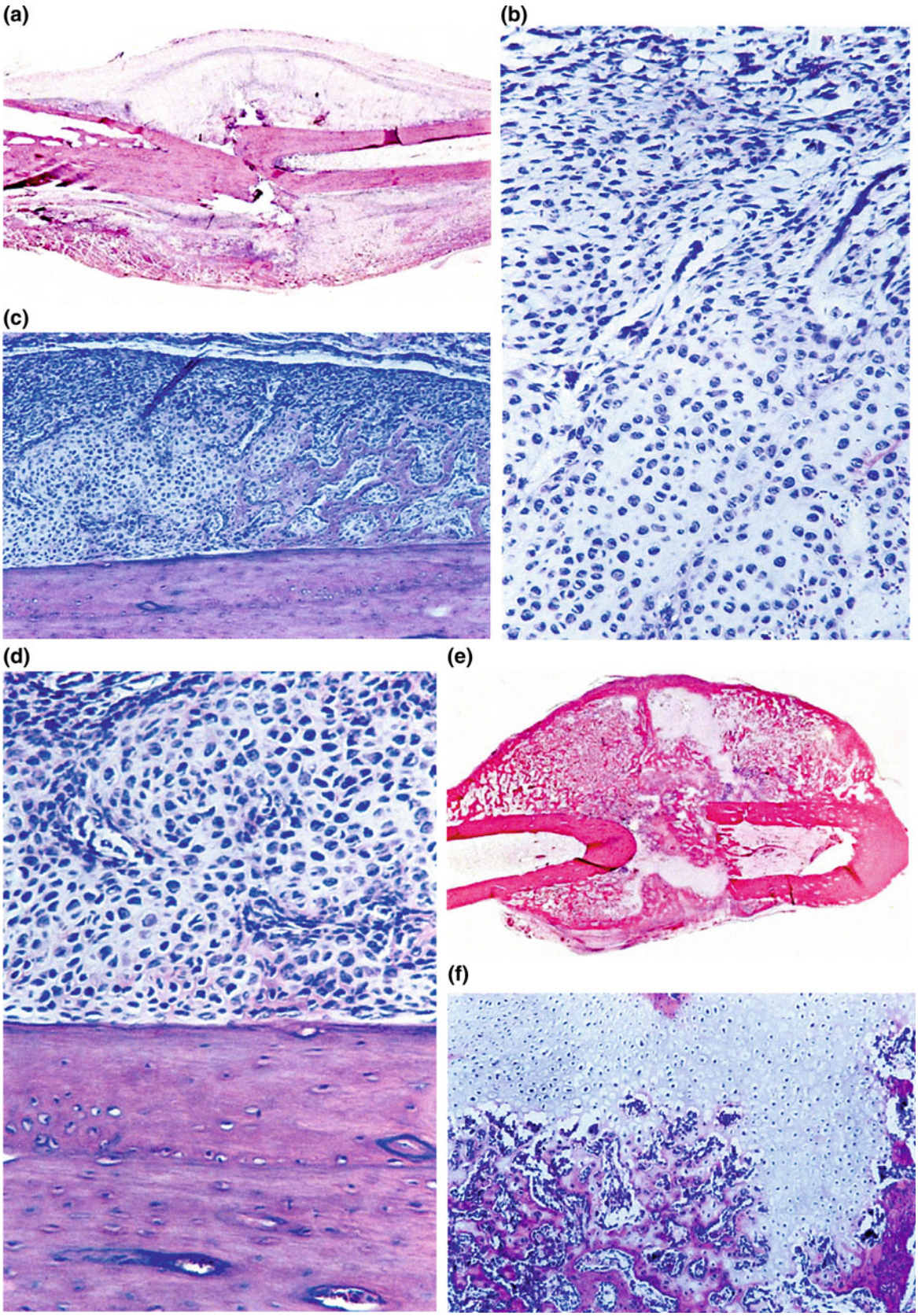
cambial layer undergoes intense proliferation and differentiation to initiate and carry out repair. Some observers feel that adjacent mesenchymal soft tissue cells from injured muscle, tendon, fascia or undifferentiated connective tissue also participate in repair by induction along the cartilage/bone lines. Bone repair begins from the periphery of the cortex, several centimeters away from the fracture site, as the inner layer of the elevated periosteum lays down intramembranous woven bone against the cortex in a stable and still well vascularized part of the repair site. Closer towards the fracture however the relative movement of the repair environment and the relative tissue hypoxia due to damage to the blood supply leads to the formation by the inner periosteum and undifferentiated mesenchymal cells of a large cartilaginous mass both outside the cortices, ***external callus***, and within the cortices, ***internal callus***. The callus which is initially cartilaginous and fibrocartilaginous serves to stabilize the fracture site, an action which then favors bone formation. Vascularity advances in the increasingly stable environment deeper into the callus from the periphery of the cortex furthest away from the facture site and from the reconstituted periosteum at the outer margin of the external callus. In doing so woven bone is relatively rapidly synthesized on calcified cartilage cores of the callus until the repair cartilage has been converted completely to bone by the endochondral mechanism. This further stabilizes the fracture site. The next stage of the repair process involves transforming the woven bone to lamellar bone, resorbing the external callus which is no longer needed since the fracture ends have been bridged and stabilized by healing tissue, and remodeling the Haversian cortical bone to lie along the longitudinal axis. This process of healing is referred to as endochondral bone repair since the synthesis of cartilage to bridge the fracture ends repeats the same mechanism used at the growth plate, namely chondrocyte hypertrophy, cartilage matrix calcification, invasion of hypertrophic chondrocyte lacunae by osteoprogenitor cells and blood vessels, and bone tissue formation. The term endochondral simply refers to the tissue replaced in forming the definitive bone tissue since the bone formed eventually has the same structure and molecular composition as bone formed by other mechanisms.

Bone healing using this mechanism was understood in basic outline in the 1700 s and was clearly described by Dupuytren in the early 1800 s long before the development of histologic or radiographic assessment [64]. The histologic criteria have been extensively assessed over the past century and continue to warrant attention [65–71].

Histology sections from a healing mid-femoral shaft fracture in the rabbit illustrate key features of endochondral repair (Fig. 2.7a–m). Even in this model of repair, which at first glance is structurally diverse, we can see the biophysical principles directing bone repair. Intramembranous bone forms initially on the outer cortex at the most peripheral but also most stable and best vascularized region of the repair site. Once the cartilaginous callus stabilizes the fracture site, vascularization moves inward from the periphery and endochondral bone repair occurs. This is initially woven and mediated by mesenchymal osteoblasts (MOBL) but once there is sufficient woven matrix, surface osteoblasts (SOBL) synthesize lamellar bone on the woven bone cores. The lamellar bone then progresses towards the Haversian conformation encircling and closing in on vessels. The final stage in this repair process involves the resorption of extra-cortical bone and remodeling of cortical bone to lamellae parallel to the longitudinal axis.

2.17.8 Bone Repair Terminology in Rigid Stable Environments (Primary and Direct)

When a stable environment for repair is established by early surgical fixation of the fragments the need for a large external cartilage callus is bypassed. The purpose of the external cartilage callus of the endochondral bone repair mechanism is to stabilize the fracture site to allow internal bone fragment to bone fragment repair to occur. With very rigid fixation the entire endochondral sequence can be bypassed and bone can form without callus and indeed without the interposition of cartilage tissue at all. Features of the repair environment however will still dictate the nature of the bone repair including the type and orientation of the synthesized bone matrices. When bone is formed without the mediation of a cartilage phase in anatomically reduced and rigidly stabilized fractures or osteotomies radiographs show repair bone to be deposited within the cortices and perhaps the marrow cavity with no external callus and no, or virtually no, periosteal elevation. The terminology used to describe these mechanisms of repair needs to be defined since different groups use similar terms in slightly dissimilar ways. Many will use the terms primary and direct bone repair interchangeably to indicate bone repair without the radiologic appearance of any periosteal new bone reaction or external callus. We define ***primary bone repair*** as repair which occurs strictly within the cortex in situations where fractures or osteotomies are rigidly compressed in anatomic fashion with no interfragmentary gap causing repair to occur with initial lamellar bone deposition already parallel to the long axis of the bone by osteoprogenitor cells within Haversian canals or osteoclast cutting cones [Fig. 2.8a, b(i, ii)]. This is also referred to as ***contact repair*** [72–74]. We define ***direct bone repair*** as repair which occurs in situations where fractures or osteotomies undergo rigid surgical fixation but leaving an interfragmentary gap greater than 0.1 mm such that repair can occur without cartilage mediation but the



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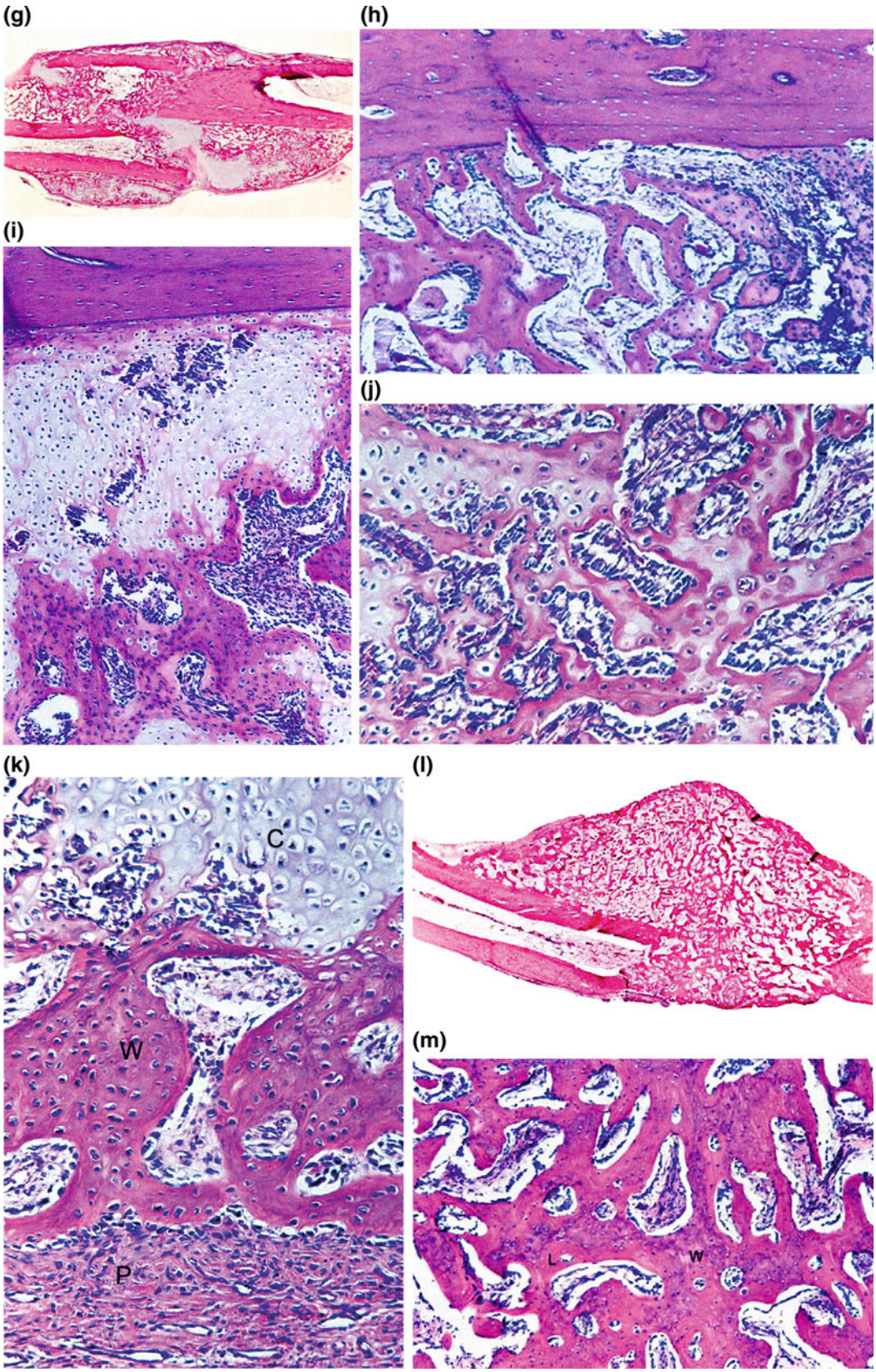

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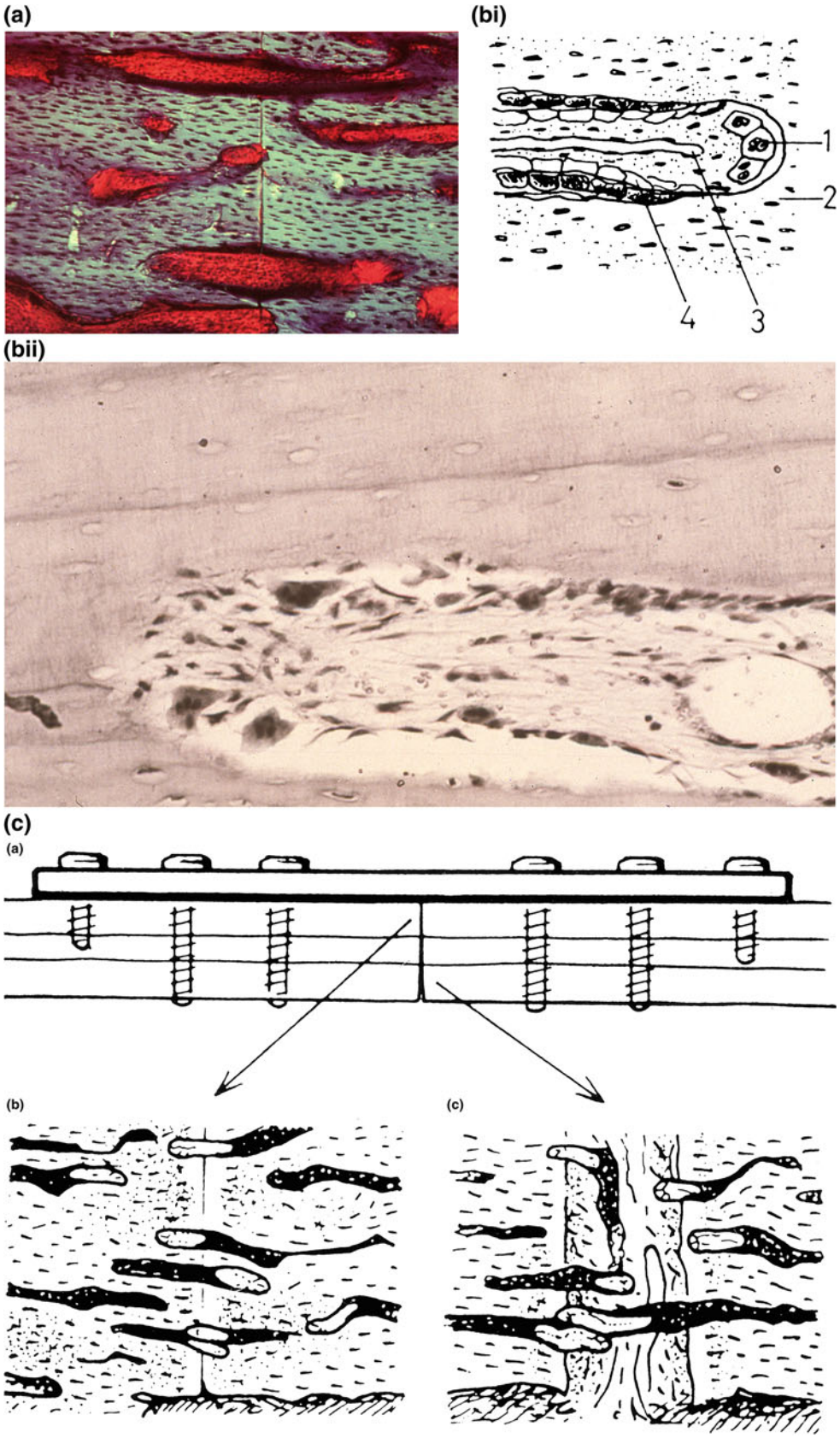
◀**Fig. 2.7** The histologic features of endochondral bone repair of a mid-diaphyseal femur fracture in a one-week old rabbit are shown. All sections are paraffin embedded and stained with hematoxylin and eosin. **a** Longitudinal section of healing mid-diaphyseal fracture at 1 week in rabbit femur shows the early stage of endochondral bone formation. There is external and internal callus which, at upper portion, is cartilaginous. The outer fibrous layer of the periosteum has been reconstituted. (Reprinted with permission from Shapiro F, Bone development and its relation to fracture repair. The role of mesenchymal osteoblasts and surface osteoblasts. Europ Cells Materials (eCM) 2008;15:53–76. Copyright 2008 European Cells and Materials; with kind permission of full reproduction from eCM journal). **b** Higher power views of the upper portion of the external callus specimen at 1 week show cartilage (*below*) and overlying fibrous tissue (*top*). **c** Higher power view of the far right region of repair (*upper cortex*) at 1 week shows the periosteal new bone formation against cortex at right but cartilage formation against cortex at left closer to the more mobile and less well-stabilized fracture site. **d** Cartilage tissue against persisting cortex at 1 week is shown. This will soon be converted to bone as vascularization and periosteal bone move from the mechanically stable periphery to the central region adjacent to the fracture site. [Summary **a**–**d**: Early repair tissue furthest away from the fracture site against persisting cortex at 1 week shows the periosteum at a stable, well vascularized region immediately starts repair with bone formation. New bone against the cortex is already being lined by surface osteoblasts while immediately above undifferentiated mesenchymal cells are synthesizing woven bone.] **e** Endochondral repair in the rabbit femur at 5 weeks is shown. There is abundant bony callus with membranous bone formation along with endochondral repair in the femur. Newly synthesized bone is replacing the cartilage mass using the endochondral mechanism but some (light staining) cartilage still persists centrally. **f** Higher power view of (**e**) shows persisting cartilage from external callus above with vascular invasion of the cartilage with classic endochondral bone formation on cartilage cores. **g** Endochondral repair in the rabbit femur at 6 weeks is shown. There is relatively little cartilage of the original external callus persisting. **h** This figure shows maturation of the initially synthesized periosteal woven new bone with surface osteoblasts and some lamellar segments now present. **i** There is now vascular invasion of the cartilage callus with new bone formation and surface osteoblasts. **j** Classic endochondral bone formation on mineralized cartilage remnants is seen, as would occur in normal metaphyseal bone formation. **k** The outer fibrous layer of the periosteum (P) is seen *below*, new woven bone formation (W) with some surface osteoblasts in place continues bone formation with lamellar tissue, and cartilage at *top* (C) is undergoing endochondral ossification. **l** Endochondral fracture repair at 7 weeks is shown. The cortical fragments at left and far right are now fully bridged by repair bone. There is still a prominent external callus but all the cartilage tissue has been replaced by bone. **m** A higher power view from the ventral portion of the external callus shows woven bone (W), most of which has been covered with more recently synthesized lamellar bone (L)



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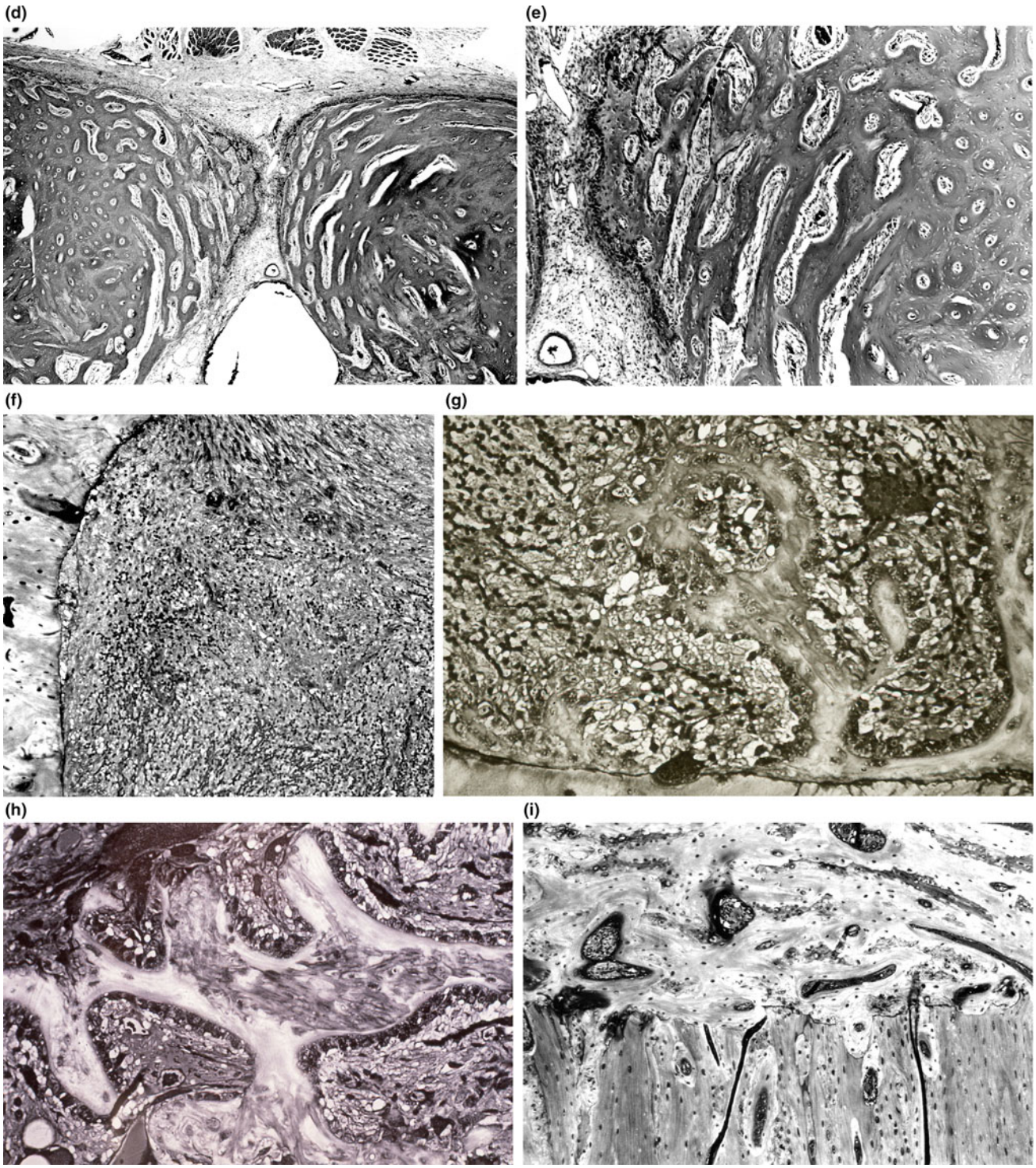

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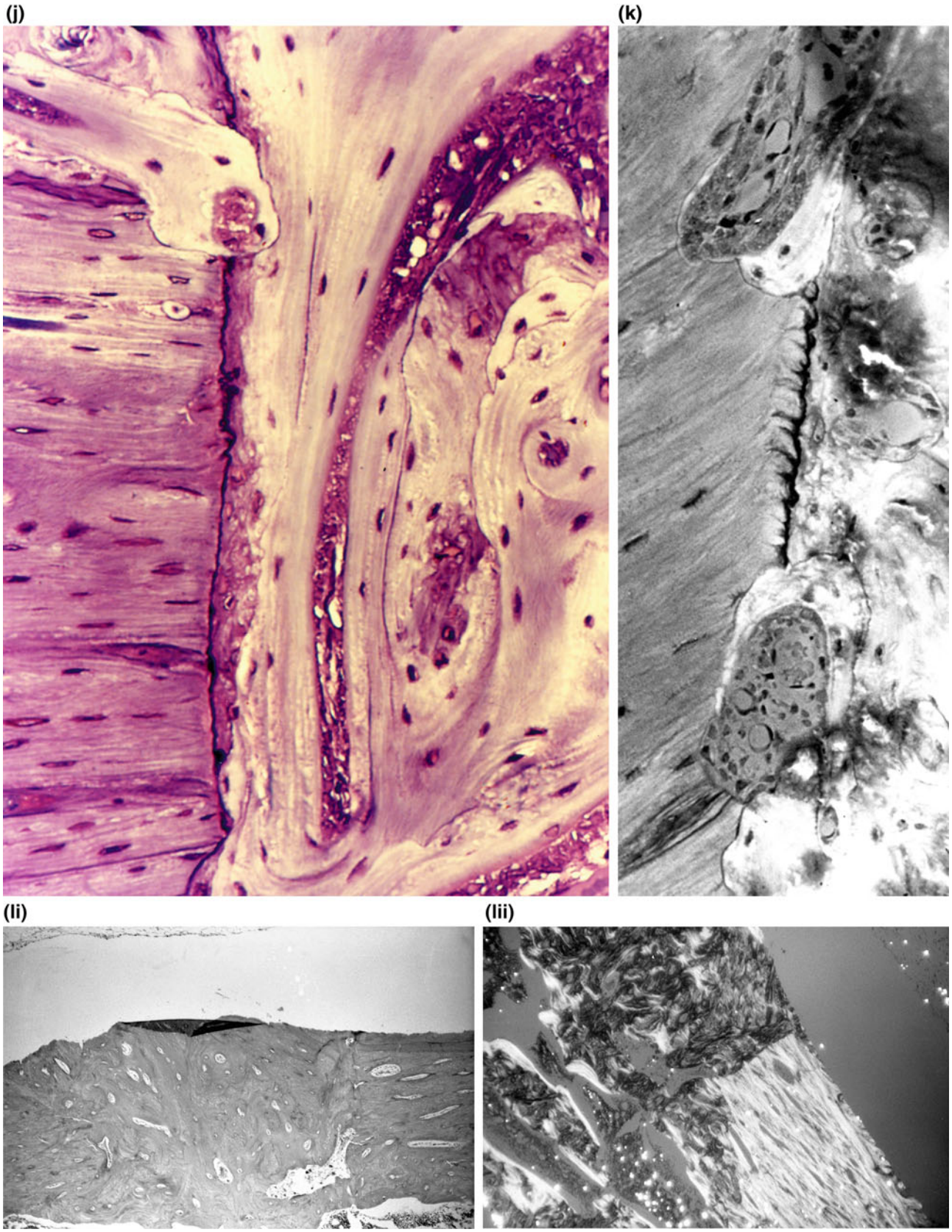
bone formed originates from marrow cells and is aligned at right angles to the long axis of the bone such that it must subsequently undergo remodeling to align lamellar bone along the longitudinal axis (Fig. 2.8c). This is also referred to as ***gap repair*** [73] or ***direct transformational bone repair*** [46]. The term direct transformational bone repair uses "direct", since there is no mediation of a cartilage phase with bone tissue formed initially, and "transformational" since initial woven bone synthesis is soon modeled to a lamellar conformation at right angles to the longitudinal axis and then



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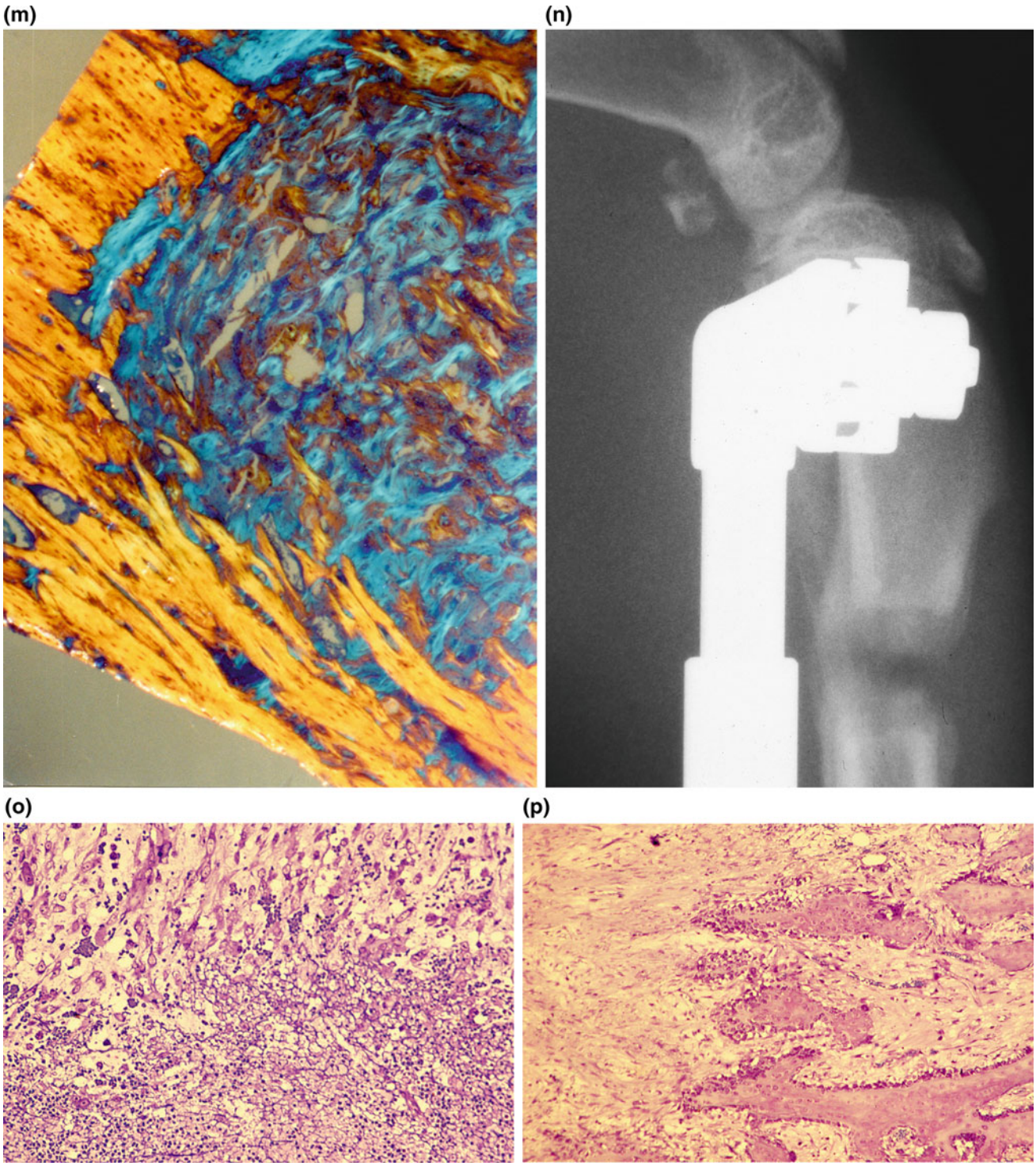

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remodeled again to a lamellar conformation parallel to the longitudinal axis. Where this mechanism of bone repair occurs it appears that lamellar bone (perpendicular to the long axis, can be formed directly in the gap when that gap is 0.2 mm wide or less whereas larger gaps form woven bone initially and then lamellar.

Even with the classic compression plating studies of transverse osteotomies it was recognized that the cortex immediately under the plate was stabilized with no interfragmentary gap allowing for primary trans-osteotomy Haversian bone or contact healing while the opposite cortex had a slight opening leading to the gap healing

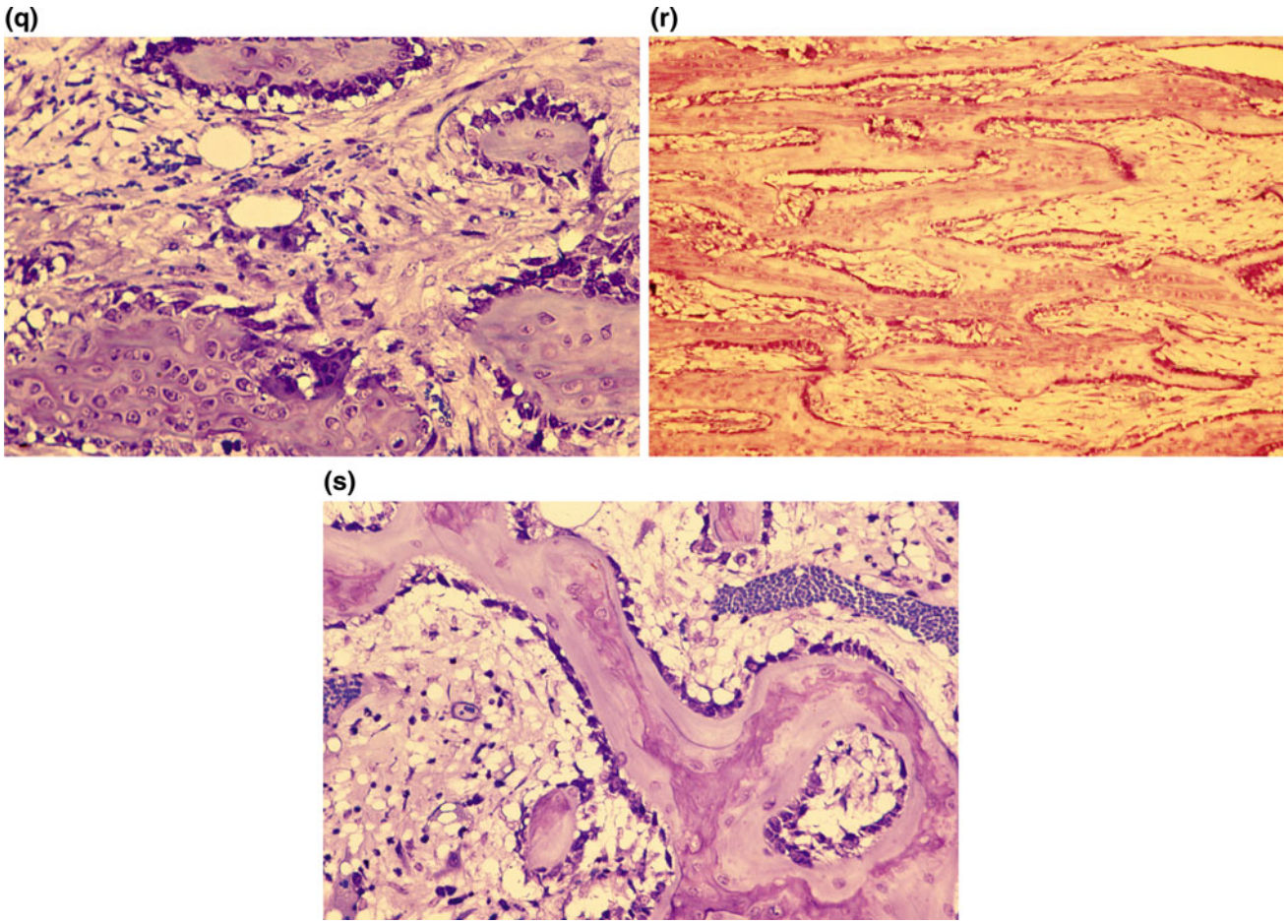


Fig. 2.8 (continued)

mechanism [72, 73, 75, 76] (Fig. 2.8c). Repair by ingrowth of bone tissue initially perpendicular to the long axis of the bone with partial or complete transverse osteotomies has been noted by other observers [77, 78].

2.17.8.1 Primary Bone Repair

Primary bone repair, also referred to as contact healing, refers to bone repair within the cortex following anatomic reduction of a fracture and rigid internal fixation under compression which eliminates any interfragmentary gap (Fig. 2.8a). Repair occurs by immediate synthesis of lamellar bone parallel to the long axis of the bone from osteoprogenitor cells in Haversian longitudinal vessels. A pathway through the dense cortical bone is made by what is referred to as an osteoclast cutting cone where osteoclasts resorb bone and are immediately followed into the space created by vessel ingrowth and osteoblasts that synthesize lamellar matrix on the pre-existing cortical walls [Fig. 2.8b(i, ii)]. The rigid plate stabilization eliminates the need for external callus formation and for entry of repair vessels and cells from the marrow since any fracture gap for them to enter has been closed. Since a dense and normally oriented scaffold for repair exists, in the form of the original cortex reduced and held by rigid compression fixation, surface osteoblasts suffice for repair without the need even for MOBL cells. This variant of bone repair has been characterized well in the dog radius [72–75, 79].

2.17.8.2 Direct Bone Repair (Oval Defect)

Cortical bone repair in the adult chicken humerus has been outlined after creating an oval unicortical 10 mm × 3 mm defect with the long axis of the defect aligned along the shaft [80]. [The unicortical defect models provide stability (since the large majority of the cortex remains intact circumferentially) but also interfragmentary space which can be varied in size and geometric shape.] The entire sequence of bone repair was observed histologically from the early formation of a loose fibrous network in the hematoma clot to the eventual healing of the site with well-ordered lamellar bone 8 weeks after operation. Stability is sufficiently great with

◀**Fig. 2.8** Primary bone repair and direct bone repair are illustrated. Both involve synthesis of bone without the mediation of a cartilage phase. **a–c** illustrate primary and direct bone repair mechanisms following non-displaced osteotomy with rigid AO plate fixation [45, 76]. **d** and **e** illustrate direct (transformational) bone repair in an oval defect chicken cortical bone model where stability is maintained by the rest of the circumferentially intact cortex [45, 80]. **f–m** illustrate direct transformational bone repair in a 2.4 mm circular cortical defect model in the rabbit tibia [45, 46]. **n–s** illustrate repair by distraction osteogenesis in a rabbit tibia undergoing lengthening with a mini-lengthener [45, 90]. **a** Photomicrograph illustrating primary bone repair following a non-displaced transverse osteotomy and compression plating in the dog radius [101]. Repair in this photomicrograph is occurring along the long axis of the bone within the cortex as osteoclast cutting cones from Haversian vessels cross the osteotomy line and synthesize lamellar bone on the cortical walls (in the longitudinal axis). (Reprinted with permission from Muller ME, Bases experimentales et principes de l'osteosynthese par compression. Internat Orthop 1978;2:115–125. Copyright 1978 Springer Science+Business Media). **b(i)** and **(ii)** These figures illustrate osteoclast cutting cones. **b(i)** shows the advancing activity passing from left to right led by the multinucleated osteoclasts which resorb bone followed by a central vessel and surface osteoblasts synthesizing lamellar bone. **b(ii)** is a histologic slide of a cutting cone passing (from right to left) through necrotic rabbit cortical bone to begin repair. **c** Illustration demonstrates the 2 types of repair that occur in the same bone following an osteotomy fixed with a rigid compression plate [76] (*top*, *a*). In the cortex immediately under the plate there is no interfragmentary space and repair by the primary intracortical or contact mechanism occurs with lamellar bone synthesized even initially along the longitudinal axis (*lower left, b*). At the opposite cortex, slight opening occurs leading to repair with bone without a cartilage stage by the gap mechanism since the slight interfragmentary space allows for vascular invasion from the marrow cavity along with mesenchymal cells which however synthesize lamellar bone at right angles to the longitudinal axis such that further remodeling will be needed (*lower right, c*). **d** Photomicrograph shows the entire repair site in a chicken humerus cortical defect model at 4 weeks post-injury. The intact persisting cortices are at far right and left (not clearly seen). Centrally there are a few undifferentiated mesenchymal cells. Passing towards either edge of the original defect site these cells have differentiated to mesenchymal osteoblasts synthesizing woven bone and closer to the cortex, where the initial repair began with woven bone synthesized on the cortical scaffold, further new bone formation by surface osteoblasts has led to new osteonal formation on the woven tissue. (Reprinted with permission from Glimcher et al, Changes in tissue morphology and collagen composition during the repair of cortical bone in the adult chicken. J Bone Joint Surg Am. 1980;62A:964–973). **e** A higher power view of one side of the defect shows the undifferentiated cells at far left and the repair cascade to the right. At far right there is lamellar osteonal formation on woven bone tissue. **d** and **e** illustrate the cascade of repair showing that the entire gap does not repair itself with tissue at the same stage of differentiation across its entire width [80]. **f** At 1 week the cortical defect is filled with blood clot, fibrinous tissue and early mesenchymal cell deposition [46]. (Reprinted with permission from Shapiro F, Cortical bone repair. J Bone Joint Surg Am. 1988;70A:1067–1081). **g** Photomicrograph of a small section of the defect, 1 week after operation. The original pre-existing cortex is below and at the far right. A thin rim of lamellar bone (confirmed by polarized light) is seen against the cortex. It is lined with surface osteoblasts. At left, toward the center of the defect, woven bone predominates. **h** At 2 weeks early woven bone has formed by mesenchymal osteoblasts near the edge of the defect. The woven bone then serves as a scaffold on which lamellar bone is synthesized and shown here rimmed with a layer of surface osteoblasts. **j** At 3 weeks early remodeling (*upper left*) begins, with an osteoclast leading the way, as vessels from persisting cortex begins to relate to those in repair site. **k** At 4 weeks, vessels with osteoclasts and osteoblasts begin aligning the matrices of the lamellar bone along the same axis. **l(i)** Photomicrographs of the junction of repair bone with pre-existing cortical bone, 6 weeks after operation. Photomicrograph of a paraffin-embedded, hematoxylin and eosin-stained section shows the junction of the repair bone (*center left*) and the pre-existing cortex (*right*). Two vessels can be seen breaching the junction. The bone that fills the defect is densely packed and lamellar in conformation. **l(ii)** The same region was photographed through polarizing lenses. A sharp demarcation is noted between the repair lamellar bone (*dark, left*) and the pre-existing cortex (*light, right*), even though both are of the lamellar conformation, with differences that are scarcely discernible by regular light microscopy. The polarization indicated the main orientation of the collagen fibers in the lamellae. This will gradually remodel over several months to years to align the repair lamellae along the long axis of the bone. **m** Photomicrograph of a cross section of a site of repair 8 weeks after operation. The plastic-embedded, toluidine blue-stained section was photographed through polarizing lenses. The bone at the pre-existing cortex (periphery) and in the site of the former defect (center) is lamellar, but the *yellow–blue* color differentiation shows the dramatically different orientation of the fibers. Even though some remodeling is seen at the periphery of the defect, the predominant fiber orientation of the repair bone clearly differs from that of the pre-existing cortical bone. A similar appearance is seen at 12 weeks. **n** Radiograph of tibia at 3 weeks shows distraction gap with a central lucent region but good bone formation passing from each cortex towards the center of the distraction gap [45, 90]. **o** Repair from the gap region at 1 week shows undifferentiated mesenchymal cells above and blood cells and fibrinous material below. **p** At 2 weeks closer towards the persisting cortex at right woven bone is seen with surface osteoblasts beginning to synthesize lamellar bone, centrally woven bone synthesis is seen, and at left undifferentiated mesenchymal cells persist. **q** Also at 3 weeks, a higher power view shows woven bone formation immediately surrounded by surface osteoblasts (which will synthesize lamellar bone). **r** At 4 weeks the lamellar bone with surface osteoblasts begins to predominate nearer the original cortex with cell alignment along the longitudinal distraction and long bone axis. **s** By 6 weeks the gap is filled with new bone. This transverse section (to long axis of the bone) shows some initial woven bone (*deep purple*) surrounded by lamellar bone (*lighter purple*) and surface osteoblasts converting bone to the lamellar osteonal orientation

this model, since most of the cylindrical cortex remains intact, that bone repair without mediation of a cartilage phase occurs but there is a range of tissue differentiation across the entire defect owing to its relatively large size and irregular geometry. Repair does not occur uniformly with the same tissue pattern across the entire defect. The initial synthesis of repair bone at 1 week is woven and localized adjacent to the persisting cortex. The four-week specimen across the entire defect is extremely informative in terms of matrix deposition patterns since it captures the entire cascade of repair. Bone at the periphery which was originally woven is already being transformed into new osteonal lamellar bone adjacent to the persisting cortices. One can readily recognize the initially synthesized cores of woven bone around which lamellar

bone has been deposited into early Haversian systems. Closer towards the center of the defect woven bone predominates but some surface osteoblasts are now seen while in the center of the defect undifferentiated mesenchymal cells persist which are just differentiating into mesenchymal osteoblasts and beginning to synthesize woven bone (Fig. 2.8d, e). Repair was complete by 8 weeks with all bone tissue either remodeled or being remodeled to a lamellar conformation.

2.17.8.3 Direct Bone Repair (Circular Defect)

Cortical bone repair in rabbit femoral and tibial cortical defects produced by 2.4 mm unicortical drill holes has been assessed [46] (Fig. 2.8f–m). This also allows for repair in a specific environment of rigid stability with an intersegmental gap of a specific size. This mechanism is often referred to as gap healing but we refer to it as direct transformational bone repair. New bone formation begins in the marrow and advances into the base of the defect by one week (Fig. 2.8f). Initially, new bone synthesis occurs peripherally, apposed to the pre-existing rim of lamellar cortical bone. The initial deposits on the cortex have a distinct woven matrix conformation. The repair process is associated with a rich vascular front which initially forms from the marrow and moves into the defect at right angles to the long axis of the bone. There is no bone formation initially from the periosteum or from the Haversian intracortical systems. Bone formation does not occur at a uniform rate across the entire defect. As one examines an entire repair field from cortex to cortex, the central part of the defect is filled with mesenchymal cells and towards the periphery, repair is slightly more advanced with the mesenchymal cells having differentiated into mesenchymal osteoblasts which surround themselves with a woven bone matrix. By 2 weeks, the initially synthesized woven matrix at the periphery of the defect begins to be surrounded itself by a better oriented, essentially lamellar matrix, rimmed in orderly fashion by surface osteoblasts. By 3 weeks, repair bone has filled the defect. The accumulations of woven bone are now rimmed completely by plump surface osteoblasts and resorption of woven bone segments by multi-nucleated osteoclasts is underway. A distinction is seen between mesenchymal osteoblasts, which surround themselves with an osteoid matrix of woven conformation, and surface osteoblasts, which lay down osteoid in lamellar conformation on the previously synthesized woven matrix. The surface osteoblasts lay down bone in the lamellar conformation quite early once a scaffold of woven bone matrix has been deposited.

The proportion of lamellar bone increases quickly such that only a few cores of woven bone persist at 4 weeks. The lamellar repair bone becomes organized into the Haversian system-osteonal conformation. As the initial vascular ingrowth is from the marrow cavity, and as this pattern persists, the Haversian systems deposited are parallel to the vessels and at right angles to the Haversian systems of the cortex. The earliest signs of linkage of the intracortical Haversian vessels and vessels at the site of the defect are seen at 2 weeks, but they are more prominent by 3 weeks as multiple osteoclast cutting cones, followed by osteoblasts, form. By 6–8 weeks, Haversian systems from the pre-existing cortex are beginning to traverse the peripheral parts of the repair bone, but the alignment of the matrix and vessels of the repair bone throughout the site of the defect is still predominantly at right angles to the long axis of the cortex as long as 12 weeks after operation (Fig. 2.8i–k). Polarizing light microscopy shows lamellar repair but markedly different fibril plane orientation even several weeks after injury [Fig. 2.8l(ii), m].

The lamellar repair bone osteocytes are long, oval, and elliptical; their long axes are aligned parallel to the lamellation and thus perpendicular to the long axes of the lacunae in the adjacent cortical lamellar bone. The canaliculi are well developed and show the characteristic and more regular orientation of normal cortical canaliculi. The canaliculi in repair woven bone osteocytes pass out from the round cell bodies in poorly aligned fashion, whereas those from the elongated lamellar repair osteocytes are well aligned. At one week it is difficult to detect canaliculi in the woven bone, but by 2 weeks they are more in evidence.

This pattern for repair in circular defects is a well-documented phenomenon [81–83]. Close examination of several studies that used a cortical drill-hole model indicates that woven bone is sometimes formed initially at one week in defects that are as small as 0.2 mm as well as in 0.5-mm defects, the 2.4-mm defect that we reported, and the even larger oval defect in the chicken humerus. If defects as small as 0.2 mm demonstrate formation of woven bone initially, then much gap-healing in clinical situations occurs by the mechanism described as gap healing or direct transformational bone repair. Even when the mesenchymal cells pass directly to lamellar conformation—for example, when the gap measures 0.01 to 0.2–0.4 mm, the source and orientation of repair cells, vessels, and matrices indicate a different mechanism than truly primary trans-Haversian repair, in that osteonal remodeling must still occur. The presence of lamellar bone at right angles or perpendicular to the long axis of the bone implies a point of structural weakness not fully strengthened until remodeling the osteons of persisting and repair bone along the longitudinal axis [46, 72, 75, 77]. Studies of bone defect models in stable environments help to identify the specific effects on repair of the size and stability of the gap [73, 84] and the effects of mechanical stability on repair bone vascularity [85].

Monfoulet et al. [86] have studied drill hole defects in the mouse femur to identify pertinent models of cortical and cancellous bone regeneration. They also discussed other models for studying bone repair in a controlled environment.

Mechanobiology is the study of how mechanical or physical conditions regulate biological processes. Epari et al. [87] have reviewed in vitro models used to investigate the influence of mechanics on bone healing and regenerations. Known factors influencing repair characteristics include mechanical stability, interfragmentary movement, the strain rate and timing of mechanical loading, the number of applied loading cycles, defect size, the direction of loading (axial, shear, and torsional), and multidimensional factors such as axial compression, translational shear, and alternating compression and tension. The physical forces are converted into biochemical signals that affect the cellular responses and matrix synthesis [88, 89]. There is increasing recognition that shear strain and fluid flow are the 2 key mechanical stimuli that govern mesenchymal tissue differentiation. Mechanotransduction involves 3 main processes: mechanosensing (biochemical coupling), signal transduction, and effector-cell response. Differentiation, for example, to osteoblast or chondroblast lines significantly influences collagen type synthesis. Amongst possible mechanosensing mechanisms are the ion channels, integrins, G proteins, and the linkage between the cytoskeleton and certain phospholipase C isoforms. It is now recognized that cyclical or intermittent loading may be more effective than continuous loading inducing bone formation. Osteoblasts and osteocytes relate to adjacent cells via their processes in the canaliculi of bone and gap junctions. Integrins also play an informative role being transmembrane molecules attached at one end to the extracellular matrix and at the other to the intracellular cytoskeleton. Other signaling molecules are prostaglandin (PG), nitrous oxide (NO), and Wnt/B-Catenin. These factors need to be related as well to time defining both final healing and the influence of mechanics at intermediate time points of healing. The information gained from these mechanobiology studies has been incorporated into the design and principles of use of metal plates and rods for fracture and osteotomy stabilization and of external fixation systems for distraction osteogenesis for limb lengthening.

2.17.9 Distraction Osteogenesis

Another mechanism of bone repair is distraction osteogenesis, where bone formation occurs in a stable environment due to external fixation but one subjected to intermittent or continuous incremental lengthening. This mechanism was identified in relation to long bone lengthening to allow bone repair to occur without need for additional internal stabilization or bone grafting. Distraction osteogenesis of the tibia in a rabbit model using an external fixator illustrates the features of this mechanism [90] (Fig. 2.8n–s). Shortly after osteotomy blood clot is present within the marrow cavity and surrounding the osteotomy site. Histologic sections reveal a collection of the red blood cells within a fibrillar mass. The majority of initial repair emanates from the periosteal site but the marrow site is soon involved. There is a sharp demarcation of repair within the marrow cavity between the gap region where cellular responses are quite active and the persisting marrow which remains quiet virtually up to the line of osteotomy. At 3–4 days fibrinous clot is seen in the distraction gap with blood vessel and mesenchymal cell invasion from the persisting marrow cavity and rapidly reconstituting periosteum. At 7 days woven bone synthesis is noted with initial deposition on the cut cortical bone ends. Marrow vessel continuity is restored within several days after sectioning the intramedullary vasculature. At 14–21 days a central lucent zone in the widening distraction gap is present radiographically and a spectrum of regenerate bone is seen histologically. Repair is not uniform along the length of the distraction gap. Adjacent to cortical ends lamellar bone on initially deposited woven bone cores predominates and as repair is assessed toward the central zone correspondingly less mature repair tissue is seen ranging from woven bone to mesenchymal osteoblasts to undifferentiated mesenchymal cells at the central radiolucent regions. The sequence is repeated from the opposite cortical bone ends to the center of the distraction gap. There is a definite tendency for the newly synthesized woven bone to be aligned in longitudinal fashion parallel to and along the longitudinal axis of distraction (Fig. 2.8r). Intense osteoclast mediated resorption of the initially synthesized woven bone occurs along with repair. On occasion foci of cartilage are seen at the periphery of the distraction gap adjacent to the elevated periosteum. Cartilage does not form however in the gap tissues along the long axis of distraction. In specimens greater than 40 days post surgery reformation of a lamellar cortex and fatty marrow are seen. This mechanism of repair has been well defined at the histologic level by several investigators [91–96].

In most instances there is direct intramembranous bone formation. The initial response of the mesenchymal cell leads to the formation of osteoid which is present in random orientation characteristic of woven bone. The longitudinal distraction, however, tends to align the woven bone deposition along the long axis. The central region of the distraction gap is filled with the least differentiated mesenchymal cells. Shortly after woven bone has been

synthesized the osteoblasts align themselves preferentially on the surface and synthesize bone in a lamellar pattern. By 3 weeks the entire distraction gap has been filled with new bone. This is concentrated exclusively, however, in the cortical and sub-periosteal regions with some bone seen within the marrow cavity but essentially no new bone in the marrow proximal or distal to the osteotomy sites. With time the woven bone is absorbed and bone with a lamellar conformation deposited. The distraction model also shows the MOBL/SOBL interplay.

2.17.10 Other Mechanisms of Bone Repair via Fibro-osseous and Chondro-osseous Tissue Accumulations

For several decades, infrequent but recurring studies on bone development and repair have raised the question of other mechanisms, usually encompassing bone synthesis via fibro-osseous or chondro-osseous tissue accumulations. There is no doubt that these appearances can be seen on histological sections in some animal models and in human tissue descriptions. As a rule, such findings are associated with bone that is undergoing imperfect healing such as with pseudarthrosis or delayed union. The context where such repair can be seen is with relatively excess motion and relatively poor blood supply where both fibrous and cartilaginous elements are favored but stability is sufficient that bone repair is attempting to gain a foothold. This might help explain the finding of "chondroid" bone formation by some in distraction osteogenesis models in murine species [96]. Observations on chondrocytes directly synthesizing bone have been made from tissue culture and embryo studies of hypertrophic chondrocytes seemingly differentiating into osteoblast-like cells rather than all undergoing apoptosis [97, 98]. It needs to be recognized that many molecules are synthesized by both chondrocytes and osteoblasts and cannot be used to define one tissue type from another. As a general rule, these tissue accumulations do not underlie a dependable route for solid bone repair.

2.17.11 Metaphyseal Bone Repair

Fractures in metaphyses heal in a much more rapid fashion and with fewer problems than cortical fractures. There is direct bone formation without the need for extraperiosteal callus or cartilage formation since the fractures: (i) tend to be impacted and stable; (ii) occur in the highly vascularized metaphyseal marrow; and (iii) occur amidst bone trabeculae within the marrow which immediately present a very large surface area upon which new repair bone can be deposited. Fractures through the metaphyses show only a few millimeters of necrotic tissue while those in dense cortical bone have more extensive evidence of empty osteocyte lacunae. There has always been high clinical awareness of the tendency to rapid repair with metaphyseal fractures but several studies provided histologic evidence [69, 99, 100]. Charnley performed knee arthrodeses with a compression device after removing the cartilage surfaces and apposing flattened femoral and tibial metaphyseal tissue. Histologic biopsies taken by a core along the line of union 4 weeks post surgery showed bone repair with woven bone initially opposed to trabecular surfaces followed rapidly, in adjacent regions, by lamellar bone deposition. The repair was so efficient that there was only a slightly increased amount of bone tissue present. Repair trabeculae tended to link pre-existing trabeculae from femoral and tibial sides. There was absence of cartilage tissue, interpreted as evidence of a lack of interfragmentary mobility. The efficiency of repair was due to the fact that osteoblastic action was confined to bone surfaces which are extensive in cancellous bone compared to cortical bone. Charnley and Baker [99] observed that the woven bone trabeculae soon increase in thickness by surface deposition of new bone matrix, the fibers of which, instead of being arranged irregularly as in the woven bone, were arranged in sheets parallel to the surface forming imperfectly lamellar bone which, with time would become more mature. Uhthoff and Rahn showed the same findings in experimental animal models (rats, rabbits, dogs) in whom they made stable metaphyseal fractures [100]. As long as the fractures didn't displace, trabeculae throughout the region were lined with osteoblasts, cartilage did not form internally and no periosteal callus was observed. The closing of the gap occurred through the deposition of lamellar or woven bone on existing trabeculae or through interposition of woven bone.

2.17.12 Bone Repair Mechanisms in Clinical Settings. The Influence of Mechanical Stability

Knowledge of the several mechanisms of bone repair is important for optimal clinical management of fractures, osteotomies and bone fusion procedures and for the development of future operative and non-operative interventions to enhance bone repair. Bone has a remarkable ability to repair itself to full structural and functional effectiveness. The ideal end result of repair should be a complete reconstitution of lamellar bone oriented along the longitudinal axis of the bone, merged across the fracture site with a seamless

incorporation into the adjacent bone, and remodeled to the point of no indication as to where the fracture or osteotomy was. The biomechanical environment for repair, chosen to a great extent by the surgeon, leads to different mechanisms of repair but the end result of full repair is the same. If stabilization is by cast, splint or traction then the endochondral repair mechanism mediated through cartilage synthesis is activated. Motion between the fragments leads to the formation of external callus, the purpose of which is to enhance stabilization of the fragments. Rigid internal fixation with anatomic reduction, compression, and an absence of the interfragmentary gap can lead to primary bone union within the cortex along the Haversian canals. Much rigid internal fixation however, especially with osteotomies where segments of bone are removed and dissimilar cortices reapposed, leads to repair without external callus but by the mechanism of gap or direct transformational bone repair. Over the past several years there has been awareness that compression plates can cause localized devascularization and osteopenia leaving the underlying cortex weakened and subject to delayed fracture after plate removal. This has led to further innovations in plate stabilization, such as the limited contact dynamic compression plate (LC-DCP) [39], and locking plates with unicortical (or bicortical) fixation [40] where the tightness is between the plate and the screw rather than the plate and the underlying bone cortex surface. Perren has detailed the concept of ***biological internal fixation*** designed to minimize damage to the blood supply both by limiting periosteal elevation and lessening the direct bone contact and rigidity of plate stabilization [101]. This still allows for effective repair but switches the mechanism to direct transformational bone repair (gap healing) and in some instances to elements of endochondral bone repair for the biologic stabilization. Regardless of the techniques used, it is incumbent on the surgeon to understand and control the repair mechanisms being triggered.

2.17.13 Abnormalities in Bone Repair

Abnormalities of the bone repair mechanisms can occur and need to be understood and addressed.

2.17.13.1 Delayed Union

Delayed union refers to the situation where healing of a bone is delayed beyond the expected time range for full healing but the radiographic findings indicate that while healing is slower than normal it is occurring and there are not yet definitive signs to indicate that it will not occur with the current treatment approach. Clinically accepted ranges for healing in various age groups, sites, and with specific patterns of fracture/osteotomy and treatment techniques are known and, while not absolute, serve as the clinical frames of reference.

2.17.13.2 Non-union

Non-union refers to the situation where healing of a bone has not occurred well beyond the expected time range for full healing and the radiographic findings indicate that the healing is so poor that there are definitive signs that it will not occur with the current treatment approach. Such signs include a partial or full gap between the fragments without connecting bone, poor to absent periosteal new bone formation, increasing space or angulation between fragments, broken/bent/displaced internal fixation, increasing osteopenia of bone fragments (instead of increased density), or lytic areas of bone at fragment interface sites. The time frame for declaring a non-union is generally in the 6–8 month range. Non-unions are generally described as being hypertrophic [abundant callus formation with good vascularity but a persisting gap, due to inadequate mechanical stabilization], oligotrophic [minimal callus formation with biologic viability maintained], or atrophic [essentially no callus with minimal vascularity and often resorption of bone ends] [102].

2.17.13.3 Pseudarthrosis

Pseudarthrosis in the older orthopedic literature referred to specific clinical and radiographic findings indicative of a well-established non-union. The term refers to a false (pseudo) joint (arthrosis); the non-union is so well established that there is motion between the two fragments with fibrous or fibrocartilaginous tissue covering the fragment ends, a peri-osseous capsule stabilizing the two fragments (imperfectly) and often fluid and a partial synovial lining in and around the space between the 2 bones. This term is best used even today for this specific pathoanatomic series of findings.

2.17.13.4 Causes of Delayed Union, Non-union and Pseudarthroses

Many causes need to be considered.

(i) *Local causes* include excess motion between the fragments (instability), poor blood supply, interposition of muscle or excess periosteal/fibrous tissue between fragments, distraction of fragments, stabilization of fragments with too large a gap, excessive soft tissue damage, and periosteal stripping at the fracture site.
(ii) *Systemic/Extrinsic* causes include infection, severe anemia, malnutrition (low protein), or collagen defects (severe osteogenesis imperfecta).

Surgical and medical interventions are usually needed to treat formal non-unions or pseudarthroses by eliminating or overcoming the local and systemic causes.

2.17.14 Biological Augmentation of Bone Repair

2.17.14.1 Biological Conditions Necessary for Bone Repair

Once mechanical stability is achieved, several biological conditions are needed for bone repair to occur. These include:

(a) *An osteoconductive matrix*. This refers to the scaffold upon which the new bone is deposited to allow for continuity between and healing with the fragments of bone. The matrix provides stability onto which the bone repair cells can grow and sufficient space for repair cells, new matrix and vascularity to inter-relate.
(b) *Osteoinductive signals*. These refer to the proteins and growth factors allowing mesenchymal cells to differentiate along the bone forming line to synthesize the collagen matrix to fill the gap and bind to the pre-existing bone fragments.
(c) *Osteogenic cells*. These cells are sufficiently differentiated to be able to synthesize bone matrix and allow for mineralization along the pre-existing or newly provided scaffold.
(d) *Vascularity*. Bone repair only occurs in a well-vascularized environment. Undifferentiated mesenchymal cells accompany blood vessels into all sites of bone development and repair.
(e) *Osteointegration*. The repair bone must interdigitate seamlessly with the adjacent bone matrix of the fragments.

2.17.14.2 Stem Cells

Bone is formed, as are all tissues, from initially undifferentiated cells that are eventually directed to a bone forming line of osteoblasts. Much research is currently directed to inducing primitive stem cells to differentiate into a bone forming line. Tseng et al. [102] have defined the stem cell pool as it relates to augmenting bone repair. The definitions below are from their descriptions.

Stem cells: primitive, unspecialized cells with the ability for indefinite self-renewal and the ability to differentiate into distinct lineages of mature cells.

Stem cells can be: *totipotent* (ability to transform itself into every type of cell in the adult body and cells of extra-embryonic tissue required for fetal development, that is the fertilized egg and cells produced by early cleavage post-fertilization); *pluripotent* (maintaining the capacity to divide into the 3 main types of body tissue—endoderm, mesoderm, and ectoderm and give rise to any post-fetal specialized cell type); and *multipotent* (can self-renew but only to differentiated cells and matrices of a particular tissue).

Stem cells can be: *embryonic* (ESCs—embryonic stem cells—are pluripotent cells isolated from the inner cell mass of the blastocyst that can be propagated indefinitely in an undifferentiated state) and *adult* (multipotent cells found in specific tissue compartments with more limited regenerative capability). In a review of stem cell-based bone repair Fei et al. [103] pointed out that ESCs are derived from human embryos, have a possible immune response and some tumorigenic potential. Adult stem cells (mesenchymal/stromal stem cells [MSCs]) are autologous and can still differentiate to osteoblasts when derived from bone marrow. While they can simply be injected into the site needing augmentation, to be truly effective they need to be expanded in vitro and then given. Fei et al. [103] have reviewed the experimental use of BMSCs to generate bone in animal models and in a few clinical studies. Other features of the use of mesenchymal stem cells in bone repair have been reviewed by Khosla et al. [104].

Adult stem cells are well defined as hematopoietic stem cells differentiating into cells of the circulating blood and immune systems and mesenchymal stem cells in the non-hematopoietic bone marrow but also in compartments in periosteum, muscle, dermis, synovial membrane, and adipose tissue. It is the mesenchymal cell pool that can be induced into the tissues of tendon, bone, cartilage, muscle and ligament.

In a further definition of a stem cell, it has the capacity for self-renewal by dividing asymmetrically. One cell is exactly like the mother cell (self-renewal) but the other cell moves along the differentiation pathway more advanced than the mother cell [105].

Reviews on current and investigational efforts to enhance bone regeneration show the wide spectrum of approaches taken and the biologic bases of those approaches [105–107].

2.17.14.3 Undifferentiated Mesenchymal Cells

The undifferentiated mesenchymal cell is the basic cell type enhancing bone repair as it has the potential to differentiate along the preosteoblast to osteoblast line in the proper environment. Stem cells isolated from bone marrow and expanded in research laboratories are now being used (in autograft fashion) to augment bone repair in the pediatric population. At a more basic level, drilling is often performed through necrotic or densely sclerotic bone to the underlying normal marrow to allow for revascularization which carries

with it undifferentiated mesenchymal cells which can then differentiate along a pre-osteoblast to osteoblast line. Another way to supplement the number of mesenchymal stem cells at repair sites is to locally insert bone-marrow aspirate from the iliac crest of the patient. This can be as simple as direct transfer although cell number is increased by further concentration of the bone-marrow post-aspiration [106].

2.17.14.4 Molecular Enhancement

Amongst the molecules used most commonly clinically to enhance bone repair are recombinant human bone morphogenetic protein-2 (rhBMP-2), rhBMP 7 (OP1), vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF beta), and platelet derived growth factor (PDGF).

Bone Morphogenetic Protein (BMP). The BMPs are potent osteoinductive factors which induce the mitogenesis of mesenchymal stem cells and their differentiation towards the osteoblast cell line [105–109]. At least 16 BMPs have been identified but BMP2 and BMP7 are the most potent bone cell stimulants. Since the early 2000 s they have been used clinically as recombinant forms rbBMP2 and rbBMP7. With the exception of BMP1, the BMPs belong to the TFG-β superfamily. Much of the investigative work on the clinical use of BMPs relates to the optimal delivery systems since local application is essential for effective function (they are cleared quickly with systemic use) and effectiveness is increased the longer the factor is present at the repair site. Many different carrier materials have been used such as demineralized collagenous bone matrix, resorbable polymers such as polyactide, gelatin hydrogels, and calcium phosphate ceramics [108].

Platelet-Rich Plasma (PRP). Platelet-rich plasma is an autologous blood product with platelet concentrations above baseline that is being used increasingly to enhance bone and soft-tissue (i.e., tendon, ligament) healing [106, 110]. The platelets have an extensive store of such growth factors and cytokines as platelet derived growth factor (PDGF), TGF-β, insulin-like growth factor (IGF-1) and vascular endothelial growth factor (VEGF). The effects on repair for the most part have not been significant so far in most studies [109].

Fibroblast growth factor 9 (FGF9). Fibroblast growth factors 2, 9, and 18 and the receptors (FGFR) 1-3 play a major role in skeletal development [52] but have not been studied in detail in bone repair. Recently FGF9 was found to play a role enhancing bone repair in a mouse model. It was suggested that FGF9 was involved by helping to initiate angiogenesis through VEGF-A.

Angiogenesis and Bone Repair. Since vascularization is an essential pre-requisite for bone repair, delivering the mesenchymal cells to the repair site, molecular stimulation of angiogenesis could also serve to enhance bone repair [107]. Street et al. [111] showed that exogenous VEGF enhanced blood vessel formation, ossification, and new bone formation in mouse femur fractures and promoted bone bridging in a rabbit radius segmental defect; conversely a VEGF inhibitor decreased angiogenesis and dramatically inhibited healing of a tibial cortical bone defect. The main factor currently identified in enhancing angiogenesis is VEGF but other involved factors include FGF, TGF-β, PDGF, and IGF. Combinations of angiogenic and osteogenic factors can be effective in stimulating bone healing and regeneration [107]. Experimental combinations showing benefit have been VEGF and BMP2 and VEGF and PDGF.

2.17.14.5 Autograft Bone Graft

Autograft bone graft still plays an essential role to fill space (osteoconductive effect), stabilize deformity correction (primarily with pelvic procedures), and enhance repair (osteoinductive effect by mesenchymal and pre-osteoblast cells). Cortico-cancellous bone from the iliac crest or from the proximal femur after varus or valgus osteotomies is the most common source in the pediatric patient. The grafts provide both osteoinductive and osteoconductive effects with immediate intraoperative placement.

2.17.14.6 Allograft Bone Graft

Allograft bone graft is useful to provide an osteoconductive scaffold effect. It is used in the pediatric population primarily with spinal fusion surgery and pelvic acetabular repositioning and augmentation (shelf) procedures. It is generally obtained from human cadavers and further devitalized by irradiation or freeze-drying. It comes in many preparations—cancellous (varying fragment sizes), cortico—cancellous, cortical, and whole bone cylindrical segments. It is exclusively a scaffold and/or structural spacer.

2.17.14.7 Bone Graft Substitutes

The limitations of autografts (donor-site morbidity) and allografts (infection, disease transmission) have led to the development of bone-graft substitutes or matrices [112]. A variety of materials is used including polymers (natural and synthetic), ceramics and combinations of the two. They need to have similar three-dimensional characteristics of autograft tissue so they can allow for vascular, cell, and new bone ingrowth and often for the delivery of growth factors and antibiotics as well. Pore size, pore interconnectivity, and total porosity are essential in scaffold development.

Polymers. Different polymers provide different physical attributes, mechanical properties, degradation times, and modes of degradation. Natural polymers used include type I collagen, hyaluronic acid, fibrin, and chitosan and synthetic polymers are polyanhydrides, polylactic acid (PLA), polyglycolic acid (PGA), and polypropylene fumarate to name a few.

Ceramics. Ceramics are compounds made from inorganic, non-metallic materials that possess a crystalline structure. They have a high level of stiffness but tend to be brittle. Ceramics in use include calcium phosphate, calcium sulfates, tricalcium phosphate, and bioactive glass. They are similar to bone since the inorganic component of bone is the ceramic calcium hydroxyapatite. They have a slow rate of degradation.

Polymer-ceramic composites are also available. The substitute matrices come in both preformed and injectable preparations. The injectable matrices are initially in a liquid or gelatinous state, are flowable, and will then harden in an aqueous environment at body temperature.

2.17.14.8 Tissue Engineering

Tissue engineering seeks to generate viable bone using principles derived from orthopaedic surgery, biology, physics, and materials science. It requires input from: (i) *progenitor cells* (mesenchymal stem cells and osteoblast lineage cells); (ii) *biocompatible porous scaffolds/matrices* of appropriate three-dimensional architecture with sufficient space for vascular and cell ingrowth, surface chemistry to accept bone matrix deposition, mechanical properties (strength, modulus, toughness, ductility), and composition to allow for eventual replacement by reporption/degradation; and (iii) *bioactive growth factor molecules* which can direct stem cells and progenitor cells along the bone forming cell lineage.

The pre-requisites for bone regeneration include:

Osteoinductivity—stem cells (mesenchymal) and progenitor cells to differentiate along the bone forming line;
Osteogenicity—pre-osteoblasts and osteoblasts to synthesize bone matrix capable of mineralizing;
Growth factors—to stimulate and direct the cells involved in osteoinductivity and osteogenicity;
Mechanical stability—to allow vascular invasion and interfragmentary or gap healing;
Osteoconductivity—appropriate scaffolds on which new bone is synthesized;
Biocompatible matrices—natural or synthetic scaffolds (matrices) that must be accepted by the body;
Osteointegration—interdigitation of repair and persisting matrices in a structurally stable fashion;
Resorption/Degradation—scaffolding to resorb or degrade over time with complete structural repair and matrix remodeling.

The tissue engineering concepts are expanded on in several articles [102, 105–110, 112, 113].

2.18 Mechanisms of Cartilage Repair

Cartilage repair occurs by different mechanisms depending on which type of cartilage has been injured. In this section we will review repair of articular cartilage and of physeal cartilage.

2.18.1 Repair of Articular Cartilage

Articular cartilage possesses a limited capacity for complete repair in contrast to bone which has the potential to repair itself completely and reconstitute its original structure. While no meaningful repair of the cartilage occurs in partial-thickness lesions (limited to the cartilage itself), many studies have demonstrated that cartilage repair is initiated after creation of a full-thickness defect that penetrates through the subchondral bone into the cancellous bone of the marrow cavity. In full thickness defects undifferentiated mesenchymal cells from the bone marrow enter the defect and have the potential to differentiate along a cartilage line.

It has been recognized for hundreds of years that articular cartilage has an extremely limited capacity for self-repair. William Hunter noted in 1743 that from Hippocrates to the then present age it was universally agreed that ulcerated cartilage was a troublesome thing and once destroyed it was never repaired [114]. Redfern in 1851 performed a series of experimental studies on articular cartilage in dogs as well as examining human cartilage pathology [115]. The work involved use of microscopy. Cartilage repair differed from other tissues since "articular cartilage contains no blood vessels, consequently ulceration and other changes of structure confined to it are never complicated by inflammatory exudations …" He also recognized that articular cartilage contained no nerves. His experimental and observational studies referred to what we today call partial thickness injury since he was describing repair capabilities in the absence of blood vessels. Redfern clearly recognized that remaining non-damaged cells of cartilage were those involved in any repair. In short, the cartilage repaired itself by a fibrous tissue. He made linear cuts into the articular cartilage of the patella and femoral condyles in dogs. Some studies were assessed as long as 24 weeks post-injury. He concluded "that wounds in articular cartilage are capable of perfect union by the formation of fibrous tissue out of the texture of the cut surfaces. The essential parts of the processes appear to be the softening of the inter-cellular substance of the cartilage, the release of the nuclei of its cells, the formation of white fibrous tissue from the softened inter-cellular substance, and of nuclear fibres, by the

elongation of the free nuclei." (By 'perfect union' Redfern refers to the stable healing between the fragments which are firmly united not to full reconstitution of articular cartilage.) Redfern thus recognized that the cells of articular cartilage, even though in a non-vascular space, played a role in tissue healing with a tendency to repair by fibrous tissue and by means of increasing cellularity, some of which appeared in what we now describe as chondrocyte clones. Most subsequent authors, while generally accepting the mechanism described by Redfern, felt that the healing is even less prominent in terms of uniting across the defect [116]. Redfern further elaborated by indicating that "ulcers in articular cartilages heal by transformation of the surrounding cartilage tissue into fibre …."

Paget who was both a surgeon and pathologist stated in 1853 that "there are, I believe, no instances in which a lost portion of cartilage has been restored, or a wounded portion repaired, with new and well-formed permanent cartilage, in the human subject." [117].

Mankin's [116, 118] and Campbell's [119] reviews of the response of articular cartilage remain valuable in summarizing the extensive subsequent work in this area. Over the following century work continued on many animal models to assess the nature of articular cartilage repair.

Partial-thickness defects refer to damage which leaves the lowermost calcified zone of the articular cartilage and the subchondral bone intact and thus prevents invasion of blood vessels and undifferentiated cells which could participate in a repair response.

Full-thickness defects refer to damage that passes through the calcified zone and subchondral bone into the epiphyseal bone allowing for invasion of blood vessels and undifferentiated cells into the articular cartilage where they can participate in a repair response.

It is recognized that chondrocytes from immature cartilage are capable of mitotic activity but adult chondrocytes have little potential for cell replication [119]. Adult cells however can increase synthesis of intercellular components to a limited extent in the presence of a need for repair.

Superficial, partial-thickness defects. Mankin indicated that "numerous studies have defined the relatively meager and, indeed, ineffectual response of articular cartilage to lacerating injury" [118]. The response was limited by the lack of the inflammatory and repair components as seen in vascularized tissues. There was evidence that "increased anabolic and catabolic activity accelerate through the first few days after injury but are short-lived …." Studies showed no evidence for complete repair even in young animals. Even minimal defects were not repaired.

Full-thickness defects into subchondral metaphyseal bone. A significant repair response was observed by many studies with full-thickness defects, beginning as early as the late 1800s [118]. It was recognized in experimental studies and assessment of fractures extending through the articular cartilage that repair was by fibrous or fibrocartilaginous tissue or, at best, by abnormal hyaline cartilage and that it occurred from cells arising from bone marrow or synovial membrane with occasional contribution of adjacent articular cartilage. Some observers noted a hyaline-like chondroid repair which regressed over time back to a more fibrous structure.

An extensive amount of experimental work was done on clarifying cartilage repair. Bennett et al. [120] performed numerous lesions of cartilage of femur in immature and mature dogs with study from 4 to 28 weeks with microscopy. They clearly pointed out the importance of differentiating between repair of lesions of cartilage with injury to subchondral bone and repair of lesions made entirely within articular cartilage. This then allowed for an understanding of repair mediated by proliferation of connective tissue from neighboring tissues in the former compared with independent regeneration of cartilage in the latter. A study of their own work and a review of the work of others [121–123] led to the observation that lesions which did not reach to subchondral bone did not heal at the borders of the defect and that if connective tissue or fibrocartilage was found in the defect closer inspection would find some area of injury to the subchondral bone.

Many observers noted death of cartilage cells (empty chondrocyte lacunae) adjacent to the site of injury (regardless of depth) and intracartilaginous increase of clustered chondrocytes in injuries contained within cartilage with however no repair or minimal repair at best. Many (see [124]) showed that when repair occurred it did so from cells gaining access from adjacent tissues and passing through the stages of fibrin formation, granulation tissue, fibrous tissue and transformation or metaplasia into cartilage (usually via a form of fibrocartilage). Bennett et al. [120] reported "that adult articular cartilage does have a limited ability to repair aseptic lesions within its substance by independent regeneration of cartilage. The powers of such regeneration, however, are feeble and not always demonstrable." This was their first type of repair. The second type provided an outside source of cells from a surrounding pannus (vascularized connective tissue) which spread over and into the defects from the articular margins. The original source could be the synovial membrane or adjacent ligament attachment with tissue passing onto the surface (pannus) and fibroblasts entering into the fibrin clot and beginning their transformation at the superficial levels adjacent to the articular surface. They also comment that "the great variety of ways in which mesenchymal cells may differentiate or dedifferentiate because of location and function, causes one to consider also the possibility of detached synovial cells becoming implanted in such a mass of fibrin, growing as fibroblasts and thus taking part in the organizing process." (This idea

has been raised again in more recent studies.) The third mechanism was where lesions extended into subchondral bone allowing vascularized tissue with mesenchymal cells to pass into the defect from below.

They concluded that in 4 of 6 defects that were entirely in cartilage and not covered by pannus, proliferation of cartilage cells was seen but repair was never complete and repair tissue filled only a small portion of the defect [125]. Where defects extended into subchondral bone repair or where pannus invaded from the surface the repair passed through stages of fibrous tissue and fibrocartilage to an imperfect form of hyaline cartilage. "The fibrous tissue originated in the connective tissue of the bone marrow, in the marginal synovial membrane and apparently, in some instances, from articular cartilage cells".

Shands, in his classic study, showed repair in full-thickness defects by a mechanism progressively revealing fibrin to granulation tissue, to connective tissue, to cartilage cells in connective tissue, to fibrocartilage, and then into hyaline cartilage [124]. He also wrote an extensive review of previous articular cartilage repair studies.

Subsequent studies continued with these animal models to expand on and define these observations. Meachim created partial-thickness linear lesions cut by scalpel in mature rabbit knees [126]. Multiple cuts were made in the patellar and femoral groove cartilages followed by histologic (toluidine blue) and autoradiographic studies focusing on the proteoglycans and mucopolysaccharides. No significant translesional repair was noted up to 34 weeks. There was loss of intercellular matrix in the lesional regions and also synthetic responses (short-lived, about 4 weeks) leading to increased proteoglycan synthesis and chondrocyte clusters (indicative of cellular hyperactivity).

DePalma et al. [127] studied partial- and full-thickness defects in the distal femoral condyles of mature and immature dogs with follow-up as long as 66 weeks. Partial-thickness defects not involving the subchondral bone showed no significant reparative change up to 66 weeks both in mature and immature dogs in weight-bearing or non-weight-bearing cartilage regions. In full-thickness defects passing through subchondral bone there was complete filling with immature cartilage by 16 weeks. The new cartilage was derived from subchondral granulation tissue which through fibrous tissue metaplasia produced a tissue which histologically appeared to be cartilage.

Calandruccio and Gilmer [128] reported that proliferation of superficial articular cartilage in dogs could in a few instances repair a defect.

Fuller and Ghadially [129] made partial thickness defects with a thin shaving approximately 2 mm in diameter of distal femoral cartilage in immature rabbits (great care being taken to keep the lesions partial-thickness). Light and electron microscopic studies failed to show a significant repair reaction capable of filling the defect.

Mitchell and Shepherd showed cartilage repair at multiple full-thickness perforations through subchondral bone in adult rabbit femurs [130]. The material resembled hyaline cartilage, resurfaced the joint by 4–6 months, did not effectively bond to the adjacent cartilage (based on the histologic sections shown) and then degenerated to fibrous tissue after one year.

2.18.1.1 Detailed Description of Repair of Full Thickness Articular Cartilage Defects

Histological observations have been made in repair models of full-thickness cartilage defects in the rabbit [131]. After 2.4 mm wide defects the following observations apply. These observations accurately represent the nature of the repair response with the microfracture technique for osteochondral defects in the human.

A few hours after drilling, the defect was noted to be filled with blood clot. The observations were made on histologic preparations examined by light and polarizing microscopy. One day after the procedure, a fibrinous net-work appeared, with bands aligned superficially along an arc passing from one edge of the defect to the other. At 2–5 days, the superficial fibrinous scaffold was organized in an arcade array (Fig. 2.9a, b). Spindle-shaped, undifferentiated mesenchymal cells were present: they had advanced, along with blood vessels, from the marrow spaces into the periphery of the clot. At 3 days, mesenchymal cells were prominent at the periphery of the defect and had migrated toward the center of the clot. In the depths of the defect, the marrow contained many active osteoblasts synthesizing woven bone. Organized invasion of capillary vessels from the marrow continued. At 5 days, capillary vessels from the adjacent marrow and undifferentiated mesenchymal cells filled the entire defect.

By 1 week, the clot had been completely removed from most sections. The surface fibrinous arcade persisted and was infiltrated extensively with mesenchymal cells (Fig. 2.9c, d). The fibrous strands appeared to serve as a scaffold, orienting the undifferentiated mesenchymal cells so that, superficially, they lay parallel to the long axis of the strands. Synthesis of woven bone had progressed from the depths of the defect adjacent to the living, persisting marrow trabeculae (Fig. 2.9e, f). There were no viable chondrocytes in the articular cartilage immediately adjacent to the defect, as indicated by empty lacunae [Fig. 2.9g(i, ii)]. The area of necrotic cartilage cells adjacent to the drill-hole was approximately three to ten cell-columns wide.

The first evidence of synthesis of a cartilage extra-cellular matrix, as indicated by the staining of the matrix by safranin O, was observed at 10 days [Fig. 2.9g(i, ii)]. The cartilage matrix was synthesized initially between the superficial

fibrous stroma and the deeper areas of newly formed woven bone. By 12 days, an increasing number of the mesenchymal cells, beneath the superficial layers of fibroblast-like cells, had differentiated into chondroblasts, and many of these were now typical chondrocytes located in lacunae surrounded by safranin O-stained cartilage matrix.

By 2 weeks, the cartilage repair tissue had reached the surface level of the normal articular cartilage at the sites of several defects (Fig. 2.9h, i). In these repair sites, there was a thin surface layer of safranin O-negative (green) extracellular matrix with flattened, fibrocartilage-like cells, beneath which was a deeply safranin-O-stained cartilage matrix with abundant chondrocytes. The chondrocyte lacunae in the residual cartilage bordering the edge of the drill-hole usually remained empty. In the non-viable residual cartilage adjacent to the drill-hole, the cartilage cells had not been replaced either by cells of the remaining normal cartilage or by newly differentiated chondroblasts from the defect. In addition, the extracellular matrix had not been resorbed. The repair tissue at the periphery of the defect usually appeared well apposed with the residual cartilage on light microscopy. However, polarized light microscopy revealed that the collagen fibrils of the repair tissue were not well integrated with those of the residual cartilage (Fig. 2.9j). In some specimens, the repair tissue was separated from the residual cartilage and adjacent bone by a gap (Fig. 2.9k). These are critical observations that have an effect on the survival of the newly synthesized cartilage.

At 16 days, the surface of the repair cartilage remained level with the surface of the adjacent original cartilage. A large number of chondrocytes was seen in a central triangular wedge of cartilage tissue, located just beneath the surface and extending into or toward the mid-section of the repair tissue. At a deeper level, there was abundant woven bone. Most of the chondrocyte lacunae in the normal, original articular cartilage immediately adjacent to the drill-hole remained empty, although some chondrocyte-cloning was seen at the edges of the original cartilage.

A well demarcated layer of chondrocytes was observed in the sites of almost all of the defects at 3 weeks. Although, in a few of the specimens, the surface layer of the repair cartilage was slightly depressed compared with the surface of the adjacent normal cartilage, in most specimens, the surface of the repair cartilage remained at the same level as that of the adjacent original cartilage at this stage. The most superficial layer of the repair cartilage was more fibrous than the normal surface layer, but it was still similar in histological appearance to the tangential or surface zone of normal articular cartilage. Hypertrophic chondrocytes were now seen at the deeper levels of the chondrocyte layers and participated in a true endochondral sequence. Deep to this, the marrow had continued to synthesize intramembranous woven bone directly.

At 4 weeks, virtually all of the defects had a well-developed layer of typical articular cartilage containing chondrocytes (stained red with safranin O) just below the superficial, more fibrous layer of the flattened fibro-cartilaginous cells. Many sections with excellent repair were seen and, in those with the best repair tissue (Fig. 2.9l), fibrillar continuity between the repair and the residual cartilage, as seen on polarized light microscopy, was also good (Fig. 2.9m). Chondrocytes deep within the cartilage layer had continued to undergo the typical sequence of differentiation, hypertrophy, and degeneration seen in the endochondral sequence. Bone deposition on the cartilage cores had also occurred. At this time, many of the defects had been repaired and reconstituted with typical articular cartilage; the defects now consisted of a well-formed layer of articular cartilage containing viable chondrocytes, with the level of the repair cartilage continuous with that of the adjacent normal cartilage. There was generally very good physical apposition of the repair cartilage with the edge of the original, normal articular cartilage that composed the wall of the defect, but there was no evidence of replacement of the dead chondrocytes or of resorption and reconstitution of its extracellular matrix. In a few sections, a very thin separation was observed at the interface between the repair cartilage and the normal cartilage lining the wall of the drill-hole defect.

At 6 weeks, as in the previous stage of repair, the cartilage matrix was strongly stained with safranin O, but it was covered with a surface layer containing flattened, fibrocartilaginous cells. The surface layer at this stage tended to be somewhat thicker than that of the normal cartilage adjacent to the defect. Hypertrophic chondrocytes persisted in the deeper parts of many defects. Sections in which there appeared to be close apposition between the repair and the residual cartilage on light microscopy continued to demonstrate a lack of fibrillar continuity on polarized light microscopy (Fig. 2.9n).

There was a well-developed, regenerated hyaline articular cartilage in most of the defects at 8 weeks (Fig. 2.9o, p). The subchondral bone was more mature as a result of remodeling. The repair cartilage at this stage was always more cellular than the adjacent normal cartilage, except in a few instances in which the fibrous layer on the surface of the cartilage was hypocellular or acellular. In most of the defects, the chondrocyte layer was level with the adjacent normal cartilage, but in a few (as noted earlier), the surface of the repair cartilage was somewhat depressed. It is important to note again that the chondrocyte lacunae of the immediately adjacent layer of normal articular cartilage

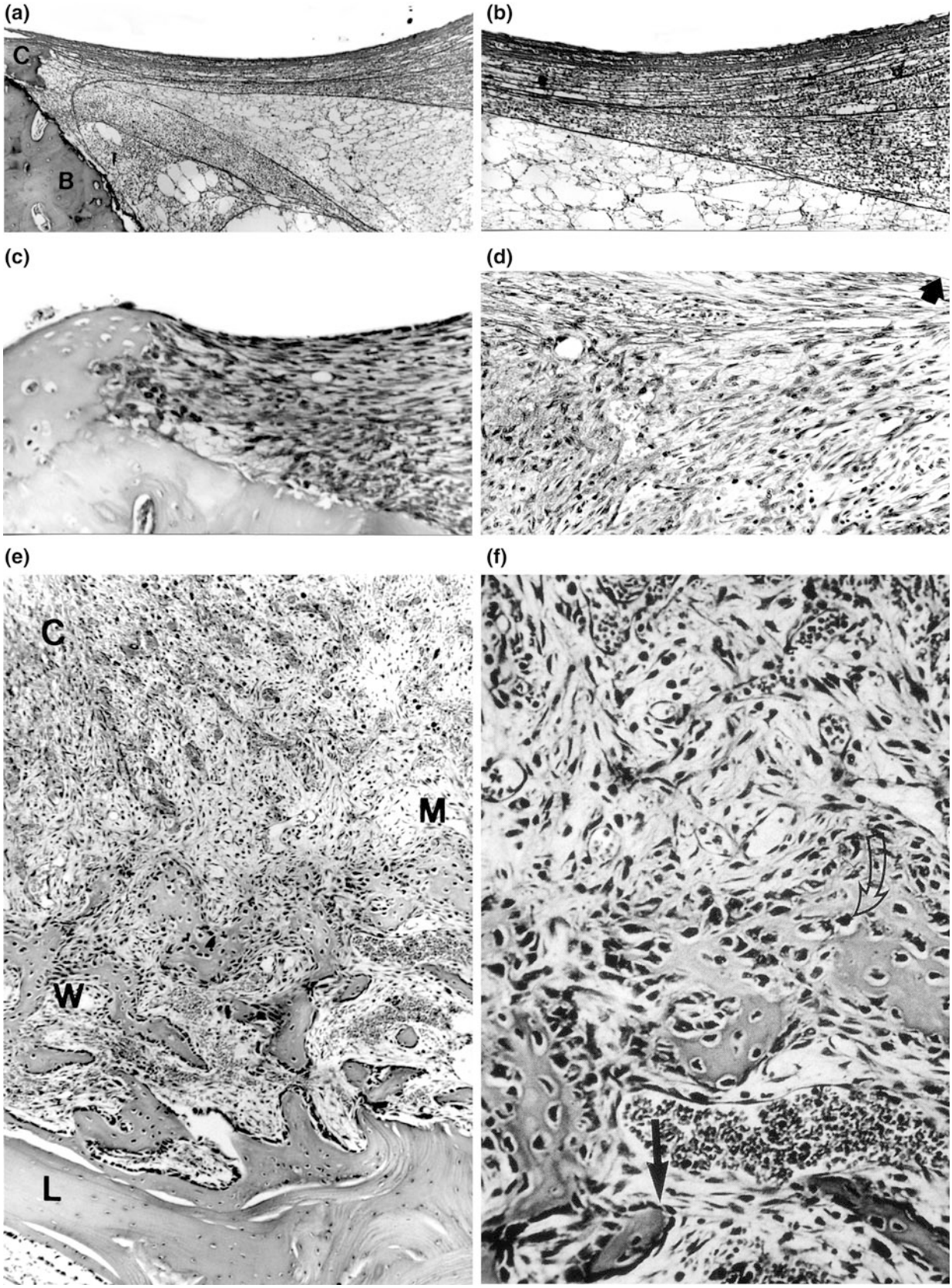
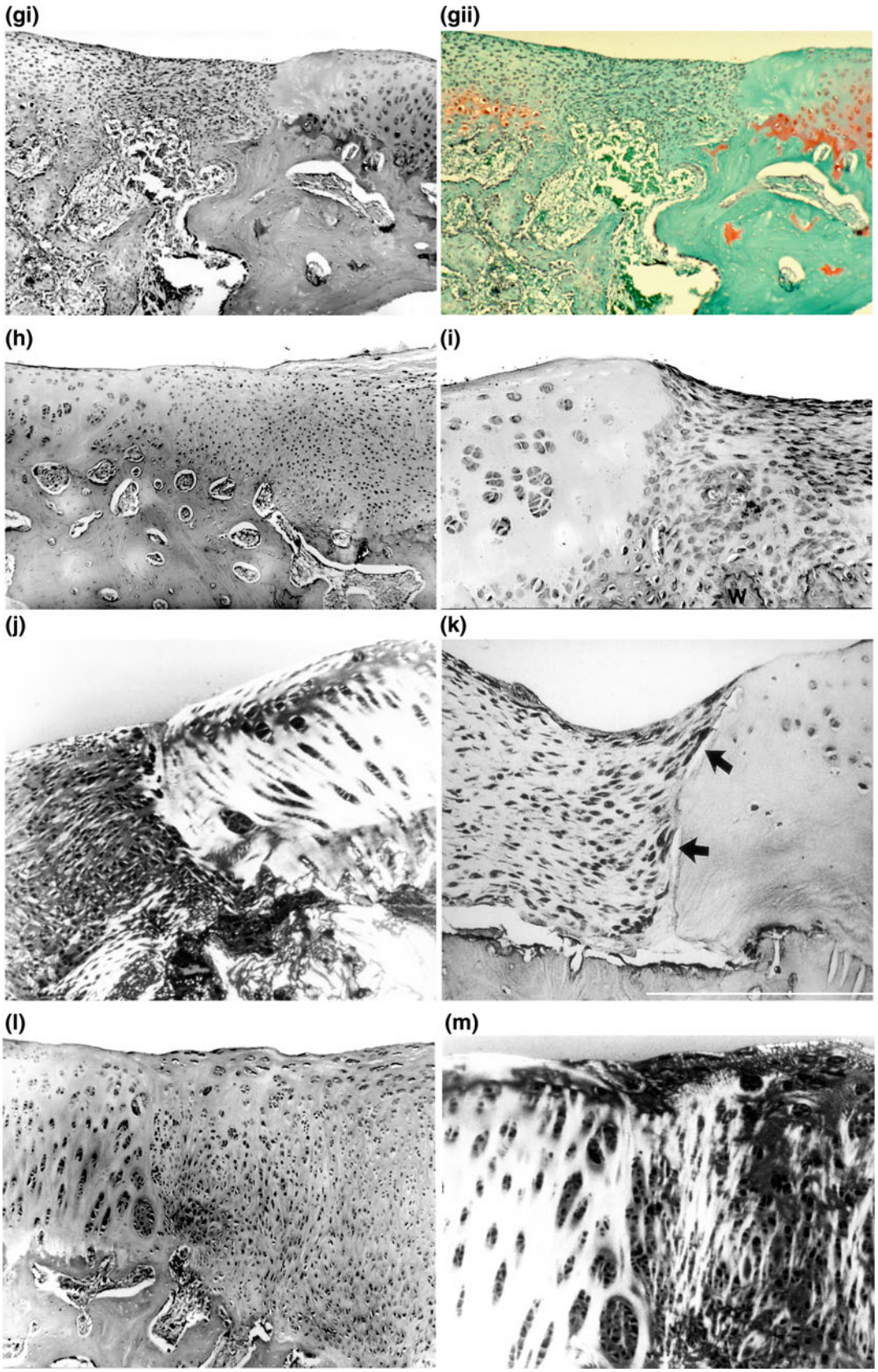


Fig. 2.9 (continued)



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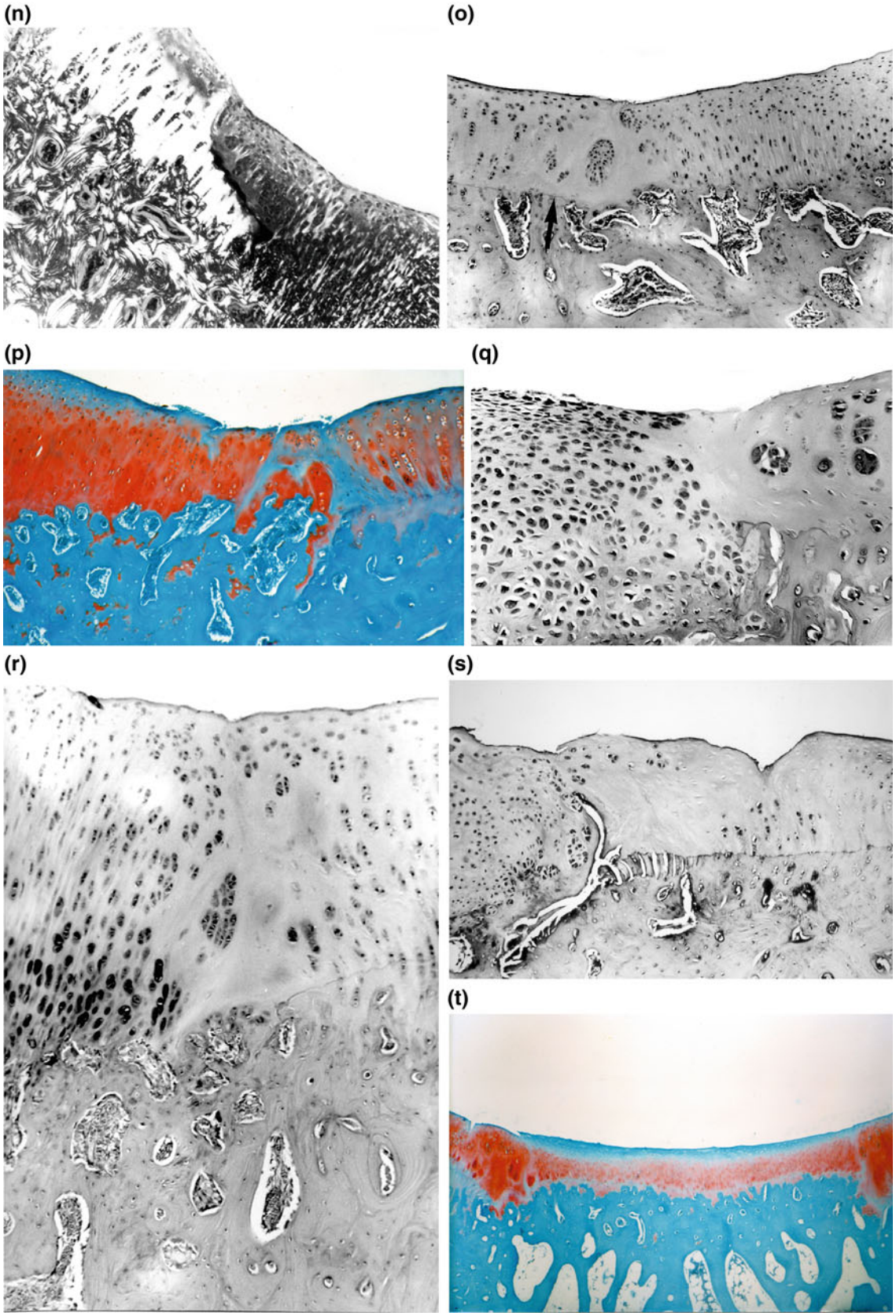

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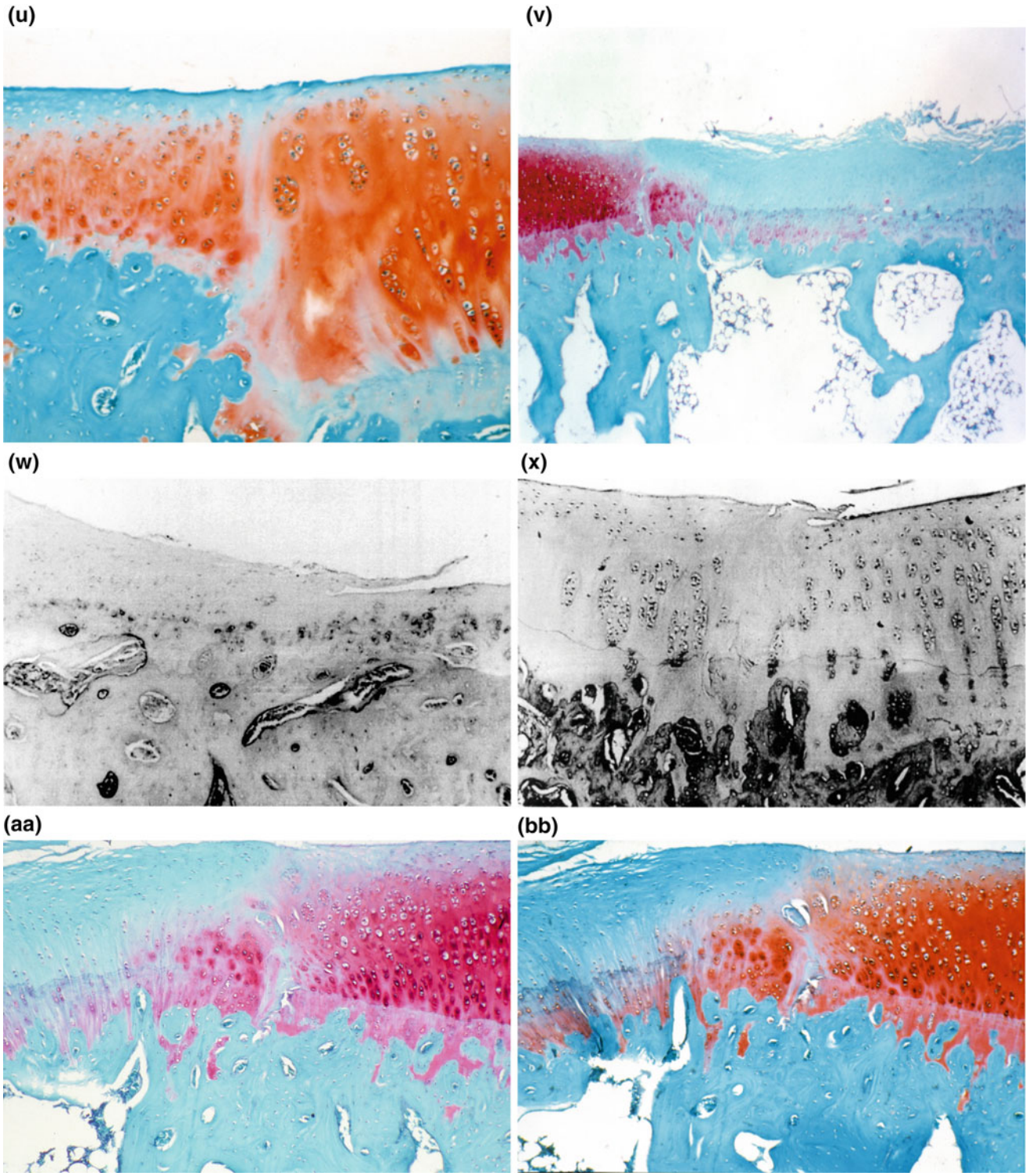


Fig. 2.9 (continued)

remained empty. In many instances, there was persistent chondrocyte cloning at the base of the normal cartilage.

At 10 weeks, the appearance of the repair articular cartilage had changed little, but some early degenerative changes were seen (Fig. 2.9q, r). The surface of the repair cartilage, in most instances, remained level with the adjacent normal articular cartilage. The repair cartilage was often seen to be intimately apposed to the persisting cartilage on light

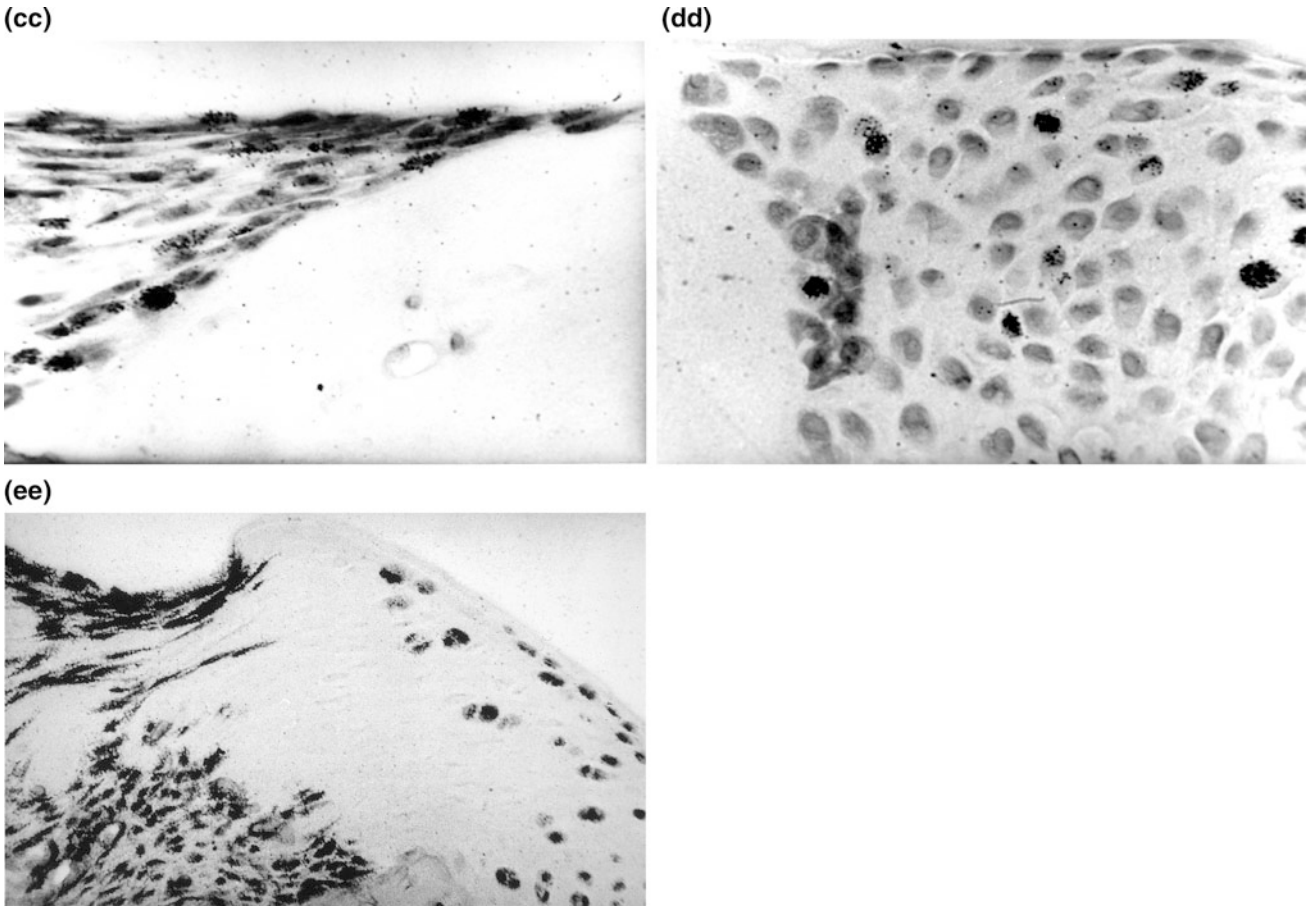


Fig. 2.9 Mechanism of cartilage repair in full-thickness defects of articular cartilage in a rabbit model is illustrated from 5 days to 48 weeks post-surgery. (Reprinted with permission from Shapiro et al. Cell origin and differentiation in the repair of full-thickness defects of articular cartilage. J Bone Joint Surg Am. 1993;75A:532–553). **a** Photomicrograph, 5 days after creation of the defect, showing fibrinous arrays at the surface of the defect. These were seen as early as 2 days postoperatively. There are fibrinous strands across and within the site of the defect. The articular cartilage (*C*) and bone (*B*) are seen at the *left*. **b** A higher-power photomicrograph at 5 days of a portion of the surface repair site shows the parallel orientation of the fibrinous strands. **c** Residual articular cartilage is seen at the far *left* and repair tissue at *right*, one week after creation of the defect. The fibrinous strands at the surface are parallel to, and aligned well with, the residual surface of the articular cartilage. The mesenchymal cells from the marrow are aligned along an arc parallel with the fibrinous tissue. The articular cartilage cells immediately adjacent to the defect have died and their lacunae are empty or show pyknotic cells. **d** A small segment of the surface is seen at the upper right (*arrow*) at 1 week. The fibrinous strands at the surface region provide an orienting scaffold, along which the undifferentiated mesenchymal cells course. A specific orientation cannot be defined toward the center of the defect at the *lower left*. **e** A segment of the repair tissue from the depth of the defect at 1 week. Immediately adjacent to persisting lamellae (*L*) of bone, there is early formation of woven bone spicules (*W*). Above the woven bone, there is an intense proliferation of mesenchymal cells (*M*) and, at the upper left (in the central part of the defect), some clot (C) persists. **f** A higher-power photomicrograph of the repair tissue immediately adjacent to the persisting lamellae in (**e**) shows undifferentiated mesenchymal cells and early formation of blood vessels above. Below, in the region of woven bone formation, some mesenchymal cells have surrounded themselves with osteoid (mesenchymal osteoblast [*open arrow*]). Once a sufficient amount of woven bone has been synthesized, osteoblasts (referred to as surface osteoblasts [*solid arrow*]) are aligned on the woven bone. **g** (**i**) The repair tissue (*left*) in *black* and *white* photomicrograph is closely adherent to the residual cartilage (*right*) at 10 days. The chondrocyte lacunae at the edge of the cartilage, adjacent to the site of the defect, are empty, indicating cell death in association with the trauma caused by creation of the defect. At the far right, articular cartilage chondrocytes appear normal. **g**(**ii**) In the repair site (same image in color), most of the tissue is still composed of undifferentiated mesenchymal cells, but there is early evidence of cartilage formation just below the surface at the far left. This tissue stained red, owing to the synthesis of glycosaminoglycans, which are characteristic of cartilage. The proteoglycan content of the residual non-viable articular cartilage at the right of the defect is already markedly diminished in comparison with the *red-stained* cartilage at the far right (safranin-O –fast *green* preparation). **h** At 2 weeks there is close apposition of the repair tissue (*right*) to the residual articular cartilage (*left*), and an absence of chondrocytes in the cartilage immediately adjacent to the defect. **i** Repair tissue is shown at the right and residual cartilage at the left at 2 weeks. There is a region of empty lacunae in the residual articular cartilage immediately adjacent to the edge of the defect, but the cells of the residual articular cartilage at the far left appear normal. **j** Polarized light microscopy shows a lack of fibril continuity between the repair and the persisting cartilage at 2 weeks, despite the apparently close apposition in the light microscopy sections shown in (**h**) and (**i**). The demarcation between the residual cartilage (*light area*) and the repair cartilage (*dark area*) is abrupt. **k** On occasion, the repair plug fails to adhere to the adjacent cartilage and bone, and areas of discontinuity (*arrows*) are seen. **l** Light microscopy shows close apposition of the repair tissue (*right*) with the residual cartilage (*left*) 26 days post-surgery. The surface of the repair tissue is continuous with that of the original cartilage. The residual cartilage cells at the repair junction have remained viable. The superficial,

flattened layer in the repair tissue is analogous to the tangential zone of normal articular cartilage, but it is always somewhat thicker than that seen in the normal cartilage. The cellularity of the repair tissue is greater than that of the original cartilage. **m** Polarized light microscopy of the interface between the repair cartilage and the residual viable cartilage shows greater fibrillar continuity than that seen in (**j**), where the adjacent cartilage was non-viable. **n** Photomicrograph, made with polarized light, showing an oblique junction between the repair cartilage (*dark area*) and the residual cartilage (*light area*), 6 weeks postoperatively. There is still abrupt fibrillar discontinuity, despite the appearance of close apposition on light microscopy. **o** Repair tissue is seen at the right and residual cartilage at the left at 8 weeks. The tidemark persists on the left (*arrow*), but it has not yet been re-established in the repair segment. The repair bone from the depths of the defect has been synthesized to the level of the tidemark of the adjacent bone, whereas all tissue superficial to that is cartilaginous. The repair tissue is hypercellular compared with the residual cartilage. There are still acellular regions at the junction between the repair and the residual cartilage, but some cartilage cloning is seen in the residual cartilage at the edge of the defect. **p** Color photomicrograph of the junction of the repair tissue and the residual cartilage at 8 weeks. The residual cartilage (*right*) still demonstrates the tidemark, whereas this structure has not yet formed in the repair tissue. The proteoglycan content (*red stain*) of the repair cartilage is excellent. **q** Residual cartilage is shown at the left and repair tissue at the right at 10 weeks. The tidemark still has not re-formed in the repair tissue. Hyper cellularity in the repair tissue is still noted, as are regions of a cellularity and chondrocyte-cloning of the original cartilage at the edge of the defect. **r** The repair tissue is seen at the left at 10 weeks. The over-all structure of the repair tissue remains good. There is close apposition of the repair and the persisting cartilage, hypercellularity of the repair cartilage, and intervening acellular areas. **s** Clear failure of the apposition between the repair cartilage and the residual acellular cartilage is seen in the lower two-thirds of the junctional area, although superficial continuity is present. **t** There is still excellent continuity of the surface repair cartilage (*left*) with the original residual cartilage (*right*) at 24 weeks. The tidemark has been reconstituted (hematoxylin and eosin). **u** The repair tissue is seen at the left and the residual cartilage at the right at 24 weeks. There is still excellent continuity of the repair at the junctional interface. The tidemark has been re-established. The repair tissue is still somewhat hypercellular in relation to the original residual cartilage. The acellular zone of original residual articular cartilage centrally is striking. The original cartilage is twice as thick as the repair cartilage in this example. There is surprisingly good continuity of cartilaginous tissue even 24 weeks after creation of the defect. Although green-stained surface tissue is present, the bulk of the repair cartilage is still characterized by red-stained tissue indicative of the synthesis and persistence of cartilage proteoglycans. **v** Extensive degeneration of the repair cartilage (*right*) is seen 48 weeks after creation of the defect. Superficial fibrillation is associated with the repair tissue. The repair cartilage is now hypocellular with total loss of proteoglycan (safranin O-fast *green stain*). **w** In the repair tissue, there is considerable degeneration of the cartilage that has been synthesized at 36 weeks. The cartilage is thin, with loss of cellularity and clear evidence of surface fibrillation. **x** The tidemark has been clearly reconstituted and the repair tissue is at the left at 36 weeks. There is also excellent continuity of the underlying bone. The articular cartilage is intact in the region of the repair, with only slight areas of surface fibrillation. The acellular area (the periphery of the residual cartilage) is prominent. A similarly excellent result was observed in several specimens at 48 weeks. **aa** Color photomicrograph showing repair tissue at the left and residual articular cartilage at the right at 48 weeks. There has been considerable degeneration of the repair tissue. Very little red stain is present, indicating an almost exclusively fibrous nature, with disappearance of proteoglycans. This region is now hypocellular. Fissures, which are indicative of a poor mechanical stability of the repair tissue, are seen at the upper left. The tidemark persists. **bb** Another repair site at 48 weeks shows return of rpair tissue to a fibrous state although it appears united with the original cartilage and the tidemark has been established. **cc** Autoradiographs were made after labeling with tritiated thymidine 1 week after creation of the defect. Repair cartilage sampled 2 days after labeling (9 days after creation of the defect) shows non-viable residual articular cartilage, with empty chondrocyte lacunae at the lower right and repair cells at the left. At this stage, the repair cells are mesenchymal in nature, but uptake of thymidine label is shown throughout the cell mass. **dd** Thirteen days after tritiated thymidine labeling (20 days after creation of the defect), there is clear development of a cartilaginous mass in the repair defect. The chondrocytes are labeled with thymidine, indicating their transformation from undifferentiated mesenchymal cells to differentiated chondrocytes. **ee** Autoradiograph made 1 week after labeling with tritiated cytosine. The level of uptake (black-staining cells) is high in the repair tissue (left) and in the residual articular chondrocytes (right), which is indicative of cell viability. There is a clear region without uptake, indicating non-viability of the cartilage, at the immediate periphery of the defect

microscopy, but little fibrillar interdigitation was demonstrated on polarized light microscopy. Gaps between the repair and the persisting articular cartilage were sometimes seen (Fig. 2.9s). The repair cartilage and the normal cartilage continued to stain well with safranin O.

Although well-organized repair cartilage persisted in most defects at 12 weeks, early signs of degeneration were observed in the repair cartilage, with surface fibrillation seen in an appreciable number of defects. From 12 to 20 weeks, continuing signs of degeneration of the cartilage repair tissue were seen morpho-logically in an increasing number of the defects. The intensity of the safranin-O staining of the cartilage matrix was diminished compared with that of the adjacent normal cartilage. More prominent horizontal and vertical fissures of the repair cartilage were seen not only in the upper layers but also, in some sections, extending into the deeper layers. Despite these changes in many of the defects, the repair cartilage in the remaining defects had maintained its structural, histochemical, and cellular properties.

By 24 weeks, the degenerative changes in the repair cartilage were more advanced in many more defects. There was continuing diminution of the intensity of the safranin-O staining from superficial to deep. Fissuring had begun in the superficial layers of the re-pair cartilage and was both parallel and perpendicular to the surface, and there was hypocellularity in the superficial layers of the repair cartilage. Hypertrophic cartilage cells were no longer seen in the deeper layers of the regenerated cartilage. The tidemark had been re-established in most defects. The subchondral bone was now lamellar. It is important to note, however, that in many defects excellent repair tissue persisted (Fig. 2.9t, u).

Superficial fibrillation was seen in even more defects by 36 and 48 weeks (Fig. 2.9v–x), in several instances, extensive acellular areas were present in the repair cartilage (Fig. 2.9v). Almost all of the defects, however, eventually had a well-developed tidemark.

Staining with safranin O increasingly disappeared from superficial to deep (Fig. 2.9p, t, u). Some of the repair sites remained intact with cartilage persisting even though Safranin O staining indicated extensive loss of proteoglycan at 48 weeks (Fig. 2.9aa, bb). Although extensive new bone had been formed both by the endochondral sequence and by direct intramembranous bone formation from osteoblasts differentiating from the mesenchymal cells, the full reorganization of the subchondral compact osseous plate had not occurred in a number of sections in which the degeneration had been severe. At 48 weeks, cartilage tissue was still present in the defects, but degenerative changes were observed clearly in most of the sections (Fig. 2.9v, aa, bb). Moreover, the degenerative changes were now much more extensive. However, in a small number of the defects, the repair articular cartilage had retained its integrity. An important observation is that, in these instances, the subchondral bone beneath the tidemark had been reconstituted to its nor-mal gross architecture and state of organization as com-pact lamellar bone.

Tritiated thymidine (Fig. 2.9cc, dd) and tritiated cytosine (Fig. 2.9ee) labeling more clearly defined cellular activity in the early repair sequences. The entire repair sequence is summarized in Table 2.1. These studies outline important biological features of the repair mechanisms in full thickness articular cartilage defects including: the importance of the fibrinous edge-to-edge surface arcades that orient the ingrowth of mesenchymal cells; the autoradiographic demonstration of the origin of a complete spectrum of reparative cells from the undifferentiated marrow mesenchymal-cell pool; the failure of full interdigitation of the repair matrix with the residual rim of cartilage, which itself was rendered necrotic by creation of the defect; and the necessity of long-term studies (beyond 6 months) because seemingly well repaired tissue can de-generate prematurely.

Furukawa et al. [132] performed early biochemical studies on the repair tissue with this model. Hunziker and Quinn [133] specifically studied the biological effects of surgical procedures (drilling, shaving, debridement) on the viability and function of articular chondrocytes bordering the wound edge. They showed that the lesions induced a significant and long-term loss of cells from tissues near the wound edge. This adjacent chondrocyte necrosis at the margins of the cut surfaces has been noted almost from the beginning of surgical experimentation using the cartilage defect model. This helps explain the relatively poor healing of repair cartilage to adjacent cartilage as demonstrated in previous studies, the fact that such procedures designed to help repair can actually inhibit, and the extreme importance of getting repair tissues to not only fill a gap but also bond biologically to the persisting cartilage. Jackson et al. [134] also noted that the repair tissue generated integrates poorly with the persisting cartilage in their study in the goat. Experimental findings underlie the commonly used microfracture technique of Steadman and colleagues for treatment of full-thickness articular cartilage defects

Table 2.1 Morphological repair sequence in cylindrical 3-mm-diameter full-thickness articular-cartilage defects

Time-period sequence	
First few hours	Red blood cells flood defect
1–2 days	Fibrinoid material in edge-to-edge arcade arrangement; clot persists; increased capillary proliferation in adjacent marrow
3 days	Spindle-shaped mesenchymal cells prominent at surface; acellular central area with clot and fibrin persisting; mesenchymal cells present in depths of defect and invading periphery of clot; woven intramembranous bone in adjacent marrow
7 days	Superficial and deep mesenchymal cells merge; fibrinous arcade infiltrated extensively with mesenchymal cells throughout defect
12 days	Superficial fibrous cell layer seen; deeper layer of chondroid cells forming; woven bone formed in adjacent marrow; chondrocyte lacunae in residual cartilage adjacent to defect frequently empty
3 weeks	Chondrocyte layer well developed; hypertrophic chondrocytes at deeper levels of chondrocyte layer; endochondral bone formed in depths of defect; intramembranous woven bone formed in adjacent marrow; repair cartilage closely apposed to residual cartilage in some sections but separated by slight gap in others
4–8 weeks	True hyaline appearance to repair cartilage; hypertrophic cells present at lower levels of chondrocyte layer, but these decrease progressively with time
12–24 weeks	Chondrocyte layer well developed; hypertrophic cells at undersurface of chondrocyte layer no longer present; tidemark present (24 weeks); lamellar bone in adjacent marrow; superficial cartilage degeneration seen with fibrillation, hypocellularity, and decreased proteoglycan
36–48 weeks	Persistence of hyaline articular cartilage, tidemark, and underlying lamellar bone; superficial cartilage fibrillation, vertical fissuring, and decreased staining of matrix with safranin O, with progressive worsening with time

From Shapiro et al. [131]

especially following injuries in pediatric and adolescent age knees. In the clinical setting, all unstable cartilage fragments at the rim of the defect are debrided with a hand-held curved curette along with any remaining segments of the calcified cartilage layer. An arthroscopic awl is used to make multiple holes (the microfractures) in the exposed subchondral bone plate. The holes are 3–4 mm apart allowing access into the marrow to a depth of 2–4 mm. The release of blood and marrow fat droplets into the defect marrow elements forms and stabilizes while covering the lesion.

2.18.1.2 Detailed Description of Repair of Partial Thickness Articular Cartilage Defects. Meniscectomy Model

While linear lacerations of the articular cartilage made by a sharp scalpel are commonly used in experimental models to study partial-thickness defects, they are clearly an uncommon cause of injury clinically. Medial meniscectomy and the creation of "bucket-handle" lesions of the medial meniscus induce mild to moderate osteoarthritic changes in the tibial articular cartilage of mature rabbits [135]. These changes closely resemble findings in the human knee after meniscal tears and are representative of partial-thickness injuries. The degenerative lesions studied by gross inspection and histological sections, almost exclusively involve the medial tibial articular cartilage. The model assesses both cartilage damage and repair with the subchondral bone intact and no repair cell invasion from marrow mesenchymal cells. The pathologic changes begin superficially, pass to the deeper layers, and are characterized by a loss of the glistening of the cartilage surface, peripheral osteophytes, structural irregularities of the matrix, peripheral cloning, hypocellularity, and diminished amounts of glycosaminoglycan. Osteoarthritis assessed from 2 to 16 months following surgery and using a grading system from 0 (normal) to 15 (severe degeneration) showed mean grades at the various time periods from 3.5 to 7. The mild to moderate nature of the osteoarthrosis is shown by the development of the abnormalities without rapid progression to the severely destroyed joints which characterize many other models.

(a) *Gross observations*. The earliest gross change observed was a decrease of the normal "glistening" of the surface of the tibial articular cartilage. This was more marked medially. In no animals did the degenerative changes progress to more than grossly visible mild fibrillation, and in no animal was a full thickness loss of cartilage seen. Peripherally, medial osteophytes were observed frequently in both groups, often as early as 2 months postoperatively. A small, fibrous rim of tissue formed at the site of the excised medial meniscus. The size of this regenerated fibrous structure varied considerably, ranging in width from roughly one-fifth to two-thirds the size of the original meniscus. The surgical lesions in the medial meniscus never healed, with inner and outer portions of the meniscus remaining completely separate. The sham procedure did not produce observable gross changes in the articular cartilage or synovium.

(b) *Histologic observations.* The normal histological appearance of tibial articular cartilage with the safranin O-fast green stain is seen (Fig. 2.10a). Similar findings were noted in the meniscal lesion and meniscectomy groups. Degenerative changes in the cartilage were noted in all animals as early as 2 months following surgery. The degenerative changes were much more marked in the medial tibial articular cartilage with changes on the lateral side being either very minor or usually absent. Changes were rarely noted in the articular cartilages of the distal femur or patella.

(i) **Structural irregularities**. Structural irregularities in the articular cartilage were limited almost exclusively to the medial tibia. The earliest changes occurred at the surface of the tangential zone of cartilage. The changes subsequently progressed towards the deeper zones of the cartilage. After development of surface ir-regularities, small vertical clefts extended into the tangential and transitional zones. Later, these lesions were found to ex-tend into the radial zone. The changes rarely approached the tidemark. Occasionally, transverse clefts occurred which in some instances appeared to link up with vertical clefts resulting in loss of articular cartilage. The surface of the lateral articular cartilage remained intact. Early changes were seen at 2 months [Fig. 2.10b(i–iii)]. By 7 months they were well developed (Fig. 2.10c–e) and then progressed slowly in severity.

(ii) **Cellularity**. Changes in the chondrocytes were first observed in the superficial zones of the articular cartilage. With time, involvement was noted toward the deeper radial zone. Cloning of the chondrocytes was also observed, most prominently in the peripheral portions of the cartilage. The cloning was most evident in the 7-month specimens. In regions of matrix fibrillation, fissuring, and loss of Safranin O staining properties, there was invariably a loss of definition of chondrocytes usually accompanied by hypocellularity. The decrease in the number of chondrocytes and changes in the matrix were always focal and never involved the complete thickness or width of the articular cartilage. Either very minimal or no changes were observed histologically in the articular cartilage of the lateral tibial condyle.

(iii) **Safranin O staining**. The ability to ob-serve the lateral articular surface in the same tissue section as the medial served as an excel-lent internal control. There was a progressive decrease in Safranin O staining of the medial tibial cartilage. These changes were first ob-served in the more superficial layers of the cartilage, but the diminished uptake of Safranin O eventually progressed to the deeper layers of cartilage as well. Some chondrocytes in the focal areas of degenerative changes were sur-rounded by a thin zone of intensely stained red matrix. There was excellent correlation between the intensity of the Safranin O staining of the cartilage matrix and the degree of cellularity; loss of Safranin O staining in any region was accompanied by hypocellularity. The lateral tibial articular cartilage showed little or no loss of cellularity or of Safranin O staining intensity.

Floman et al. [136] used this model to assess early biochemical responses to the injuries.

2.18.1.3 Histological Assessment of Cartilage Repair in Human Biopsy Specimens

Efforts have been made by the International Cartilage Repair Society to adapt articular cartilage histological grading scores used for animal research studies to human repair biopsy samples [137]. The biopsies must be small, 2 mm diameter, full thickness cores including the calcified cartilage layer and the subchondral bone plate. The ICRS histological assessment scale assesses and grades as follows: (I) Surface [smooth/continuous = 3 points, discontinuous/irregularities = 0]; (II) Matrix [hyaline = 3, mixture: hyaline/fibrocartilage = 2, fibrocartilage = 1, fibrous tissue = 0]; (III) Cell distribution [columnar = 3, mixed/columnar-clusters = 2, clusters = 1, individual cells, disorganized = 0]; (IV) Cell population viability [predominantly viable = 3, partially viable = 1, <10 % viable = 0]; (V) Subchondral bone [normal = 3; increased remodeling = 2, bone necrosis/granulation tissue = 1, detached/fracture/callus at base = 0]; (VI) Cartilage mineralization (calcified cartilage) [normal = 3, abnormal/inappropriate location = 0]. The article outlining this approach is notable for the several histological photomicrographs of human articular cartilage in the various stages.

2.18.1.4 Magnetic Resonance Imaging of Articular Cartilage

MRI plays a major clinical and investigational role in assessing morphology, joint pathology and particularly articular cartilage structure and biochemical composition [138–140]. It is used increasingly for non-invasive analysis of articular cartilage. It is very helpful in focal lesions such as those in osteochondritis dissecans especially in assessing size, depth, and indirect assessments of stability. The delayed Gadolinium Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC) technique helps to assess the concentration of glycosaminoglycan within the cartilage matrix [141]. MRI is particularly helpful for focal defects and their repair as the study can determine the degree to which the defect is filled and the integration of repair tissue. Cartilage is mainly composed of water, collagen, glycosaminoglycans/proteoglycans and cells. The first 3 constituents can be imaged for separate determinations. Collagen fibril orientation, amount and molecular structure all influence the T2 relaxation parameter. Cartilage glycosaminoglycan (GAG) can be measured by MRI. A widely used MRI contrast agent is Magnevist (Berlex, Wayne, New Jersey) uses gadolinium or Gd-DTPA^{2-}. This agent has a negative charge. Cartilage glycosaminoglycans have abundant negatively charged carboxyl and sulfate groups. If Gd-DTPA^{2-} penetrates cartilage it distributes to higher concentration areas where the GAG content is relatively low and is excluded from regions rich in GAG. It is possible to quantify GAG concentration by determining the distribution of Gd-DTPA^{2-}. This technique is referred to as delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC) and is very useful clinically to assess early articular cartilage degeneration where GAG levels are decreased [141]. The dGEMRIC measurement of GAG corresponds to the measures of GAG by biochemistry and histology, thus allowing for a non-invasive in vivo measurement of articular cartilage health. Since the Gd-DTPA^{2-} is distributed inversely with the GAG concentration (Gd-DTPA^{2-} higher in areas where GAG is low, and relatively low in areas where GAG is high) it serves as an indicator of articular cartilage health/disease particularly in hips and is used to project need for and response to operative therapies.

2.18.1.5 Early Surgical Interventions to Minimize Articular Cartilage Damage

Extensive efforts were made beginning in the 1920s to intervene surgically in joints (usually the knee) to minimize cartilage damage and provide symptomatic relief. These approaches continued for several decades with reports continuing into the 1990s based on good symptomatic relief in some patients for several years and, primarily, the lack of reparative treatments short of joint replacement. It is important to be aware of these interventions, especially since they continue to be used as preliminary approaches when biologic interventions are done.

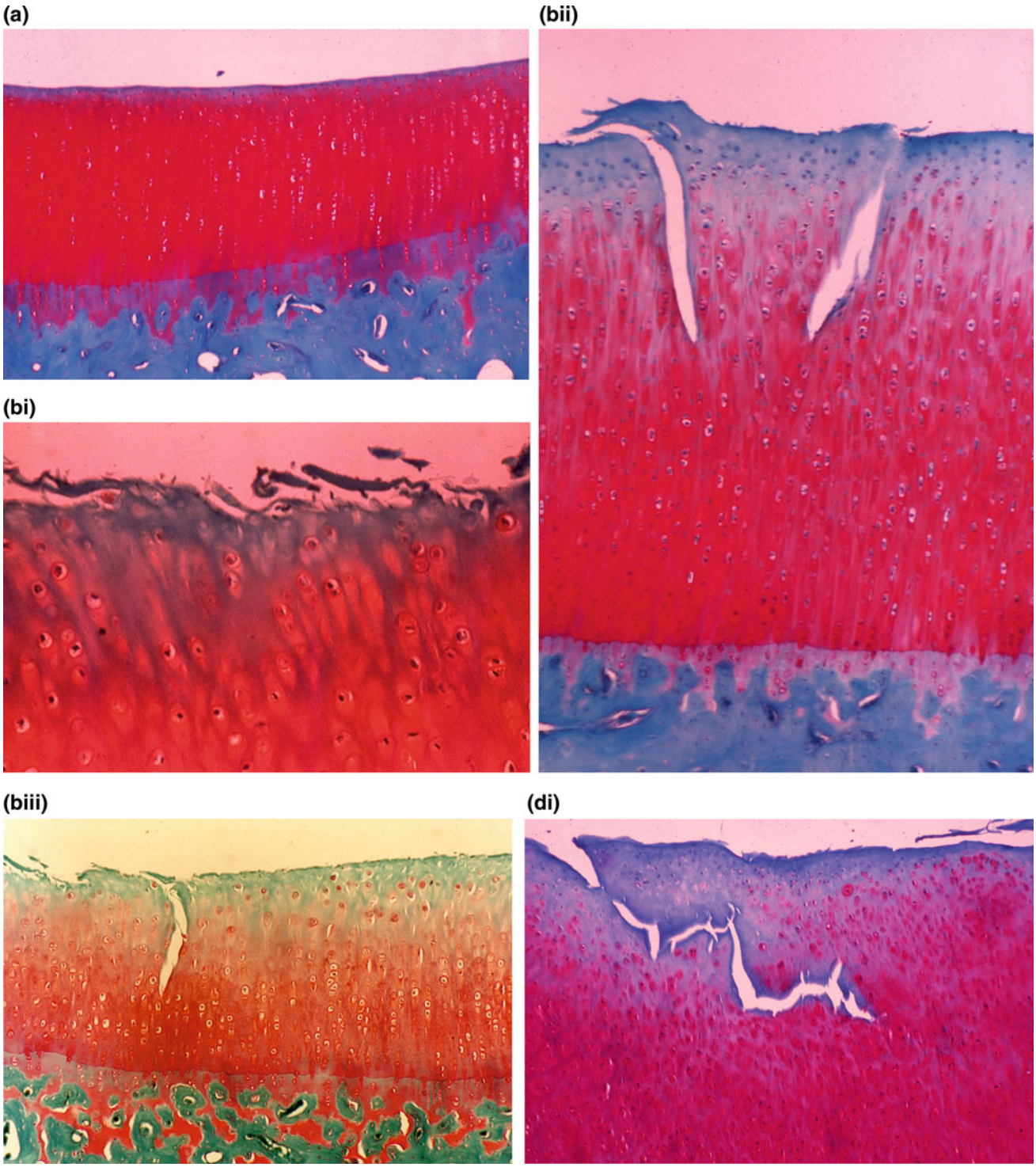


Fig. 2.10 (continued)

(a) ***Joint Lavage*** (***with arthroscopy or at arthrotomy***). Beginning in 1921 Bircher adapted equipment used for laparoscopy to examine the knee joint and allow for joint washout or lavage [142]. Burman et al. [143] also used knee arthroscopy to examine and extensively irrigate the joint with saline or Ringer's lactate. Many surgeons found the irrigation procedure alone effective to alleviate symptoms. Other than a placebo effect, it

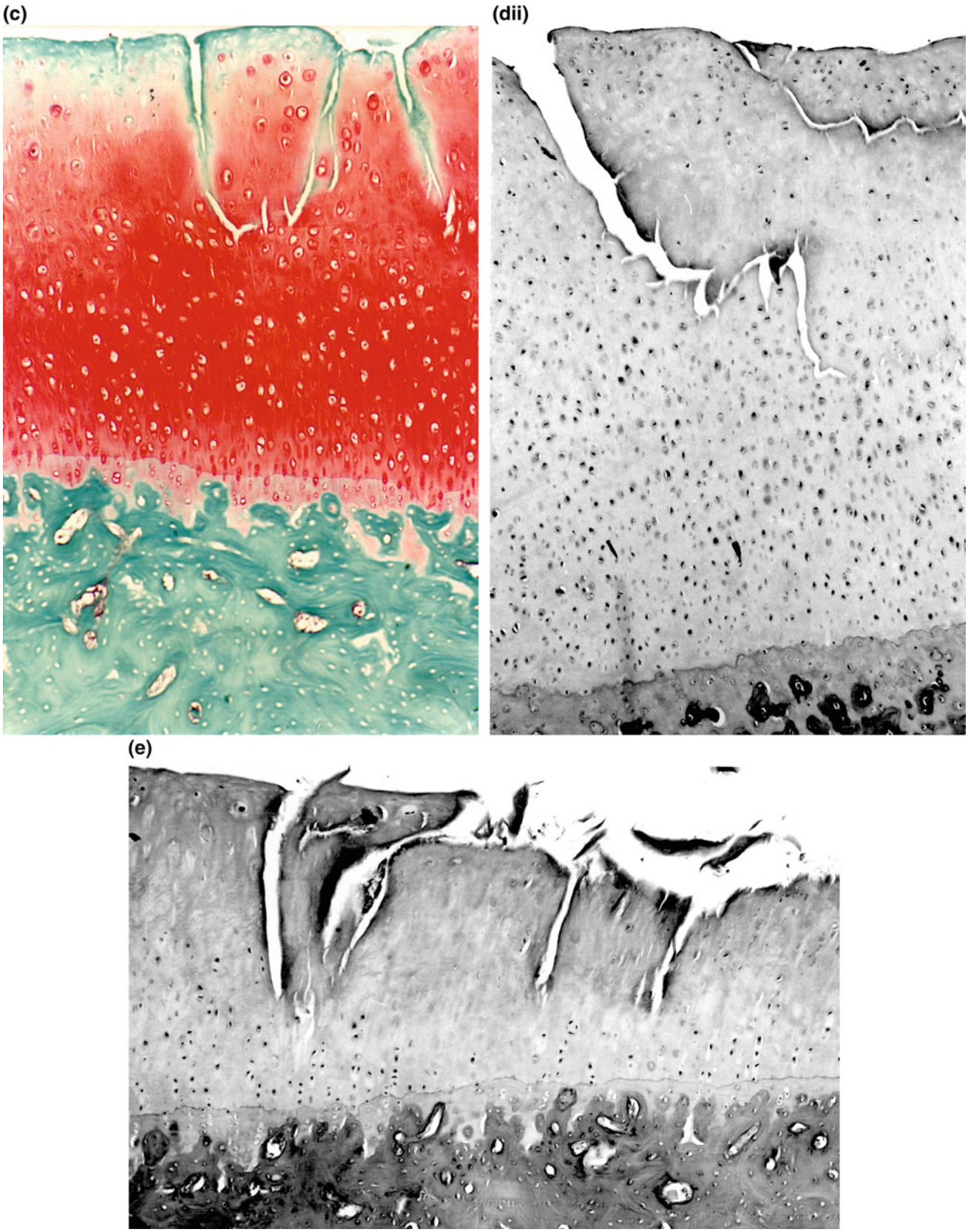


Fig. 2.10 (continued)

has been suggested that removal of lytic enzymes and small particulate debris might provide some benefit.

(b) ***Joint Debridement***. Magnuson reported on his approach to the knee referred to as joint debridement in 1941 in which lavage was accompanied by removal of loose osteochondral bodies and intra-articular osteophytes, shaving of fibrillated cartilage, and partial synovectomy [144]. Good symptomatic relief, often lasting for several years was reported by Magnuson as well as by Haggart [145] and Isserlin [146] around the same time. Some included patellectomy if the patella was badly damaged and also partial or complete meniscectomy. As recently as 1996 Hubbard was reporting favorable symptomatic results up to 5 years post-articular debridement or washout for medial femoral condyle degeneration [147]. No attempt was made to induce repair by drilling into subchondral bone at this time. Many articles discussing results with lavage and debridement have been listed by Hubbard [147] and Dennis and DiCesare [148]. The review by Hunziker [149] is both extensive and analytical concerning these interventions to which he adds chondral shaving and laser chondroplasty and the biologically oriented approaches that followed.

2.18.1.6 Biologic Enhancement of Articular Cartilage Repair in Focal Lesions

Treatments for relatively localized focal defects of articular cartilage which use biological methods to enhance healing are now in use clinically. They are also the focus of extensive ongoing laboratory investigation.

(a) ***Microfracture Technique***. The microfracture technique is the clinical application of the investigational principle where full-thickness cartilage defects passing through subchondral bone allow for blood vessel and undifferentiated mesenchymal cell invasion and the subsequent development of the fibrin, fibroblast, fibrocartilage, and hyaline cartilage sequence. Pridie reported on the subchondral drilling method used as part of the debridement technique for severe adult osteoarthritic knees at a meeting in 1959 [150]. Insall subsequently studied and reported on 62 cases using the Pridie approach in which 64 % had good results at followup [151]. Extensive debridements of the knee were done including shaving of fibrillated cartilage, meniscectomy if warranted and even patellectomy and cruciate ligament (full or partial) removal. The Pridie procedure involved placing multiple drill holes ¼ inch in diameter through the subchondral bone to allow bleeding from the marrow. A rigorous physical therapy regimen followed. The fibrocartilaginous repair that followed was felt to sustain the good results for several years [151]. The technique was done in the 41–69 year age group (3 younger) who were considered active. Steadman and colleagues developed and refined this technique and reported good results at an average 11 year followup [152]. Their patients were much younger than the Pridie–Insall group, the associated procedures were far less extensive, the defects were narrower (0.5–1.0 mm wide) and 3–4 mm apart (preserving the subchondral bone plate better) and surgery was done arthroscopically. They reported 75 %

◀**Fig. 2.10** Partial-thickness defects in articular cartilage are shown after experimental creation by medial meniscectomy alone in the rabbit knee. **a** Histologic section of normal proximal tibial articular surface in a skeletally mature rabbit. The safranin O-fast green stains the proteoglycan-rich articular cartilage *red* and the subchondral bone *greenish-blue*. (Reprinted with permission from Shapiro and Glimcher, Induction of osteoarthrosis in the rabbit knee joint. Clin Orthop Rel Res. 1980;147:287–295. Copyright 1980 Wolters Kluwer Health). **b(i–iii)** Photomicrographs illustrate mild degenerative changes in the medial tibial articular cartilage 2 months after meniscectomy. There is initial loss of proteoglycan superficially, death of superficial chondrocytes and surface fibrillation (**bi**). Superficial vertical fissures are then seen (**bii** and **iii**). In the superficial one-third of the cartilage, especially adjacent to the fissures, many of the chondrocyte lacunae are empty and loss of proteoglycan begins superficially and passes more deeply with time. Superficial fibrillation is seen. The deeper parts of the cartilage are intact as regards matrix integrity, staining properties, chondrocytes, and the tidemark. **c** Photomicrograph illustrating vertical clefts in close association with superficial hypocellular areas and loss of proteoglycan is shown. The specimen was obtained 7 months following the creation of a meniscal lesion. The chondrocytes, matrix structure, and matrix-staining properties remain intact in the deeper two-thirds of the cartilage. **d(i)** and **(ii)** Photomicrographs illustrate a slightly more advanced stage of cartilage degeneration of the medial tibial articular cartilage than is seen in (**b**) and (**c**). The histologic sections were made 7 months following meniscectomy. The superficial surfaces of the articular cartilage are irregular, and oblique-vertical clefts are seen. The cells and matrix of the deeper half of the cartilage, the tidemark, the zone of calcified cartilage, and the subchondral bone are all intact. Chondrocyte lacunae in the more superficial areas of the cartilage are frequently empty. Proteoglycan adjacent to the fissures is decreased. **e** Photomicrograph illustrating the most severe changes in the medial tibial articular cartilage 7 months after meniscectomy. Numerous vertical fissures and a major horizontal fissure are apparent. Small pieces of matrix lie free. Empty chondrocyte lacunae are present throughout most of the central region of the cartilage as deep as the tidemark. The tidemark, calcified zone, and subchondral bone remain intact, however

favorable results. Mithoeffer et al. reported significant functional improvement at a minimum follow-up for 2 years in a well-studied group of 48 patients assessed prospectively [153, 154]. This technique allows for the histologic progression detailed in Sect. 2.18.1.1 [131].

(b) ***Autologous Chondrocyte Transplantation.*** Repair of localized articular cartilage defects can be induced by autologous chondrocyte transplantation. Viable cartilage is obtained most commonly from the periphery of the minor weight-bearing regions of the upper medial distal femoral condyle and then treated in the laboratory in sterile fashion to isolate chondrocytes, place them in tissue culture to expand cell mass and then transplant them several weeks later back into the same patient. The defect site is cleaned of fibrocartilaginous debris and the cells are implanted and held in place by a flap of periosteum harvested from the proximal tibia and sutured to the peripheral healthy cartilage with the inner cambial layer facing the bone and cartilage. Peterson et al. [155] reported excellent results in 58 patients with a mean age at surgery of 26.4 years and an osteochondritis dissecans lesion of the distal femur. Minas et al. [156] also reported excellent results in 155 knees with early stage osteoarthritis followed for a mean of 64.2 months. At 5 years post-operatively 92 % were functioning well with joint replacement surgery deferred.

(c) ***Perichondrial/Periosteal Grafts.*** Efforts have been made to take advantage of the ability of the cambial or inner layer of periosteum and perichondrium to synthesize cartilage in the proper environment and thus repair or regenerate damaged articular cartilage. The tissue is used as an autologous transplant, bypassing immune rejection problems and allowing for nutrition either by diffusion or spontaneous revascularization. While some experimental success has been described both technical and synthesis problems have for the most part stalled work on this approach. It is used to contain autologous chondrocyte transplants into articular cartilage defects but more as a passive cell containment vehicle than as a cell producing layer. Hunziker has reviewed this modality well [149].

(d) ***Autologous Osteochondral Mosaicplasty.*** In this procedure multiple small-sized cylindrical osteochondral grafts are harvested from the relatively less weight-bearing regions of the peripheral femoral condyles and positioned upright and parallel to each other at the defect site with the bone ends healing to the subchondral bone and the cartilage ends aligning at the same level as the healthy surface cartilage at the periphery of the defect [157]. The technique was developed by Hangody and colleagues in the early 1990s. They reported excellent results in 831 mosaicplasties done at their institution (femoral condyles 597, patellofemoral joint 118, talar done 76, femoral head 6, and humeral head 3). Graft diameters were 2.7, 3.5, 4.5, 6.5, or 8.5 mm wide. Insertion is done through a universal guide after making the cylindrical reception site with drill bit and dilator to finalize the reception tunnel. The use of different diameter width grafts maximizes defect coverage with articular cartilage tissue to the >90 % range.

(e) ***Tissue Engineering Applied to Full-Thickness Cartilage Defects.*** Limitations in effectiveness of the previous 3 methods, each of which has been widely used on knee specialty services over the past 15–20 years, has allowed for continuing investigation of enhancing repair by other biologic/physiologic means. Several overviews of the molecular biology of cartilage degeneration and repair have been written [149, 158–162]. Hunziker [149] has written an excellent article reviewing the scientific background to and basis for tissue engineering approaches to articular cartilage. Hunziker and Rosenberg [163] also revived the long suggested observations that cell recruitment from the synovial membrane might also participate in articular cartilage repair. Tissue engineering of articular cartilage refers to combining three elements: transplanted cells, a scaffold, and growth factors to synthesize a functionally effective articular cartilage surface.

(i) Transplanted cells. The cells used are either chondrocytes or mesenchymal stem cells stimulated to differentiate along a chondrogenic line. The cells must not proceed to hypertrophy, premature senescence or apoptosis, de-differentiation or differentiation along fibroblast or osteoblast lines. The chondrocytes must continue to synthesize types II, IX and XI collagen as well as the appropriate proteoglycans.

(ii) Scaffold. The scaffold or matrix is needed to allow the cells to function and proliferate three-dimensionally under physiological conditions. The matrices can be biological, such as collagen, hyaluronic acid, fibrin, alginate, agarose or chitosan or synthetic biomaterials such as polylactic acid or the copolymer of polyglycolic/polylactic acid. The scaffold must be biocompatible, structurally and mechanically stable, allow for cell and matrix interdigitation, allow for cell differentiation, and biodegradable [164].

(iii) Growth Factors. Chondrogenic growth factors are incorporated into the approach, such as TGF-β, FGFs and Wnts. To be effective the repair tissue must integrate with the subchondral bone below and the adjacent articular cartilage at the surface and within the cartilage layers.

Experience with this approach clinically is more limited than with the earlier developed methods [165]. A review by Iwasa et al. [166] showed that the tissue engineering methods could be effective but were not yet better than conventional autologous chondrocyte transplantation and did not yet show superiority of any of the tested scaffolds. This approach remains the focus of extensive laboratory investigation.

2.18.1.7 Tibial Osteochondral Allografts

For large lesions, especially post-traumatic degeneration of the proximal tibia, a considerable experience developed experimentally and clinically with fresh tibial osteochondral allografts beginning around 1970. Variable success was noted in young and middle-aged adults too young for prosthetic joint arthroplasty, but the procedure has not been applied to the adolescent population with skeletal growth remaining. Sasha et al. [167] studied 65 patients with 5 years or longer follow-up and provided a detailed reference list outlining the history and development of the approach.

2.18.1.8 Continuous Passive Motion as an Adjunct to Healing of Full-Thickness Defects in Articular Cartilage

Salter et al. [168] utilized the new concept of *continuous passive motion of a synovial joint* in vivo to compare healing of full-thickness defects of distal femoral articular cartilage in rabbits with those joints immobilized full time or walking intermittently. They followed the animals only until 4 weeks post-surgery but concluded that histology of repair was quicker and more advanced with the continuous passive motion (CPM) group. While CPM alone is not an integral part of post-operative management, many groups use CPM after the various knee joint cartilage repair procedures although the current rationale is directed more at comfort and quicker range of motion rehabilitation than it is at enhanced repair.

2.18.2 Repair of Physeal Cartilage

The pattern of cartilage tissue repair in physeal fractures is primarily dependent on the plane of the fracture in relation to the various physeal regions and the presence or absence of direct communication between the epiphyseal vessels and the metaphyseal vessels. If the 2 normally separate vessel groups come into contact a bone bridge is likely to form. If they remain separate, for example after transverse fractures located within the hypertrophic cartilage zone, the cartilage repairs itself and growth can continue unimpeded. The patterns of physeal fractures and their effects on subsequent growth are discussed in detail in Chap. 5.

2.18.2.1 Fractures Along the Vertical Axis of the Physis Leading to Contact Between Epiphyseal and Metaphyseal Vessels

This mechanism has been assessed in an experimental model in 12 6 week old New Zealand white rabbits [169]. A defect was created in the proximal tibial physis using a 3 mm wide drill which passed from the medial metaphysis through the growth plate in its medial third into the secondary ossification center. While not a physeal fracture, the study investigates bone bridge formation across the physis when epiphyseal and metaphyseal circulations communicate (which is the mechanism when physeal fractures lead to transphyseal bone bridges). A small curette enlarged the defect from anterior to posterior such that the eventual transphyseal defect was approximately 1 cm long and 3–4 mm in diameter. Sequential histologic changes at the growth plate-defect interface at 4 days, 1 week, 2 weeks, and 7 weeks are shown in Fig. 2.11a–d and summarized in Table 2.2. Cell differentiation was always induced toward bony-bridge formation with each defect in this model. There was no evidence of cartilage or fibrous tissue formation in the defect at any stage. The mesenchymal cell ingrowth had no tendency to chondroid or chondroblast differentiation, and the margin of the damaged growth plate cartilage showed no evidence of reconstitution in an effort to repair the defect.

Epiphyseal blood vessels, by means of diffusion, are responsible for nutrition of the physeal chondrocytes and are necessary for their growth and proliferation. Metaphyseal vessels are responsible for synthesizing bone on the mineralized cartilage cores at the lower part of the hypertrophic zone. Growth plate cartilage thus has a rich, dual blood supply but the vessels on the epiphyseal side are separated from those on the metaphyseal side by the cartilage, with no vessels passing into or through it.

The normal physeal cartilage is resistant to vascular invasion, due to the presence of antiangiogenic substances. When the cartilage is disrupted by trauma however along its vertical axis (at right angles or oblique to its transverse axis) it may be penetrated by vessels from the epiphyseal and metaphyseal sides and their accompanying osteoprogenitor cells. It is widely recognized that bone bridge formation following epiphyseal fracture occurs due to vessel communication through the damaged growth plate, allowing epiphyseal and metaphyseal vessels and their accompanying osteoprogenitor cells to meet. Bone formation predominates over cartilage formation, and a bridge develops.

Deposition of bone by the osteo-progenitor cells accompanying the vessels begins at 1 week and continues thereafter. The ossification in the lesion occurs initially in the periphery of the defect, where the newly formed vessels

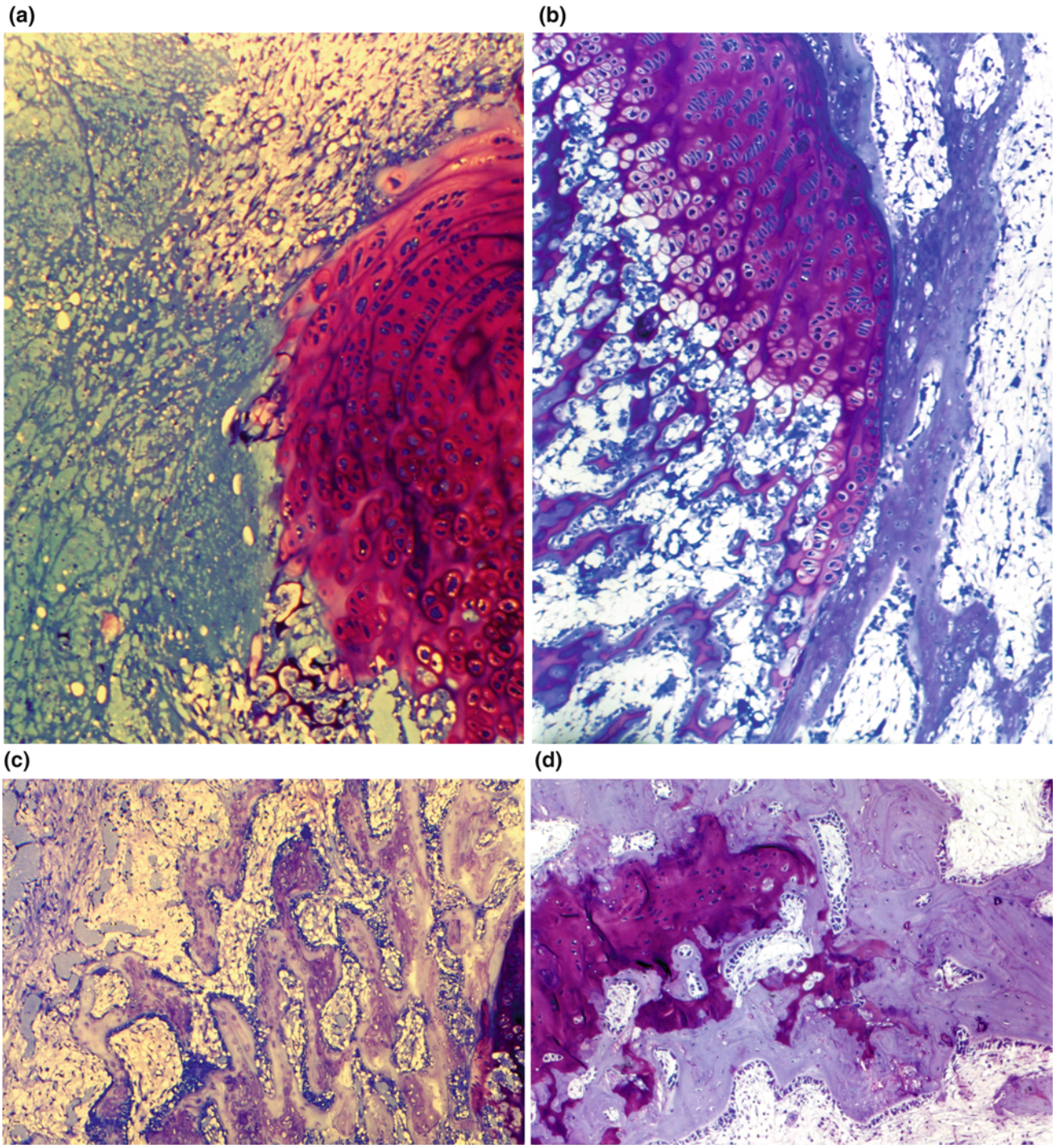

(a)
(b)
(c)
(d)

Table 2.2 Histologic sequence after creation of medial tibial growth plate defect[a]

Period after surgery	Histologic findings
4 days	Red blood cells and fibrin fill defect, early vascular invasion from epiphysis and metaphysis toward defect, mesenchymal-osteoprogenitor cell ingrowth accompanies vessels, initial repair occurs at periphery of defect adjacent to growth plate surfaces
1 week	Mesenchymal cells fill defect, woven bone trabeculae are parallel to long axis of bone and concentrated at periphery adjacent to growth plate cartilage, blood vessels traverse defect parallel to long axis of bone, no cartilage cell differentiation
2 weeks	Increased amounts of bone within defect, vessel continuity between epiphysis and metaphysis
3 weeks	Woven and lamellar bone fills defect
4–6 weeks	Lamellar bone predominates within defect, blood vessel continuity between epiphysis and metaphysis still prominent
7–8 weeks	Dense lamellar bone at periphery, marrow cavity being formed centrally

[a]From Jaramillo et al. [169]

cover the persisting cartilage. This corresponds to the dark rim seen on MR images. By week 7, bone fills the defect site, having created the trans-physeal bone bridge. The MRI signal characteristics of the mature bridge will depend on whether it is composed mainly of lamellar bone or fatty marrow. The sequence of transphyseal bone bridge formation is summarized in Table 2.2.

2.18.2.2 Fractures Along the Horizontal Axis Keeping Epiphyseal and Metaphyseal Vessels Separate

When physeal fractures pass along the transverse axis contained within physeal cartilage the 2 circulations remain separate even if there is considerable displacement of the fragments. These fractures tend to lie primarily in the hypertrophic zone where the final stages of the endochondral sequence are occurring. This is well illustrated in an experimentally created type II growth plate fracture-separation in the immature rabbit distal femur [Fig. 2.12a(i–iii)]. Once the fracture is stabilized the epiphyseal side circulation continues to allow for chondrocyte proliferation and maturation while the metaphyseal circulation allows bone formation on cartilage cores to continue. Extreme mechanical crushing of the physis can however destroy chondrocytes to the point that fibrous repair only occurs. Examples can develop in the same experimental model [Fig. 2.12b(i, ii)]. A benign prognosis should also develop after the fractures of the proximal tibia (type II) [Fig. 2.12c(i–iii)] and metatarsal (type I/II) [Fig. 2.12d(i, ii)]. Jaramillo et al. [170] have performed a histologic/MRI study of transverse physeal fractures in this rabbit model. Patterns of premature physeal arrest after growth plate fractures in children as revealed by MRI have been outlined by Ecklund and Jaramillo [171].

The biology of physeal fracture is discussed in more detail in Chap. 5. Ogden contributed extensively to the biologic understanding of these injuries [172] and Xian et al. have outlined the molecular responses to growth plate injuries [173, 174]. Wattenberger et al. created physeal fractures in a rat proximal tibia model. Similar to the findings listed above in the rabbit studies, they noted that when the fracture was contained within physis healing was uneventful. When the fracture extended through the physis to the epiphyseal-physeal border there was greater physeal disorganization and formation of vertical septa leading to

◀ **Fig. 2.11** Mechanism of bone bridge formation that occurs with circular localized trans-physeal lesions in young rabbits is shown. A medial trans-physeal tibial growth plate defect was made with a drill [169]. There is no tendency to cartilage repair. Tissue sections in b, c and d were stained with 1 % toluidine blue. (Reprinted with permission from Jaramillo et al. Post-traumatic growth-plate abnormalities: MR imaging of bony-bridge formation in rabbits. Radiology. 1990;175:767–773. Copyright 1990 The Radiological Society of North America (RSNA)). **a** Portion of the growth plate defect site (at *left*) adjacent to the persisting growth plate 4 days after surgery. The defect site is filled with fibrinous material and red blood cells. Early repair responses are seen at the periphery of the defect adjacent to the persisting growth plate cartilage. Blood vessels accompanied by mesenchymal cells and osteoprogenitor cells are approaching the defect from both the epiphyseal (*above*) and metaphyseal (*below*) regions. Safranin O-fast green stain. **b** Portion of the growth-plate defect site (at *right*) adjacent to the persisting growth plate 7 days after surgery. Newly synthesized woven bone is seen within the defect. The persisting growth plate is at left. There is no histologic evidence of cartilage repair either by expansion of the existing growth plate chondrocytes or by differentiation of mesenchymal cells within the defect site to chondroblasts. 1 % toluidine blue stain. **c** Portion of the growth-plate defect site adjacent to the persisting growth plate (far right) 2 weeks after surgery. Abundant new bone is now present within the defect. Lamellar bone is being deposited on the initially formed cores of woven bone. In other sections and at higher magnifications, vessel continuity was seen to have been established between epiphyseal and metaphyseal vessels. **d** Portion of the growth-plate defect site (at right) adjacent to the persisting growth plate (*left*) 7 weeks after surgery. Since the growth plate immediately adjacent to the bony bridge has been tethered, its growth potential has been greatly limited, as evidenced by its relative thinness and lack of proliferating and hypertrophic zones. Defect site is filled with mature lamellar bone (*blue*), which is undergoing marrow cavitation

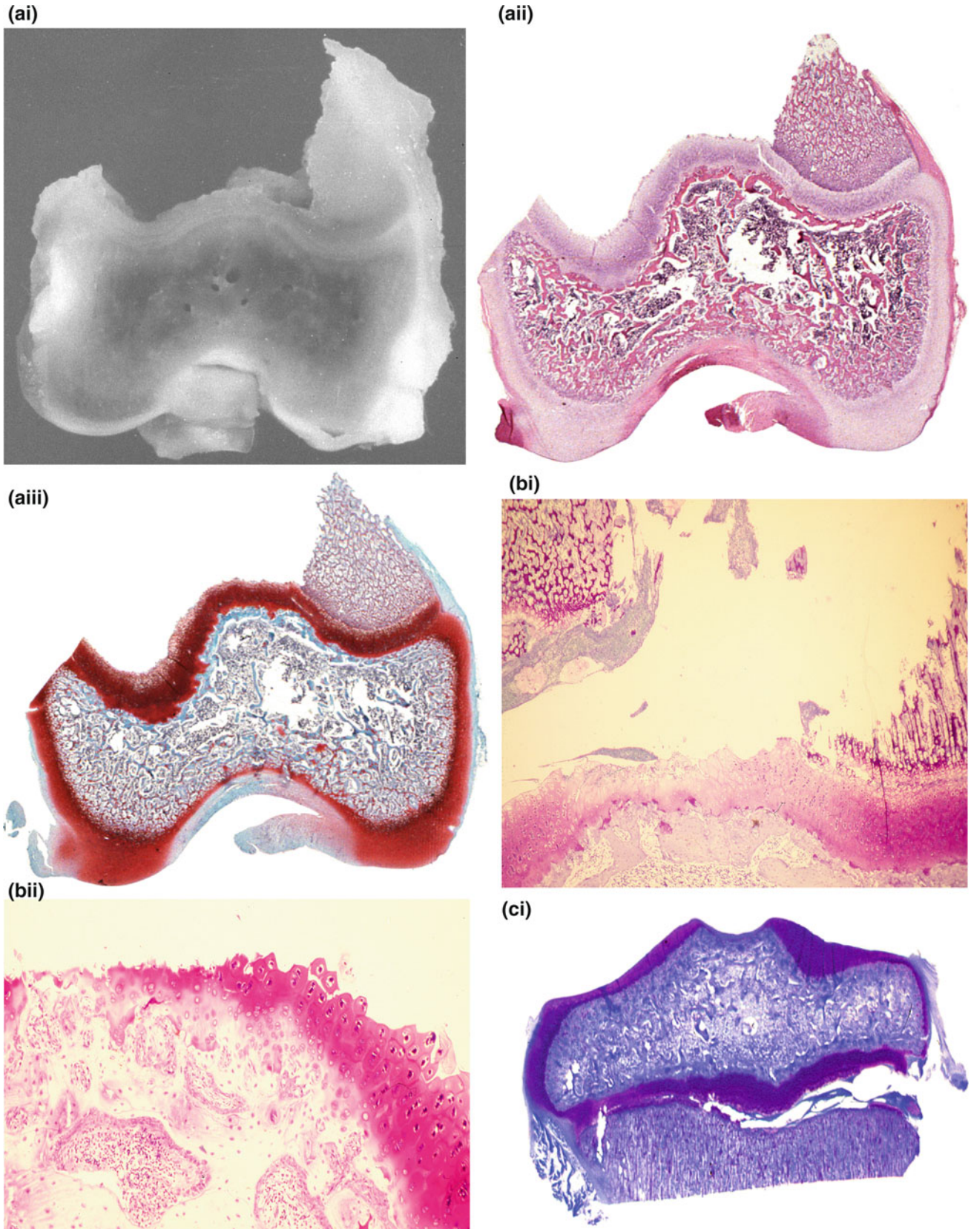


Fig. 2.12 (continued)

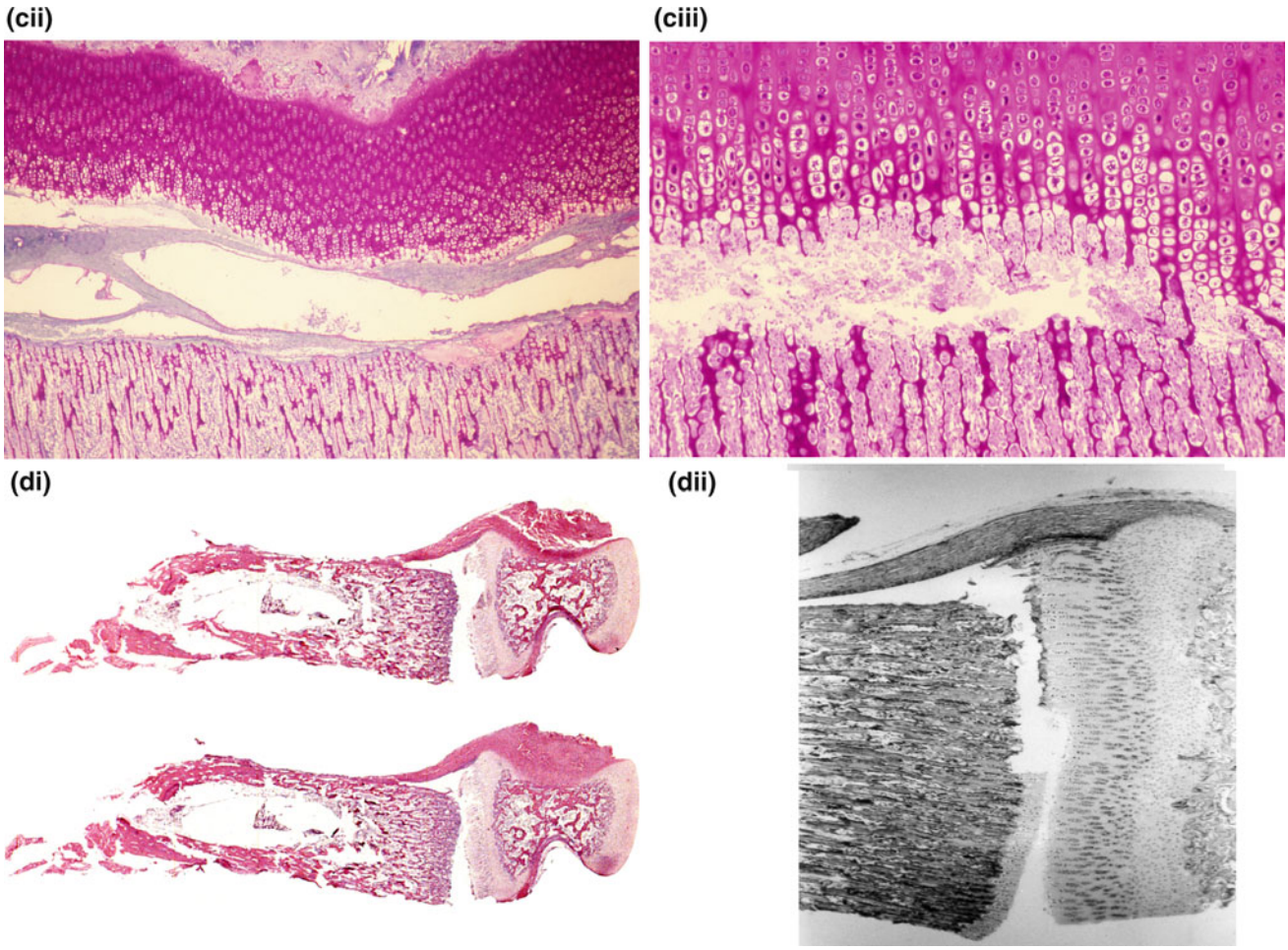


Fig. 2.12 Patterns of transverse physeal fractures are shown in experimental models from the immature rabbit. The lesions were created manually immediately after sacrifice [170]. (Reprinted with permission from Jaramillo et al. Cartilagenous path of physeal fracture-separations. Radiology. 2000;215:504–511. Copyright 2000 The Radiological Society of North America (RSNA)). **a**(**i–iii**) This type II fracture separation of distal femur would have a good prognosis. (**i**) Distal femur after decalcification and mid-line sectioning in the coronal plane. The physis is adherent to the epiphysis across the entire width of the bone and of the same thickness throughout. The type II metaphyseal fragment is prominent; (**ii**) histologic section from the specimen shown in i stained with hematoxylin and eosin and showing physis intact; (**iii**) histologic section stained with safranin-O-fast green also showing physis adherent to epiphysis and of the same thickness throughout. **b**(**i**) and (**ii**) Distal femur type II injury in another specimen (with same orientation as (**a**) shows damage to central physeal undulation of the type that would lead to growth arrest. (**i**) The central physeal cartilage is damaged and fractured towards the epiphyseal (proliferating zone side) which would predispose to limited growth and possible bone bridge formation; (**ii**) shows a small region centrally with no physeal tissue on the epiphyseal fragment which indicates that the full thickness of physis at this region (even if it persists on the metaphyseal fragment) has lost its source of blood supply. **c**(**i–iii**) Low-power photomicrograph of proximal tibia shows plane of fracture-separation at lower part of the hypertrophic zone. The fracture line exits through a small portion of the metaphysis at far left; (**ii**) the fracture line through the lower hypertrophic zone is seen; (**iii**) at higher power magnification the fracture level is more clearly seen. This Type II lesion should not lead to growth problems. **d**(**i**) and (**ii**) Rabbit distal metatarsal growth plate fracture-separations are seen from a lateral view. The physis remains with the epiphyseal fragment, level of fracture is at the lower hypertrophic zone-metaphyseal level and the dorsal periosteum is intact. (**ii**) The fracture line is within the hypertrophic zone and then passes slightly into the metaphyseal level adjacent to the intact periosteum. The periosteum at the "concavity" above remains intact. This would appear radiographically as a Type I fracture-separation

physeal bars (in which marrow cells, osteoblasts, and osteoclasts migrated) [175].

2.18.3 Meniscus Repair and Regeneration

While meniscal injuries of the knee occur primarily in the adult population they are increasingly being seen in children and adolescents owing to earlier and more intensive participation in competitive sports as well as the use of more sophisticated imaging for assessment [176, 177]. Discoid menisci also become symptomatic in adolescence. The 2 menisci play a vital role in knee function medially and laterally between the femoral condyles and tibial plateau. They help provide stability, shock absorption, lubrication,

proprioception and load distribution. An important anatomic feature is their relative avascularity. The medial meniscus is vascularized in the outer 10–30 % (adjacent to its attachment to the capsule) and the lateral in the outer 10–25 % of its width [176, 178]. Peripheral tears are thus amenable to repair, but tears or degeneration of the inner 2/3 rds tend to worsen with time since they lack the blood supply which mediates repair by providing a source of new cells. It is now well recognized that complete meniscectomy, while providing short term relief, ultimately leads to the development of osteoarthritis over a 5–10 year period in the human. Removal of a meniscus is now an experimental approach to induce partial thickness articular cartilage damage, superficial to deep as outlined in Sect. 2.18.1.2 above. As a result efforts are now made to either excise only the damaged portion of the inner rim to preserve some function. Damage to the outer 1/3 rim often undergoes surgical repair to allow the vascularity to regenerate and help in the healing process.

The meniscus is now the subject of intensive investigation and treatment by surgical and biologic means to restore its function. The following approaches are taken [176]:

(i) total meniscectomy alone is rarely performed; if degeneration is so great that the procedure needs to be done, strong consideration is now given to adding *meniscal transplantation* since vascular anastomosis is not needed, cell viability is not a factor and immunologic rejection is not a factor. Allograft is currently the best biologic option.
(ii) partial meniscectomy also tends to have relatively poor results and treatment is directed either to *surgical repair of lesions* especially in the vascular outer zones; *enhancement of repair by biologic methods* such as abrasion, gluing, synovial flaps, or fibrin clots; or *biocompatible meniscus scaffolds* which are then repopulated by cells either native or tissue engineered *stem cells* along with *growth factors.*

2.19 Tendons

2.19.1 Brief Overview of the Anatomy, Histology, and Molecular Biology of Tendons

Tendons are fibrous structures composed primarily of parallel bundles of type I collagen aligned along the longitudinal axis. They attach muscles to the cartilaginous and later bony skeleton and serve to transfer tensile loads. In the embryo and fetus they are highly cellular, have good vascularity and their fibroblasts synthesize the extracellular matrix collagen in a longitudinal orientation. Collagen provides tensile strength while proteoglycans provide for viscoelastic capability. Electron microscopic studies have revealed that fibroblasts synthesize collagen beginning within the intracytoplasmic space and then extrude small linear fibrils into the extracellular space. Self assembly then occurs in hierarchical fashion to unite adjacent fibrils into bundles which then further aggregate, or macro-aggregate, into fascicles. The discontinuous small fibril segments initially lengthen by end-to-end fusion and widen by side-to-side fusion to form mature continuous fibrils.

Type I collagen is the major protein constituent of tendon. Type III collagen is prominent in the early phases of tendon collagen synthesis in development and repair. Decorin is a proteoglycan involved in collagen fibril organization and is found in tensile segments of tendon. Aggrecan is a proteoglycan also involved in collagen fibril organization but is found in compressed segments of tendon. Other proteoglycans present are fibromodulin and biglycan. Other molecular tendon components are type V collagen, type VI collagen, cartilage oligomeric matrix protein (COMP) and proline arginine-rich end leucine-rich repeat protein (PRELP). Most of the non-extractable material is cross-linked type I collagen. The molecular components of tendon have been outlined in detail [179–181].

There is no universally accepted terminology for the increasingly complex hierarchy of fibril accumulation and relationships but the description of Elliott summarizes the views of many [182]. Three collagen chains unite to form a tropocollagen molecule. Five tropocollagens constitute a microfibril and microfibrils aggregate to form fibrils. The baseline component of the tendon is the collagen fibril which closely relates to and is cross-linked with adjacent fibrils to form the structural unit of tendon which is the collagen fiber or primary tendon bundle, a bundle of collagen fibrils lying between rows of tendon cells. Others consider that the fibers are grouped into secondary tendon bundles and these are further grouped into larger, tertiary tendon bundles. A bundle of fibers is a fascicle. Figure 2.13a shows the hierarchical formation from collagen fibril to intact tendon. These may form with some degree of rotation which increases the mechanical properties of a particular tendon. With time the fibroblasts mature and become flattened along the long axis at which time they are referred to as fibrocytes. Collagen formation was well described by Birk and colleagues in a series of studies in chick embryo tendon, primarily using electron microscopy [183–185]. Matrix organization was found to occur primarily in extracellular compartments in hierarchical fashion advancing from collagen fibrils, to bundles, and then to macroaggregates. The initial extracellular events in collagen fibrillogenesis occur within narrow cytoplasmic recesses continuous with the extracellular space. These narrow recesses then fuse and fiber bundles form. The bundles then laterally associate and

coalesce forming aggregates within a third extracellular compartment. The macroaggregates are also referred to as fascicles. Stabilization of collagen is increased by the observations that the bundles undergo a gradual rotation and also branch as formation proceeds. Further study identified the growth of mature continuous fibrils due to both lateral and linear fusion of smaller fibril segments.

The cells of tendon described above as fibroblasts and fibrocytes are referred to increasingly as tenoblasts and tenocytes. While there are no specific molecular markers for tenocytes at all stages of development there are some which are present in high concentration. These include the transcription factor scleraxis, tenomodulin (induced by scleraxis), and tenascin-C, expressed by tenocytes in response to stress [181, 186]. Scleraxis is a transcription factor and highly specific marker of tenocyte precursor populations regulating extracellular matrix (ECM) gene expression in tenoblasts [187]. Tenomodulin is a late marker of tenocyte differentiation and proliferation and is upregulated by scleraxis [181]. Tenascin-C is an ECM glycoprotein implicated in tendon development at both embryonic and differentiated cell levels [181]. Smad8 is a marker of mesenchymal stem cell differentiation in tendon progenitor cells.

Matrix metalloproteins (MMP) play a major role in remodeling and degradation of tendons in development and repair while tissue inhibitors of metalloproteinases (TIMP) are also found [180].

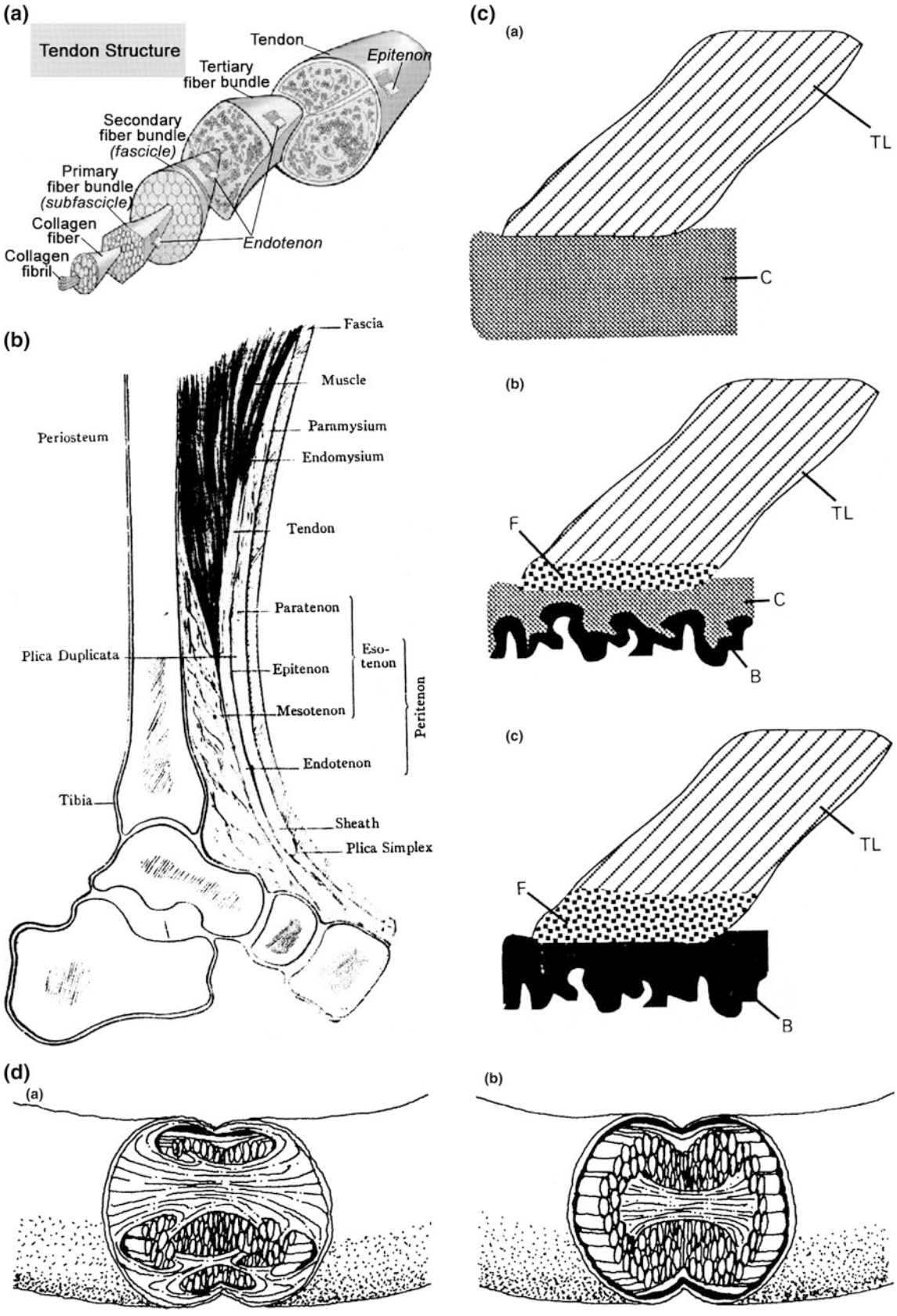
The water in tendon decreases from approximately 80–85 % in babies to about 70 % in adults. Water makes up the main component of the wet weight of tendon tissue [180, 182, 188]. Slight variation is found between different tendon types. Birch reported values ranging from 57 to 64 % [188]. Her studies also showed significant differences in material and molecular properties between spring-like tendons that are subjected to high strains with walking and positioned tendons which are subjected to much lower strains. Elastic fibers are present in the endotenon and compose about 2 % of the dry weight with collagen about 75 % of the dry weight (in man).

The fibroblasts and fibrocytes (tenoblasts and tenocytes) of developing and mature tendons are all interrelated by their cell processes which communicate with each other along longitudinal and transverse axes via gap junctions [189]. The cells of the epitenon on the surface of a tendon form a continuous layer and interdigitate with endotenon cells within the substance of the tendon. The cell-cell (or cell process-cell process) network is analogous to that linking osteocytes via the lacunar-canalicular system in bone. Tendon is very responsive to mechanical stress. Collagen synthesis increases with mechanical load with response depending on gap junctional communication between adjacent cells. Connexin 32 junctions stimulate collagen synthesis and are arranged along the line of tensile stress while connexin 43 junctions link cells in all directions and tend to translate signals that inhibit collagen synthesis.

The tendons attach to/emanate from the ends of adjacent muscle by fibrous tissue continuity with the fibrous components of the muscles (epimysium, perimysium and endomysium) and, as noted ultrastructurally, by evidence that the tendon fibrils themselves surround individual myofibrils at the junctional areas and physically attach to the sarcolemma, the outer surface of the myofibril [180, 182, 190]. It is no longer considered that the myofibril is fully continuous with the collagen fibrils of the tendon by a mechanism of transformation, a view once strongly held by some based on light microscopic inferences. At their distal attachments, the tendon fibrils pass deeply into the cartilage models of the developing bone and eventually the bone itself. These attachments are referred to as entheses [191]. Tendon is felt to grow interstitially in length based on a structure-function interrelationship with its muscle belly. The region of maximal growth is at the muscle-tendon junction while the least growth is at the tendon-bone junction.

Within the tendon, both individual fibrils and individual fascicles slide independently against one another. This is due to the endotenon, the loose connective tissue layer present between the fascicles and larger fiber bundles which also allows for passage of the intratendinous blood vessels [180]. This sliding occurs within a proteoglycan rich matrix with such molecules as lubricin present.

Tendons must glide smoothly in relation to surrounding structures and must have a blood supply for growth, maintenance and repair. Their anatomic structure is adapted to these necessities and has been described many times, although with slightly differing terminology [180, 181, 192, 193] (Fig. 2.13b). Within the tendon, clumps of collagen fibers are surrounded by a thin layer of endotenon which is continuous with a connective tissue layer or series of layers around the tendon referred to as the epitenon (Fig. 2.13a, b). Additional anatomic features of the peri-tendinous environment are dependent on whether the tendon is constrained to pass in fibrous or fibro-osseous sheaths or under fibrous retinacula for stabilization or whether it lies unconstrained in loose surrounding connective tissue [194]. When a tendon passes through a sheath or in relation to a protective bony groove (pulley) or fibrous retinaculum it is in the process of changing direction and is surrounded in that region by a synovial cavity. These are referred to as “wrap-around” tendons. When a tendon passes in linear fashion from origin to insertion no sheath is present. These are referred to as direct tendons. When constrained, it is covered by a two-layered synovium with parietal and visceral layers continuous at the ends with synovial fluid between the layers enhancing the gliding capability. When not constrained and not covered by synovial tissue the tendon is surrounded by


(a)
Tendon Structure
Tendon
Epitenon
Tertiary fiber bundle
Secondary fiber bundle (fascicle)
Primary fiber bundle (subfascicle)
Collagen fiber
Collagen fibril
Endotenon
(b)
Fascia
Muscle
Periosteum
Paramysium
Endomysium
Tendon
Paratenon
Eso-tenon
Plica Duplicata
Epitenon
Peritenon
Mesotenon
Endotenon
Tibia
Sheath
Plica Simplex
(c)
(a)
TL
C
(b)
TL
F
C
B
(c)
TL
F
B
(d)
(a)
(b)

multiple concentric layers of epitenon. The more peripheral loose, fatty or filmy connective tissue in which the tendon lies is called the paratenon which fills the interstices of the fascial compartment where the tendon lies. The paratenon allows the tendon to glide freely against the surrounding tissue.

2.19.1.1 Blood Supply of Tendons

The blood supply to the tendon is derived from four sources: (i) the myotendinous junction, (ii) the osteotendinous junction, and (iii) the surrounding soft tissues via the mesotenon either from a) extra-synovial regions through the loose tissue surrounding the tendon (called by some the paratenon) or from b) synovial regions through synovial mesenteric-like attachments (vincula) [182, 192, 195] (Fig. 2.13b). The major supply however is from the surrounding soft tissues via a specialized connective tissue layer referred to as the mesotenon. In areas where the tendon is not constrained, the mesotenon merges with the epitenon of the tendon at one part of its circumference, usually on the inner or protected region away from the subcutaneous side. [Terminology regarding the soft tissue layers surrounding a tendon within non-constrained areas is variable with the terms peritenon, paratenon, and mesotenon often used to describe the same regions. One can consider the para- or peri-tenon to be the regions furthest away from the tendon whereas those closer containing more concentrated blood vessels are the mesotenon and vincula.] Edwards refers to the loosely woven connective tissue surrounding tendons with no synovial sheath as the paratenon [195]. Smith fine-tunes the definition of the peri-tendinous tissues [196]. The paratenon is the thin filmy layer of connective tissue that surrounds each tendon. The blood vessels of the musculotendinous structures have a longitudinal orientation; all of the tendon blood supply enter/exit it via the mesotenon, a thin filmy sheet of tissue attached to the undersurface of the tendon. When not within a sheath the mesotenon usually is in the same plane as the adjacent muscle at its most distal attachment into the tendon. When constrained within a sheath, the mesotenon is usually collected or condensed into several more localized fibrous bands where the blood vessels are concentrated and this is referred to as the vincula. The parietal layer of the synovium receives its blood supply from the periphery and the inner visceral layer from the mesotenon and its specialized vinculae. Edwards describes the blood supply of the tendon within the synovial sheath in similar fashion; within the synovial sheath the tendon in a thick sheet of very vascular fibroelastic tissue, the visceral layer of the synovial membrane [195]. This layer is continuous with the parietal layer at the ends of the sheath (from which it gets some blood supply) while other blood supply comes from vessels in sheets of tissue known as mesotenons connecting the 2 layers. [The cord like mesotenon is also described as a vinculum.] Smith points out that "each vinculum appears under microscopic observation to be a condensation of the mesotenon. Many small vessels enter and leave the tendons through these small bands" [196]. Vessel studies by Smith did not identify enhanced vascularization of the tendon at either musculotendinous or tendo-osseous junctions. He concluded that "the blood supply to tendons is through the mesotenon which contains a segmented pattern of arcades" and that "the blood supply of a tendon is not significantly increased through its attachments to muscle or bone" [196]. Edwards also agreed, finding that tendon did not derive significant bloody supply from muscular arterioles or the osteo-tendinous junction [195].

While the blood supply of the tendon is considered as coming from four sources, it is the two surrounding soft tissue components that are the greatest source by far for each of the phases of growth, maintenance, and repair. Vessel continuity from muscle at one end and from the bone at the other end passes only a few millimeters into the adjacent tendon. The major blood supply approaches the tendon by vessels from the paratenon where they generally lie in a transverse direction (to the tendon) and then enter from the mesotenon. The vessels then ramify up and down the surface in the epitenon and enter the tendon along the endotenon. The vessels within the tendon are small and thin-walled. They run longitudinally parallel to the fascicles and within the endotenon. While some anastomoses between adjacent

◀**Fig. 2.13** **a** The hierarchical structure of a tendon is illustrated [211]. (Reprinted with permission from Sharma and Maffulli, Tendon injury and tendinopathy. J Bone Joint Surg Am 2005;87A:187–202). **b** The intratendinous and extratendinous fibrous tissue layers which stabilize, surround and pass into tendons and also provide the pathways for vascular supply are shown [192]. **c** Entheses are attachment sites where tendons or ligaments (*TL*) attach into bone. In the top image (*a*), the TL attaches directly into the cartilage model of the bone. As development proceeds in the middle image (*b*), the TL undergoes fibrocartilaginous (*F*) differentiation at the attachment site before entering the cartilage (*C*) and bone (*B*). The fibrocartilage is initially uncalcified but becomes calcified as it approaches the cartilage of the bone. At bottom (*c*), the TL continues as mineralized fibrocartilage (*F*) attaching into bone. Some entheses are purely fibrous, attaching directly to bone without a fibrocartilage phase [194]. (Reprinted with permission from Benjamin and Ralphs, Fibrocartilage in tendons and ligaments-an adaptation to compressive loads. J Anat 1998;193:481–494. Copyright 1998 John Wiley and Sons). **d** Two basic mechanisms of tendon healing are illustrated. *A* Extrinsic healing. This occurs where fibroblasts and inflammatory cells from the periphery invade the healing site to enhance repair but, in the process, predispose to scar formation and peri-tendinous adhesions. This method characterizes tendons which heal with prolonged immobilization. *B* Intrinsic healing. Fibroblasts and inflammatory cells from within the tendon play the major reparative role. This mechanism is enhanced by early motion and shows diminished peri-tendinous adhesions [212]. (Reprinted with permission from Beredjiklian PK, Biologic aspects of flexor tendon laceration and repair. J Bone Joint Surg Am 2003;85A:539–550)

regions occur most authors have described a series of fairly limited segmental vascularities within each tendon. Within the tendon the vessels (referred to as intratendinous vessels) lie within the interfascicular connective tissue endotenon and run in a series of longitudinal channels connected by transverse anastomotic vessels. Each artery, generally an arteriole, is accompanied by 2 veins referred to as venules. Further branching occurs as capillaries lie infrafascicular forming a capillary plexus eventually linking arterial and venous channels. The intrafascicular plexus does not appear to penetrate collagen bundles. Edwards also describes a corresponding lymphatic system around and within tendons [195].

Brockis [197] has demonstrated the blood supply of the flexor and extensor tendons of the human fingers. Where the tendons have no sheaths and lie in loose connective tissue (paratenon} the vessels pass through the loose tissue at frequent intervals to supply the tendon. Where the tendon lies within a synovial sheath the blood vessels follow a different pattern. Blood vessels pass into the tendon via the vincula (synovial bands) or at the proximal and distal ends of the tendon sheaths. Once within the tendon the vessels lie in the interfascicular connective tissue which binds the collagen bundles together. Most of the vessels run along the longitudinal axis of the tendon connecting with one another through transverse branches.

Petersen et al. have studied the intratendinous blood supply of the tibialis posterior tendon [198], tibialis anterior tendon [199], peroneal tendons [200], and quadriceps tendon [201]. Previous assessments of the blood supply of tendons commented on the segmental nature of the intratendinous blood supply with relatively few anastomoses (from segment to segment). In the study of the tibialis posterior tendon the distributions of blood vessels within the tendon was not homogeneous. The number of vessels in the substance of the tendon was consistently less than that in the surrounding paratenon. The vessels were significantly reduced in the retromalleolar region compared to proximal and distal segments. This is the region prone to spontaneous rupture (in adults) and appears to have a more fibrocartilaginous structure, as shown in other tendon studies at sites where tendons run around a bony pulley as they change direction (gliding tendon). The hypovascularity predisposes to degeneration and delayed healing.

Blood supply entering the tibialis anterior tendon was from the anterior tibial artery proximally and from branches of the medial tarsal artery distally [199]. The vessels entered via vinculae from the peritenon from the posterior side and then ran in characteristic longitudinal fashion. The number of vessels in the tendon was markedly less than in the surrounding peritenon, the distribution of vessels within the tendon was not homogeneous and the posterior part of the tendon had a continuous vascular network while in the anterior half of the tendon there was a lengthy avascular zone 45–67 mm in length.

In the peroneal tendons the supply was from the peroneal artery with the distal part of the longus also supplied by the medial tarsal artery [200]. The pattern of supply was similar to other tendons described being from the posterior peritenon and not homogeneous. Regions of avascularity occurred around grooves where changes of direction were happening; peroneus brevis through the fibular groove at the lateral malleolus and peroneus longus where it curved around the lateral malleolus and the peroneal trochlea of the calcaneus and more distally where it wraps around the cuboid.

In the quadriceps tendon the anterior part is vascularized throughout its length while there is an avascular segment posteriorly about 30 × 15 mm at the level of the patellar groove where compressive stress is greatest when the knee is flexed [201].

2.19.1.2 Entheses

Entheses are attachment sites where tendons and ligaments meet and fasten into bone. There are 2 main types of entheses, fibrocartilaginous and fibrous. The classic fibrocartilaginous enthesis has 4 zones of tissue at the tendon insertion (Fig. 2.13c). Zone 1 is dense fibrous connective tissue, the tendon; zone 2 is uncalcified fibrocartilage; zone 3 is calcified fibrocartilage; and zone 4 is bone [186, 191, 194, 202]. At some sites this transition is well marked but at others there are no sharp boundaries between the zones. The other entheses are fibrous. Fibrous entheses have the tendons or ligaments attaching directly to the bone or indirectly to it via the periosteum with no fibrocartilage differentiation. The fibrocartilaginous/fibrous terminology of Benjamin and Ralphs has been called chondral/periosteal by Knese and Biermann [203] and direct/indirect by Woo et al. [204]. Tendons and ligaments that attach to epiphyses of long bones or to bones of the carpus and tarsus do so by fibrocartilaginous entheses while those attaching to metaphyses or diaphyses are fibrous. Early descriptions of fibrocartilaginous entheses were by Dolgo-Saburoff [205] in 1929 and Cooper and Misol [206] in 1970. There is even a tidemark (similar to articular cartilage between the uncalcified and calcified zones of fibrocartilage).

The tendon-bone attachment is a unique biologic accomplishment since it unites tissues of very different mechanical behaviors with tendon compliant and bone stiff. The structure-function relationship is particularly well developed at these sites. The gradually increasing mineral content and the changing collagen fiber orientation (parallel in tendon to more randomly oriented in bone) are optimized to minimize stress and strain concentrations. Thomopoulos et al. have likened development of an enthesis to growth plate development with many of the same molecular cascades involved [207]. There are prominent roles in enthesis

development for SOX-9 (chondrogenesis), scleraxis (tenogenesis), collagen X (mineralization of cartilage in growth plate hypertrophic zone and in mineralizing enthesis fibrocartilage) as well as major roles for Indian hedgehog (Ihh) and parathyroid hormone related protein (PTHrP).

2.19.1.3 Fibrocartilage in Tendons and Ligaments

While tendon attachments to bone are specifically adapted to their function, adaptations also occur within the mid-tendon regions as well. Specifically, where tendons bend around a bony pulley or pass through a fibrous tunnel (retinacula) they have a fibrocartilaginous structure as an adaptation to compression. These regions are often referred to as "wrap-around" tendons. In a molecular sense it is the glycosaminoglycan content that is raised.

Petersen and colleagues have also shown these regions to be hypovascular and avascular [198–201]. The fibrocartilaginous regions of entheses are avascular due to the mechanical conditions to which they are subjected. There is also greatly diminished blood supply of tendons in regions where they wrap around bony pulleys.

2.19.1.4 Structure/Function Relationships in Tendon and Tendon Attachments

Tendons and ligaments generally flare out or widen at their attachment sites as an adaptation to increase anchorage and resist effects of insertional angle change. This can be seen at sites of tendo Achilles and tibialis anterior and posterior tendon attachments. The term Sharpey's fibers has been attached to the concept of fibrous septa attaching to bone by passing relatively deeply into it. The fibers pass into cortical bone and generally even between adjacent lamellae. Fibrous entheses attaching to cortical bone and the sites where the periodontal ligament is attached to cementum and alveolar bone represent true Sharpey's fibers as do sites of surgical reattachment of tendons and ligaments to bone. At fibrocartilaginous entheses attachments are not primarily to cortical bone but the soft tissue/hard tissue boundary occurs primarily at the tidemark where non-calcified and calcified regions relate.

Tendon is characterized by four primary mechanical properties: great tensile strength, flexibility, inextensibility, and elasticity [182]. Tendons have some ability to stretch and recoil elastically. The elastic recoil property appears structurally related to crimp (knots within fibrils) in regions where fibrils are twisted or bent. Tendons can be stretched physiologically in the 5–6 % range with stressful activity. In limb lengthening muscle may elongate 10 % of initial length while tendon elongates only 3–4 % [180].

2.19.1.5 Musculo-tendinous Attachments

As muscle approaches tendon there must be anatomic union between the two to allow for functioning. It is now generally agreed that the sarcolemma, the membrane covering every muscle fiber, fuses with the collagen fibers of the tendon to form the points of attachment [182]. Prior to the advent of electron microscopy and, prior to that, advanced light microscopy with special histochemistry, many felt that there was transitional continuity between muscle fibrils and tendon fibrils. As early as 1913 however Baldwin [208] was noting slender bundles of collagen fibrils inserting between processes of the sarcolemma. In short, although interdigitation of tendon and muscle is common, sarcolemma always intervenes.

2.19.1.6 Nerve Supply to Tendons

Tendon innervations comes from cutaneous, muscular, and peritendinous nerves. Most of the supply is concentrated at the myotendinous junction. The nerves ultimately travel into the fibrous septae and are present in paratenon, epitenon and endotenon. Specialized mechano-receptors are concentrated at the myotendinous junctions [186].

2.19.2 Surgical Approaches to Tendons to Correct Deformity

Surgery on tendons to correct deformity can involve tenotomy (which refers to a release or complete transverse cut of the tendon), lengthening of a tendon, shortening of a tendon, transfer of a tendon insertion, or lysis of a tendon bound by peritendinous scarring. Attention should be paid as to whether the tendon is intrasynovial or extrasynovial in any repair situation either post-trauma or with deformity correction. Intrasynovial tendons are within tendon sheaths containing lubricating and nutritive synovial fluid (e.g. digital flexor tendons of the hand). Extrasynovial tendons, like the Achilles or patellar tendons, are surrounded by thin fascial layers but no synovium.

2.19.2.1 Tenotomy

The biology of repair following complete tenotomy with separation of the cut ends. Tenotomy refers to the complete cutting of a tendon for the purpose of correcting a deformity. This is followed by manual stretching of a deformed region to a neutral or anatomic position such that the tendon ends are separated during the repair phase. The tenotomy can be (i) percutaneous, where it is cut without direct visualization following insertion of the scalpel through a small skin incision or (ii) open, referring to cutting of the tendon through a larger skin incision which allows for visualization

of the tendon as it is released. Tendons tend to undergo complete repair after percutaneous or open tenotomy, especially in childhood. This was recognized clinically and studied experimentally in animal models as early as the mid-1800s. It was the effective use of percutaneous tenotomy for correction of ankle equinus deformity by Stromeyer of Hanover, Germany beginning in 1831 that effectively launched the surgical component of orthopedics [13]. The operation was done initially in adults but was soon adopted by Little in London and others throughout Europe for equinus accompanying childhood club foot and neurogenic deformities. Stromeyer performed Achilles tenotomy using a very small incision, referred to as the subcutaneous technique, which greatly minimized infection in the pre-antiseptic era and led to successful adoption in many centers. He reported excellent results in 6 cases in 1833 and 1834. The first successful case reported in Britain by Little using the subcutaneous technique was in 1837 [16]. Adams in his classic book "On the Reparative Process in Human Tendons" published in 1860 described the healing in subcutaneous tenotomy based on post-mortem examination of 15 specimens operated for club foot with subjects dying from 4 days to 3 years post-surgery of non-related causes [15]. The work was also supplemented by his experiments in the rabbit and a detailed appendix reviewing clinical and experimental studies by several European physicians from 1816 to 1858. Animal experiments invariably showed union with tenotomy.

(a) **Adams' summary of the reparative process of the tendo Achilles tenotomy**. This remarkable study published in 1860 remains valid today [15].
   (i) Immediate results of the operation. Separation of the divided ends of the tendon occurred post-release to a variable extent and was recognized to be greater if the foot was dorsiflexed to neutral but less if allowed to remain in equinus. The question of positioning of the foot and ankle post tenotomy was widely debated at that time. Some left the foot in plantar flexion to allow gap healing to begin and then gradually stretched the foot to a neutral ankle position. Positioning in equinus with splinting was done by many in that era to allow healing to begin after which gradual stretching of the repair tissue by dorsiflexion to neutral was done. For those who used positioning in equinus post-surgery the time before beginning dorsiflexion to neutral varied from a few days to a couple of weeks. Others immediately stretched the ankle to the neutral position and allowed healing to fill the gaps.
   (ii) Influence of the sheath. The cellular sheath tended to remain intact for most of its circumference and served as a directing mechanism both for repair and to diminish adhesions. The intact sheath was felt "indirectly" to connect the two cut ends since it did not contract with the cut tendon.
   (iii) Commencement and nature of the reparative process. Very little blood accumulated in the tendon sheath and it was not considered to be a necessary occurrence for repair to occur. The major response initiating repair was ingrowth of vascular tissue from the subcutaneous cellular tissue and the tendon sheath. This increased vascularity of the tendon sheath in the human was felt to be the first step in repair. A "blastematous" response followed (=undifferentiated cellular material, in current terminology).
   (iv) Development of the reparative material. "The blastematous material" (cells with prominent nuclei) was recognized as the reparative material from which new tendon developed with any inflammatory material seen being an accidental complication rather than an essential component. The repair cells assumed an elongated shape in parallel series. Microscopic examination revealed that a fibrous tissue developed with time.
   (v) Appearance and structure of the newly formed tendon. Adams observed that "A solid bond of union is formed between the divided extremities of the tendon." The greatest length of repair Adams noted clinically was $2^{1/4}$ inches in a 9-year-old girl. The repair tissue was described as "tough" but "homogenous" rather than "fibrous." Even with full repair (up to 3 years later) the repair maintained a "grayish translucent appearance." Adams maintained that the new repair tendon tissue persisted and so closely resembled the old tendon by microscopic exam as to be "scarcely distinguishable from it." The newly-formed connective tissue remained permanent in uniting the cut ends. Repair was not initiated in the cut ends of the original tendon. The repair tissue from the defect grew into and united with the old tendon. Once the repair tissue united the two ends of the tendon, its blood supply diminished and it developed the appearance and width of the original tendon. A new sheath formed. The tendon almost invariably reunited completely. Adhesions could occur but usually were resorbed. The tibialis posterior tendon underwent a similar repair after sectioning.

This sequence of events is accepted today and basically describes the response following percutaneous tenotomy of the Achilles tendon for correction of equinus deformity in idiopathic club foot.

2.19.2.2 Tendon Repair Following Lengthening with Continuity Either Maintained or Re-established Intra-operatively by Suturing

With the exception of percutaneous Achilles tenotomy in the first few months of life for idiopathic club foot deformity and multiple tenotomies to correct severe foot deformities in non-ambulatory neuromuscular patients, surgeons now prefer to have continuity of the lengthened tendon immediately after corrective surgery as the repair process begins. Tendons heal well following lengthening and surgical repair. The techniques for lengthening that maintain continuity are the slide-in-continuity and myotendinous (Vulpius) procedures while surgical repair with sutures is needed in Z-type lengthenings.

(a) **Slide-in-continuity lengthening.** Slide-in-continuity technique for lengthening is done primarily for tendoAchilles lengthenings where it is feasible owing to the unique anatomic structure of that tendon. The procedure was originally described by White [209]. There is a 90-degree rotation or twist of the tendon fibrils between the tendon origin at the gastrocsoleus muscle and its insertion into the calcaneus such that medial fibers proximally are positioned posteriorly at the distal end. Transverse sectioning of the medial fibers proximally (through one-half to two-thirds of the tendon) and anterior fibers distally (through two-thirds of the tendon) allows for stretching and sliding of the tendon in-continuity since virtually all fibrils will have been cut once with this approach, thus loosening their hold. Suturing is not needed once manual correction has dorsiflexed the ankle to neutral and a stabilizing cast has been applied.

(b) **Myotendinous (Vulpius) lengthening.** Vulpius described his operation in 1911 and it is ideal for mild to moderate deformities in those muscles where a lengthy myotendinous component exists as the muscle tissue transitions to tendon [210]. The overlying tendinous component is cut but the underlying muscle remains intact. The orientation of the cut is usually an inverted V with the apex pointing proximally. With passive manipulation of the joint to the correct position the muscle stretches in-continuity while the tendinous components separate. During the period of cast immobilization the tendon component heals and there is no need for suture repair. This procedure is most widely used today for correction of mild to moderate tendo Achilles contractures and for hamstring lengthening in neuromuscular patients at the biceps femoris and semimembranosus muscles. Where additional correction is needed two inverted V incisions in the tendon can be made approximately 2 cm. apart.

(c) **Z-type lengthening.** In the Z-type lengthening the tendon is cut along its midline axis followed by a transverse cut to one side proximally and another transverse cut to the other side distally. The distal cut is placed medially if there is also a varus component to the deformity. As the contracted joint is straightened to neutral by gentle passive manipulation the two parts of the cut tendon move in opposite directions, lengthening the tendon by moving the origin and insertion further apart. At the desired length of correction which places the distal joint in the desired anatomic position at a right angle the 2 parts are sutured together, side to side, to allow for healing. Most surgeons stabilize the tendon with non-absorbable sutures placed in mattress fashion with the knots buried away from the subcutaneous surface of the tendon. The greater the contracture, the longer the midline cut should be since more lengthening (separation) is needed but a relatively large amount of side to side coaptation is desirable to enhance the strength of the repair after healing. Repair is mediated by vessels and cells from the surrounding paratenon, mesotenon and epitenon which differentiate to fibroblasts.

There is an almost universal tendency for tendons to heal whether there is a gap, such as following a transverse tenotomy, lengthening with continuity of the accompanying muscle, or lengthening of the tendon with suturing. The major difficulty encountered with tendon surgery is not healing but peri-tendinous adhesions leading to post-operative stiffness especially with repair in intrasynovial loctions, in particular at the wrist and hand.

2.19.2.3 Other Lengthening Methods

There are 2 other methods for lengthening tendons which are infrequently described, less well studied and used only in difficult and often unexpected situations where tendon length must be increased more than was planned in a Z lengthening or beyond the length of the transferred tendon once it is positioned at its new site of insertion. These include (a) a 180º rotation flap and (b) autologous tendon suture.

2.19.2.4 The Phases of Tendon Repair

There are 4 phases of tendon repair: hemorrhagic, inflammatory, proliferative, and remodeling [211].

(a) **Hemorrhagic stage**. Immediately after injury blood vessel damage leads to hematoma formation around the injured tendon ends.
(b) **Inflammatory stage.** The clot activates the release of chemotactic factors (vasodilators, proinflammatory molecules) that attract inflammatory cells. Erythrocytes, white blood cells (especially neutrophils), platelets and macrophages all migrate to the wound site followed shortly by fibroblasts (tenoblasts) that begin to synthesize extracellular matrix components. Angiogenic factors enhance repair and re-establishment of an intact vascular supply. Phagocytosis of necrotic cells and tissues goes on simultaneously. Tenoblast/tenocyte cells initially synthesize large amounts of type III collagen along with type I collagen.
(c) **Proliferative stage.** After a few days the proliferative phase begins to dominate at the repair site. Fibroblasts/tenoblasts synthesize large amounts of collagen, initially type III, to establish a repair scaffold which increasingly leads to type I collagen synthesis. Water content and glycosaminoglycan concentrations are high. Collagen is deposited at the repair site (collagen III) in a random array. The repair tissue is highly cellular with extensive ECM components, both collagenous and non-collagenous, and a re-established vascular network highlighting the repair response.
(d) **Remodeling stage.** After 6–8 weeks remodeling predominates with predominantly collagen type I fibrils becoming aligned and synthesized along a longitudinal array. There is decreased cellularity and decreased collagen and glycoaminoglycan synthesis. The consolidation stage (approximately 6–10 weeks) finds the repair tissue changing from cellular to fibrous but tenocytes remain active synthesizing collagen and aligning it to parallel array along lines of stress. After 10 weeks the maturation stage continues for as long as a year finalizing tendon tissue structure with diminished tenocyte metabolism and tendon vascularity. Matrix metalloproteinases (MMPs) are important during the remodeling phase. MM9 and MM13 participate in collagen degradation while MMP2, MMP3, and MMP14 are involved both with degradation and remodeling. Tissue is strengthened in the remodeling stage by increasing intramolecular and intermolecular collagen crosslink formation [211].

Tendon healing occurs by 2 mechanisms: intrinsic and extrinsic (Fig. 2.13d). Intrinsic healing occurs within and between tendon ends as tenocytes from endotenon and epitenon migrate and proliferate into the injury site, establishing the extracellular matrix and neovascular networks. Extrinsic healing is characterized by invasion of cells from the surrounding sheath and synovium. In general intrinsic healing supplies more direct repair with better biomechanical tissue organization and fewer adhesions. Extrinsic repair is more extensive but associated with more prominent adhesions. The extrinsic mechanism is activated earlier while the intrinsic mechanism is favored by greater interfragmentary stability and close coaptation. The intrinsic mechanism is activated when primary surgical repair is soon followed by gentle mobilization while the extrinsic mechanism occurs in association with prolonged immobilization.

2.19.2.5 Molecular Components of Tendon Repair

Several growth factors are activated during tendon repair. Transforming growth factor-β (TGF-β) stimulates cellular migration and proliferation in the early stages of repair. Insulin-like growth factor-1 (IGF-1) and platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) are also present to enhance repair. The molecules listed above in Sect. 2.19.1 which are components of normal tendon and play a significant role in development of tendon are also integrally involved in repair [211, 212].

2.19.2.6 The Biology of Tendon Repair in Relation to Immobilization and Mobilization

Immobilization of the repaired region after tendon surgery has long been considered as an essential component for full repair to occur. This is particularly true with childhood and adolescent surgery for tendon alterations (usually lengthening or transfer) in relation to deformity correction. With the exception of repairs of tendons passing through fibrous or fibro-osseous sheaths with synovial coverings (such as at the hand, wrist and forearm) immobilization has been a positive feature for the repair process. While some stiffness is present at the time of discontinuation of post-operative immobilization, resumption of activity and physical therapy almost always allow for a return to good joint mobility. This has not been the case with upper extremity wrist and hand surgery however, especially at the flexor forearm, wrist and hand regions, and extensive study of repair with early mobilization has been done. Immobilization at these sites enhances tendon repair (as it does elsewhere) but predisposes to peritendinous adhesions (with stiffness and joint contractures) while earlier mobilization minimizes adhesions but can weaken the repair.

In dog models Gelberman et al. have shown that repair occurs with both early controlled passive mobilization and total immobilization [213–215]. The mechanisms of repair are markedly different however. Repair is mediated with mobilization by proliferation and migration of cells from the

epitenon in the depths of the repair site which greatly diminishes adhesions since ingrowth of reparative tissue from the tendon sheath is notably lacking in this group. With total immobilization repair is characterized by excessive ingrowth of connective tissue from the digital sheath which leads to stiffness and adhesions and overwhelms the epitenon response (Fig. 2.13d). The epitenon cells in the early mobilization group also show great cellular activity and collagen production at each assessment time compared with the immobilized group.

Much clinical and experimental work on flexor tendon repair has led to a series of principles outlined by Beredjiklian [212]. (1) Core sutures (placed through the cut ends of the tendon at the laceration site) in combination with a peripheral epitendinous suture provide the most strength and prevent gapping at the repair site. (2) Stress (motion) at the repair site increases the amount of collagen deposited at the site of the injury and aids in the organization of the collagen deposited, resulting in a stronger repair but not in faster healing. (3) The strength of the tendon repair is proportional to the number of sutures and the caliber (size) of the suture crossing the repair site. (4). Nonabsorbable braided sutures (3-0 or 4-0) are optimal for use as core sutures. (5) Dorsal placement of the core sutures provides more mechanical strength than would volar placement of the sutures. However, because of the location of the nutrient vessels, dorsal sutures can also interfere with the blood supply to the tendon proper. (6) There should be equal tension across all suture strands. (7) Because the repairs of tendons that have been treated surgically and immobilized become weakest at approximately 21 days, rehabilitation must proceed with caution. Principles of post-operative therapy include: (1) Wrist and metacarpophalangeal joints should be maintained in flexion at rest. (2) Distal and proximal interphalangeal joints should be maintained in extension at rest. (3) Therapy should involve frequent application of motion (active or passive).

2.19.3 Tendon Transfer

In a tendon transfer procedure the insertion of a tendon is transferred to a different position for the purpose of changing the direction of function of the involved muscle. It is generally done for correction of asymmetric muscle function across a joint which has been causing deformity. The transfer of a tendon minimizes its deforming action at its original site and, if successfully functioning in its new insertion site, balances muscle strength across a joint by enhancing motion which was either weakened or absent pre-transfer. The procedure is designed to turn a deforming action into a normal functional force. When the procedures were developed over a century ago they were usually referred to as tendon transplantation [192], but the preferred term today is tendon transfer or myotendon transfer. These procedures are generally performed for neuromuscular disorders but may play a role in treating congenital or post-traumatic deformities. They can be done in both upper and lower extremities. In the neuromuscular group the transfer is generally done both to replace the function of a weakened muscle and to diminish the deforming force of a relatively overactive or unopposed muscle.

Nicoladoni first described tendon transfer in 1882 [216]. By the start of the twentieth century it was done with increasing frequency but, as Mayer noted, there was little to no agreement amongst those performing the procedures as to the essential intra-operative and post-operative approaches [192]. Mayer helped to place tendon transfer into a scientific framework describing his investigations in 3 classic articles in 1916 [192, 217, 218]. His early studies confirmed a previous theory that post-surgical adhesions could be prevented by placing the transferred tendon into the sheath of the paralyzed tendon. He determined to adapt tendon surgery to the normal anatomy and physiology of the tendon, including the degree of tension fixing the tendon and allowing for a direct line of passage of the tendon from muscle origin to insertion. Several principles of tendon transfer were outlined by Mayer and many others have since outlined their approaches as well. There are some criteria consistent in all reports but significant differences exist as well based on individual surgeon experience and the nature of the underlying disorder for which the transfer is being done. There are differences in particular between the transfer of muscle for focal weakness such as seen in poliomyelitis and the peripheral neuropathies compared to transfer for muscle over-activity as in cerebral palsy.

When transferred, a muscle may lose strength but generally maintains its pre-transfer strength. Tendon transfers do best with in-phase repositioning, by which is meant transfer to a position where its direction or plane of function is unchanged, for example maintaining ankle dorsiflexion by transferring the tibialis anterior (dorsiflexion and inversion) laterally but still onto the dorsum of the foot to continue dorsiflexion while minimizing inversion. Out-of-phase transfers, while still capable of functioning well might require extensive physical therapy for re-training, such as transferring a plantar flexor (tibialis posterior) to the dorsum of the foot to enhance dorsiflexion.

On occasion a tendon transfer may be only partially successful, for example by effectively removing a deforming force (at its original site) but not working actively at its new position, at a normal level of strength, often due to peri-tendinous adhesions. Some refer to this result of limited or partial function at the new insertion as a functional tenodesis.

The gliding mechanism is best maintained according to Mayer by transferring a tendon within a sheath, although this is often not possible and certainly not essential. Tension was also discussed and he considered that the distal tendon end should be sutured to the bone with the joint held at neutral position and the tendon under "just sufficient tension to render it taut." This remains an accurate concept today. If the transferred musculotendinous unit was pulled too tight it would serve as a deforming force in the opposite direction and if it was repositioned too loosely it would be inefficient in function. The gliding mechanism within a constrained space involves the synovial layer having the ability to stretch in one position and contract in the opposite position. The specialized region that does this is referred to as a plica conformation. Above the sheath the gliding of the tendon is allowed by the elasticity of the paratenon.

Mayer summarized his principles for successful tendon transfer [217]:

(i) A physiological tendon operation must conform with general surgical principles of absolute asepsis, minimal haemorrhage, and minimal trauma;
(ii) It must restore the normal relationship between the tendon and sheath (wherever possible);
(iii) The course of the tendon to its new insertion must run through tissue adapted to the gliding of the tendon. Injury to the periosteum or the crude boring of a hole through fascia or interosseous membrane is inconsistent with this demand;
(iv) The normal insertion of the tendon must be imitated wherever possible by implanting the living transplanted tendon directly into bone or cartilage, preferably at the insertion of the paralyzed tendon;
(v) The normal tension of the transplanted tendon must be re-established and the physiological length of the transplanted muscle maintained;
(vi) The line of traction of the transplanted tendon must be such as to enable it effectively to do the work of the paralyzed tendon.

Mayer further stressed that it was essential not to overstretch the transferred muscle since overstretched muscles could themselves degenerate limiting the value of their repositioning. Adhesions could develop if the periosteum (other than at the site of insertion) was damaged or if passage through interosseous membranes or fascial membranes was too tight. The tendon transplantation should never be used to correct a bony deformity [218]. Any bony deformity needed to be corrected before tendon transfer. The sole purpose of the tendon transfer was to restore normal muscle balance. Post-operative care was as essential to a good result as the operation itself. It is interesting to note that Mayer, writing a century ago (1916) in the context of limiting adhesions, stressed that "whenever the typical physiological fixation has been possible, it is safe and wise to begin active exercise of the transplanted tendon a few days after the operation" [218].

William T. Green also outlined the basic principles of tendon transfer, based on his extensive experience with poliomyelitis cases [219].

(i) The muscle to be transferred must have adequate motor strength to carry out its new function. The preferred strength levels were good (4/5 in current grading) or normal (5/5);
(ii) The range of motion of muscles on contraction must be similar to that of the muscles for which they are being substituted;
(iii) In choosing muscles for transfer the loss of their original function due to transfer must be balanced against the gains to be obtained;
(iv) The joints upon which the transferred muscle is to act should have a functional range of motion. All contractures at that joint should be corrected first;
(v) A smooth channel to allow for gliding of the tendon at its new site must be provided. A wide portion of the interosseous or intermuscular septum must be removed whenever muscles are passed from one compartment to another;
(vi) The neurovascular supply of the transferred muscle must not be damaged during the transfer;
(vii) A straight line of contraction should be provided between muscle origin and its new insertion;
(viii) The tendon should be reattached to its new site under sufficient tension to allow for a maximal range of contraction. The tendon is generally attached to bone in the lower extremity and to another tendon in the upper extremity.

2.19.3.1 Mechanisms of Tendon Attachment with Transfers

There are three common ways to reinsert a tendon to its new site. These are: (i) via a cylindrical defect directly into bone. A cylindrical drill defect, for example from dorsal to plantar surfaces through the mid-tarsus, is made into which the tendon end is passed a distance 1.5–2 cm. With healing the tendon is embedded into bone as it was at its original site. Non-absorbable suture is woven through the tendon (Bunnell-style) and the 2 strands of suture exit at the tendon end. The suture and tendon are then passed through the cylindrical bone defect with the 2 suture ends exiting through the plantar surface of the foot and the suture strands then tied over a button at appropriate tension to enhance full healing of tendon to bone at desired length and tension.

Bone and marrow tissue removed by drilling are collected and placed at the tendon-bone junction at the time of closure; (ii) via suturing into surface periosteum or perichondrium. Some suture the tendon into the periosteum or perichondrium and rely on casting to hold position during repair. This is the method recommended by Mayer and described by him in detail [192]. At the insertion site the paralyzed non-functioning tendon is left in place but is cut lengthwise and the periosteum of the underlying bone is roughened up (traumatized) so as to stimulate bone growth. The transferred tendon threaded with the fixation suture is fastened securely by several deep stitches passing through bone, ligament, and fascia. The fixation suture gives *mechanical stability*. The tendon of the paralyzed muscle is then sutured to the transferred tendon to enhance stability and further tighten the transferred tendon against the traumatized periosteum. This repair further adds *physiological fixation* to the mechanical stability of the suture. The living tendon cells of the transfer should lie in contact with the traumatized periosteum; and (iii) in the upper extremity, tendons often need to be sutured to other tendons. While essential, this is recognized as being a far less certain procedure than implanting the tendon into or against bone.

2.19.4 Tissue Engineering for Tendon Repair

Tendon is theoretically able to be synthesized by the triad of tools used for tissue engineering: cells, scaffolds, and growth factors [220–222]. While the generation of replacement tendons is primarily a need in older adults for tendon degeneration and injury there are also childhood and adolescent disorders where it could conceivably be of value. Cells being studied run the gamut from embryonic stem cells to somatic adult stem cells as well as mesenchymal stem cells isolated from bone marrow. Scaffolds are slightly further along in development with both biologic and artificial nanofiber based variants being studied. Biologic scaffolds from soft tissue regeneration include material from small intestinal submucosal extra-cellular matrix (ECM), dermal ECM and pericardial ECM. These materials are xenogeneic in origin but extensive processing removes resident cells while only minimally distorting the mechanical matrix scaffold and minimizing the inflammatory response. They are most commonly used for rotator cuff repairs. These have been extensively reviewed by Turner and Badylak [223]. Absorbable polyesters have been developed as biomaterials for scaffolds. These include PGA (polyglycolide), PLGA (lactide-glycolide copolymer), P(CL/LA) (ε-caprolactone-lactide copolymer), PLLA (poly-L-lactide), and PCL (poly-ε-caprolactone). Growth factors are used to further stimulate cell differentiation and proliferation [222].

2.20 Ligaments

2.20.1 Terminology

Ligaments are distinct anatomic connective tissue structures linking two adjacent bones via a bone-ligament-bone complex for the purpose of stabilizing, limiting, and directing the range of motion between them. They have variable gross structure as bands, cords, sheets or merging with joint capsules as capsular ligaments [224]. Some ligaments are intraarticular but most are extraarticular [225].

2.20.2 Ligament Structure

Ligaments are composed primarily of fibrils and fiber bundles of collagen oriented along the longitudinal axis in roughly parallel array. Long flattened thin cells, referred to as fibroblasts and fibrocytes, are present within the ligaments. While ligament cells have been described as being infrequent and in longitudinal array, transmission electron microscopic studies show them to be more numerous and often placed in more random array weaving in multiplanar fashion amongst the collagen matrix. Blood vessels are scanty but are present. There is a regular wavy undulation of cells and matrix along the long axis as seen by polarizing microscopy and ultrastructural studies. This "crimp" has a probable biomechanical function allowing a certain amount of protective stretching of stressed ligaments before stabilization and eventual rupture occurs [226]. Most ligaments insert into bone not directly but by a transition of tissue from fibrous ligament to unmineralized fibrocartilage to mineralized fibrocartilage to bone. Water accounts for 2/3 rds of the total weight of ligaments. Collagen makes up 3/4 s of the dry weight with the rest involving elastin, glycosaminoglycans (0.5 % dry weight) and other molecules. Greater than 90 % of the collagen is type I with type III next most common [224].

Frank has summarized normal ligament structure as characterized by: collagen fibers which are large, densely packed, aligned in parallel array, composed primarily of type I collagen 85 % with other collagen including types III, V, VI, XI, and XIV and mature collagen cross-links; small proteoglycans; elastin and other proteins and glycoproteins (actin, laminin, integrins); and low cell metabolism, low cell density, and low vascularity. Ligaments also play a role in providing proprioceptive feedback to joints by both intrinsic and extrinsic nerve stimulation [224, 226].

- *Gap junctions in ligaments*. Chi et al. have demonstrated that ligament cells (fibroblasts) are linked by gap junctions allowing for cell-cell communication. They are also linked by adherens junctions and desmosomes [227].

2.20.3 Ligament Mechanical Function

Frank has defined four aspects of ligament mechanical function—laxity, stiffness, strength, and viscoelasticity [228]. Laxity refers to "displacement of the bones to which a ligament is attached from an anatomic position to a position in which the ligament takes up a tensile load". Stiffness refers to "the amount of load required to displace the bones to which the ligament is attached in a particular direction". Both laxity and stiffness are a function of collagen fiber recruitment. The more fibers recruited the more lax and stiffer the ligament. Strength refers to "the maximum tensile load that a bone-ligament-bone complex can withstand before it fails". Failure load is a function of the number of fibers that tighten when a ligament is stretched, the quality of the fibers, and the direction of tensile load in relation to the fibers. Viscoelasticity refers to the "ability of tissues to respond to repetitive loading by altering length or load over time". These variations can account for 10 % of changes in ligament length and up to 60 % of changes in ligament loads physiologically.

2.20.4 The Biology of Ligament Repair

Ligament repair, in the extra-articular environment, follows an organized sequence of stages: Stage 1-hemorrhage, Stage 2-inflammation, Stage-3 cell proliferation and matrix synthesis, and Stage 4-tissue remodeling and maturation [229]. Extraarticular ligaments heal well in most instances in an environment of coaptation and immobilization. The adjacent host vessels supply fibroblasts which reconstruct the collagenous structure well. Surgical intervention may be needed to reappose the torn ends to an anatomic position.

Stage 1. Hemorrhage. Bleeding occurs immediately after disruption of the ligament and the gap and area of injury are filled with clot. Polymorphonuclear leukocytes and lymphocytes appear within hours. Time phase is minutes to hours.
Stage 2. Inflammation. By 24–48 h macrophages are the predominant cell type. They are responsible for phagocytosis of necrotic tissues and, via secretion of growth factors, for vascularization and granulation tissue formation. By day 3 the hematoma contains polymorphonuclear leukocytes, lymphocytes, macrophages, undifferentiated mesenchymal cells, and platelets. Prominent factors include fibroblast growth factor (FGF), transforming growth factor beta (TGF ß), and platelet derived growth factor (PDGF). Time phase is days to weeks.
Stage 3. Cell proliferation and matrix synthesis. By one week the mesenchymal cells have differentiated to fibroblasts which are now the predominant cell type. Collagen and other matrix proteins are rapidly synthesized. Types I, III, and V collagen predominate. The fibrils at this stage are randomly arrayed and the matrix disorganized. By the end of week 2 the gap is filled with this early repair tissue. With time the fibrils begin to assume a parallel orientation along the long axis of the gap. Time phase is weeks to months.
Stage 4. Remodeling and maturation. Over the next several weeks more mature and better oriented collagen is deposited and by 6–8 weeks the ligament appears grossly normal. There is a gradual decrease in cellularity, the collagen matrix becomes more dense and longitudinally oriented, and the type I/III collagen ratio progressively changes towards normal with type I predominance. The repair tissue continues to mature and strengthen for several months but even at 1–2 years post-injury collagen appearance by electron microscopy rarely returns to normal. Time phase is months to years.

Unlike bone which repairs itself to full structural and functional normalcy, even excellent ligament repair has some scar tissue persisting with less than normal tensile strength achieved. Tensile strength of a ligament has been correlated with large diameter collagen fibrils and collagen cross-links. Repair ligaments show persistently decreased collagen fibril diameters, decreased mature crosslinks, increased cellularity and vascularity, and altered proteoglycan profiles. The altered proteoglycan shows increased biglycan and decreased decorin. The healed tissue continues to mature but never reaches normal morphologic or mechanical properties.

2.20.5 Specific Features of Ligament Injury and Repair in the Skeletally Immature Patient

Basic teaching in orthopedics has indicated that ligament tears are infrequent in childhood and that injuries which would result in such tears in the adult tend instead to cause adjacent epiphyseal growth plate or metaphyseal fractures during childhood. The ligaments are considered to be stronger than the growth plates and metaphyseal bone, explaining the site of mechanical disruption. For the most part this observation is correct even at the knee but anterior cruciate ligament tears (midsubstance or intrasubstance) can certainly occur in childhood and are being diagnosed more frequently owing to earlier and more vigorous participation by youngsters in competitive sports, earlier sports specialization, year-round training and play in a single sport leading to repetitive same-site trauma and increased accuracy of diagnosis including arthroscopic documentation and MRI. In a further clinical generalization, injuries up to and including the age of 12 years at the knee joint are particularly likely to

be associated with intact ACL with fractures at the tibial eminence while the number of pure ligament tears increases as the patient age approaches skeletal maturity.

The knee represents the joint where the anatomic site of childhood injury is most likely to be misunderstood and misdiagnosed. The abduction-valgus stress mechanism causing a medial collateral ligament tear in the adult is more likely to cause a growth plate fracture-separation in the child. Tenderness at the proximal attachment of the ligament at the distal-medial femur is more likely to represent an undisplaced type I distal femur growth plate fracture-separation and a similar finding at the distal attachment can represent a proximal tibia growth plate fracture-separation. The fractures are often undisplaced and the type I pattern can be difficult to diagnose since it is not associated with a metaphyseal fragment. Type II and type III fractures are also frequent but more readily diagnosed by plain x-rays. The injury mechanism causing a tear within the anterior cruciate ligament in the skeletally mature person often leads to an avulsion fracture of the tibial spine at the site of insertion of the cruciate ligament in the growing child. Anterior cruciate ligament tears are now seen in patients between 12 and 16 years of age but even younger cases can occur.

2.20.5.1 Medial Collateral Ligament Repair (Knee) (Extraarticular Ligament)

The medial collateral ligament of the knee is commonly injured, especially in adults. It is an extra-articular ligament injury. These injuries have been assessed in detail in animal experimental studies [228–231]. The injury can lead to healing without surgical repair even with full rupture. Less than perfect ligament repair is common however and is associated with disorganized (non-aligned) collagen fibers, smaller than normal range collagen diameters, immature cross-links, an increased amount of type III collagen, large proteoglycans, high cell metabolism, increased numbers of cells, and increased vascularity. Frank has clarified these differences listed above post-injury between normal uninjured ligaments and repair tissue which has features of scar tissue [226].

2.20.5.2 Anterior Cruciate Ligament Repair (Knee) (Intraarticular Ligament)

The cruciate ligaments are covered by a fold of synovial membrane that essentially fully envelops them. While the ligaments are intra-articular they are extrasynovial. The synovial membrane is well vascularized by vessels originating predominantly from the middle genicular artery while the distal part of both cruciate ligaments receives supply from the medial and lateral inferior genicular artery [232–234]. The synovial vessels form a wide network covering the ligaments and give rise to smaller connecting branches which penetrate the ligaments transversely to connect with a longitudinally oriented intraligamentous vascular network. The ligamentous-osseus junctions of the cruciate ligaments do not contribute significantly to ligament vascularity. The density of blood vessels within the ligaments is not homogeneous. In the anterior cruciate ligament an avascular zone is located within the fibrocartilage of the anterior part where the ligament faces the anterior rim of the intercondylar fossa. The fibrocartilaginous zone of the middle third of the posterior cruciate ligament is also avascular [234].

The anterior cruciate ligament (ACL) of the knee does not heal well with or without primary surgical repair (suturing) and with or without immobilization in children or adults and in experimental animals. Primary surgical repair (suturing) without augmentation has a low level of success either not healing at all or healing with a thin or lengthened structure that is too weak to survive repeated stress. At present few surgeons resuture a torn anterior cruciate ligament even in children without supplementing the repair with such structures as semitendinosus tendon, gracilis tendon, partial patellar tendon or ilio-tibial band or in addition using tissue engineering components. Reasons for this poor repair include separation of ligament ends at time of rupture, chronic degenerative changes and scarring in the ligament pre-injury due to repetitive trauma, high impact injuries causing rupture leading to tearing and fraying of tendon and limited re-vascularization potential in an intraarticular environment. The thin synovial sheath of the ACL is disrupted and blood escapes into the synovial fluid preventing formation of a localized hematoma which normally supplies cytokines and growth factors to stimulate repair and a scaffold into which repair cells can grow and proliferate. Primary repair of the ACL with sutures gave poor results comparable to those with non-operative repair. Repair and reconstruction have since involved primary suture supplemented with grafts (autogenous or allogenic), excision of cut ends and use of grafts, excision and use of artificial replacements, all occasionally with tissue engineering components.

Overview of Anterior Cruciate Ligament Injuries in the Skeletally Immature

Sports injuries are increasingly common in young athletes and anterior cruciate ligament tears in particular show increased incidence over the past 20 years. An increased incidence of the ACL tears began to be noted after 12 years of age (before skeletal maturity) and now children less than 11–12 years are being affected. The disorder occurs in both males and females. ACL tears occur with repetitive non-contact movements involving jumping, sprinting and pivoting [235]. Partial tears are generally treated

conservatively using a regimen outlined by Kocher et al. [236]: hinged knee brace to prevent excessive extension for 12 weeks, crutches with toe-touch weight bearing for 6–8 weeks, physical therapy for muscle strengthening and return to activity with an ACL knee brace. Of these 30 % eventually needed surgery as the disorder progressed to a complete tear. Surgical management is being used even in this age group (and always for complete tears). A major operative decision is made between ligament repair which is transphyseal or physeal-sparing repair.

Evolving Diagnostic Management: The injury may be of a non-contact type but pain and hemarthrosis are valuable diagnostic findings. Plain X-rays should include 4 views [anteroposterior, lateral, tunnel (notch) and skyline (sunrise)] and should be closely assessed for growth plate fracture-separations (of distal femur or proximal tibia) or tibial eminence fractures. Diagnosis of midsubstance or intrasubstance ACL tears (partial or complete) is definitively made by MRI (with 95 % sensitivity for detecting tears) [235, 237] or by arthroscopy. As in the adult, meniscal pathology often is present with ACL injury or develops with time due to instability [238]. Treatment profiles in the skeletally immature are being refined based on the amount of growth remaining. Bone age determinations (PA wrist and hand radiographs and use of the Greulich and Pyle atlas), observation of distal femoral and proximal tibial growth plates as open, closing or closed and even Tanner staging of physiologic maturity are being used [235].

Evolving Management Considerations: For partial tears Kocher et al. [236] devised a conservative program described above. Even with careful diagnosis and management, eventual surgical repair for instability or repeat injury with complete tearing is needed in at least one-third of patients. Lawrence et al. [238] showed that prognosis was worse (in the sense of further knee joint degeneration) in a cohort of 70 immature patients with ACL tear who underwent ACL reconstruction more than 12 weeks after injury. These had a higher incidence of severe medial meniscal tears and a higher grade of lateral and patellotrochlear chondral injuries.

Studies from the 1980s showed poor results of primary suture of a midsubstance ACL tear in children and adolescents. Engebretsen et al. treated 8 adolescents showing only 3 with good function and 5 with instability 3–8 years later [239]. DeLee and Curtis also showed poor response [240]. Vavken and Murray [241] in a review of 47 studies comparing treatments (conservative/nonsurgical and surgical) of skeletally immature patients with complete ACL tears concluded that "surgical stabilization should be considered the preferred treatment in immature patients with complete ACL tears". Conservative treatment commonly led to meniscal damage and cartilage destruction. No specific surgical treatment could be identified as showing better outcomes (than other surgical treatments) but all showed "strong evidence of good post-operative stability and function."

Transphyseal repairs. In the older patient nearing skeletal maturity (mean age 13–14 years) several studies now show good results with transphyseal technique, usually with autogenous quadruple hamstring tendon graft and metaphyseal fixation [242–245]. The growth related concerns of angular deformity and limb length discrepancy are now extremely rare using tunnels of 8 mm or less width at the normal anatomic ACL tibial position. Isolated growth damage cases were reported in the earlier phases using this procedure [246] and Kocher et al. [247] reported 15 additional cases in a group survey (large tunnels >12 mm, hardware across the physis, lateral extra-articular tenodesis, and dissection in the proximity of the periphyseal groove of Ranvier.

Physeal-sparing repairs. In the even younger age group (mean chronologic age 10–11 years) physeal-sparing combined intra-articular and extra-articular repair can be done safely without growth damage. The femoral and tibial tunnels pass through the epiphyses (bone) but not the physes. Autogenous quadruple hamstring tendon graft or iliotibial band grafts are used. Reports with 12 patients [248] and 44 patients [249] showed no significant angular or limb length deformities.

Frank and Gambacorta [235] have provided an excellent treatment algorithm for ACL reconstruction in the skeletally immature patient. Beynnon et al. [250] have reviewed the treatment of ACL injuries at all ages.

2.20.5.3 Tissue Engineering and Ligament Healing

Tissue engineering is being studied and used to augment ligament repair. Hsu et al. [251] have extensively outlined the use of (i) growth factors: fibroblast growth factors (FGF), transforming growth factor-beta (TGF-β), epidermal growth factor (EGF), insulin-like growth factor (IGF), and platelet-derived growth factor (PDGF); (ii) cell therapy: mesenchymal progenitor cells (MPCs) and mesenchymal stem cells (MSCs); and (iii) extracellular matrix bioscaffolds: porcine small intestinal submucosa (SIS). Murray and colleagues have concentrated on overcoming a major impediment to anterior cruciate ligament healing which they define as lack of clot formation between the two torn ends of the ligament [252–254]. They continue to work on a bioactive biocompatible scaffold introduced into the repair site along with an enhanced suture technique with multiple #1-Vicryl (polyglactin, Ethicon, Somerville, New Jersey). These use a bovine collagen construct mixed with a platelet-rich concentrate and have shown promising results, especially in the younger immature animals. Altman et al. [255] provided an

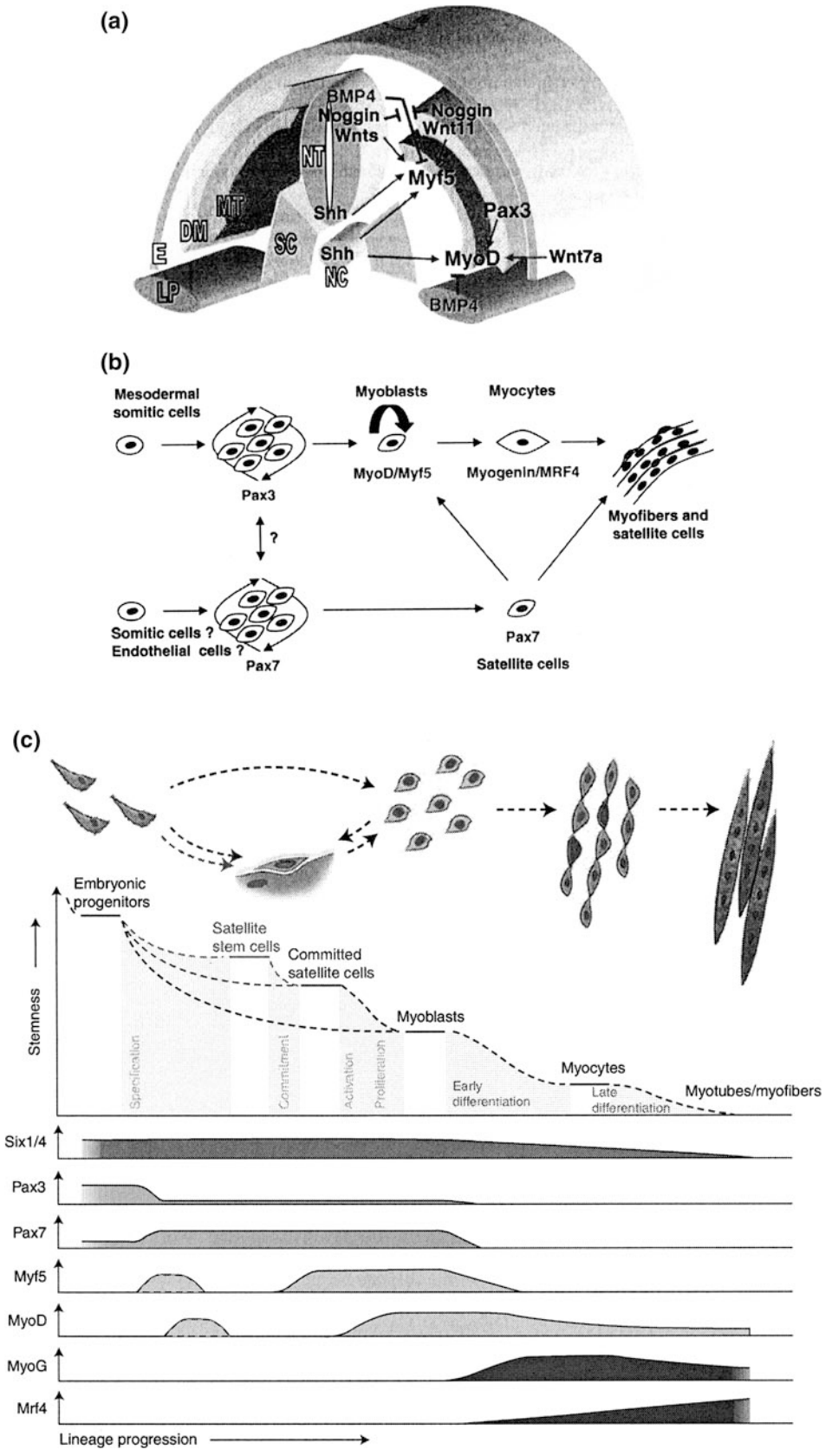


Fig. 2.14 (continued)

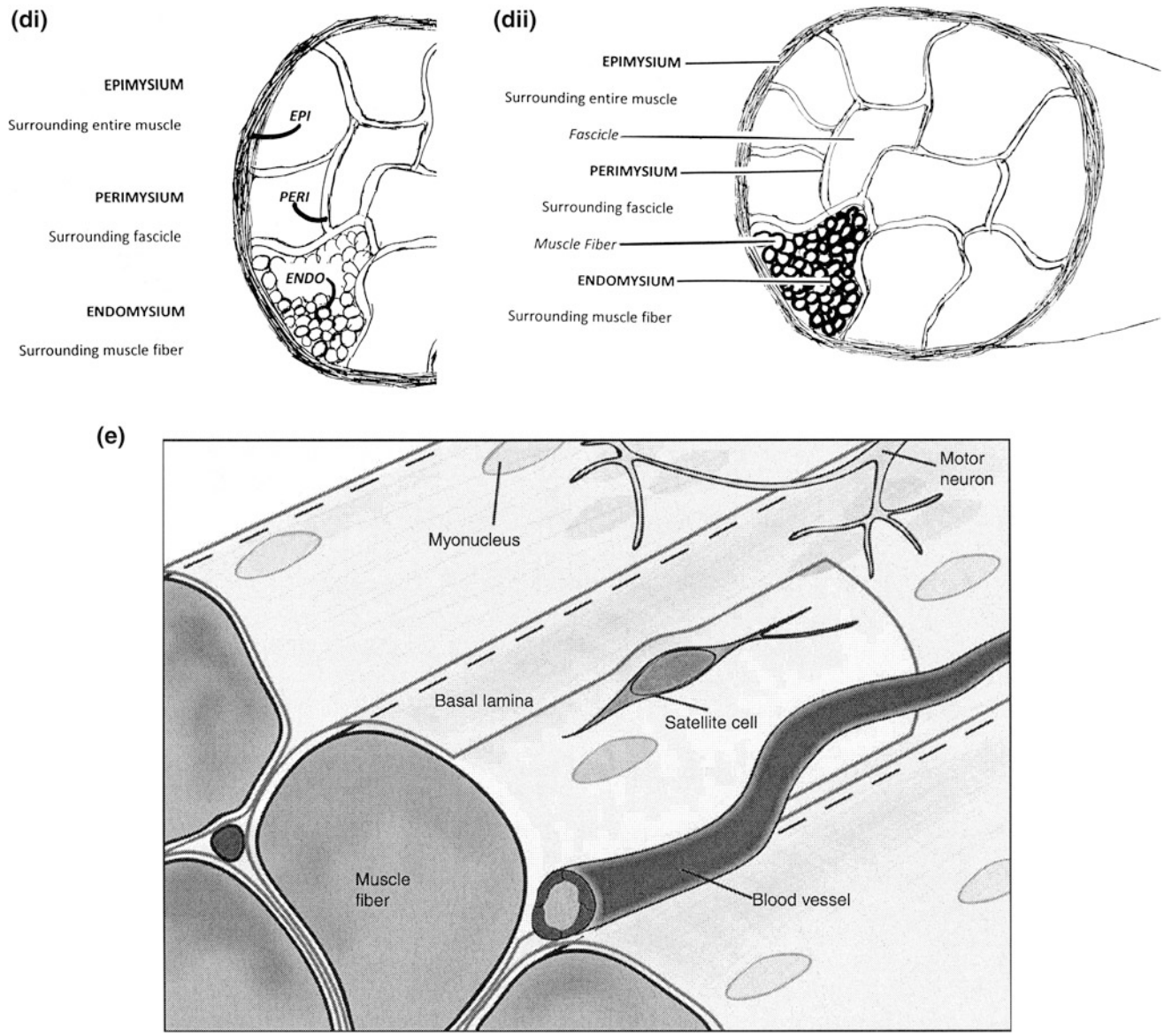


Fig. 2.14 (continued)

extensive review of bioresorbable scaffolds being investigated for anterior cruciate ligament repair.

2.21 Development and Structure of Normal Muscle

The myoblast is the mesenchymal cell committed to develop into skeletal muscle. Expression of the myocyte-specific transcription factors (myoD and myogenin) plays a central role in the commitment of undifferentiated cells to the myoblast lineage (Fig. 2.14a, b). Skeletal muscles are derived from the dorsal part of the dermomyotome. These cells express the paired box transcription factors *Pax3* and *Pax7* with low expression of the transcription factor *Myf5*. Eventually this region will differentiate into the myotome with committed muscle cells expressing high levels of *MyoD* and *Myf5*. *MyoD* and *Myf5* are both markers of terminal specification to the muscle lineage. Members of the Wnt family are particularly important for the very early formation of the dermomyotome and myotome and thus for developmental myogenesis. Sonic hedgehog (Shh) is also involved in early muscle progenitor specification. The hierarchy of transcription factors regulating progression through the myogenic lineage is now well established. Pax 1/4 and Pax 3/7 are master regulators of early lineage specification while Myf5 and MyoD commit cells to myogenic program. Terminal differentiation genes required for the fusion of

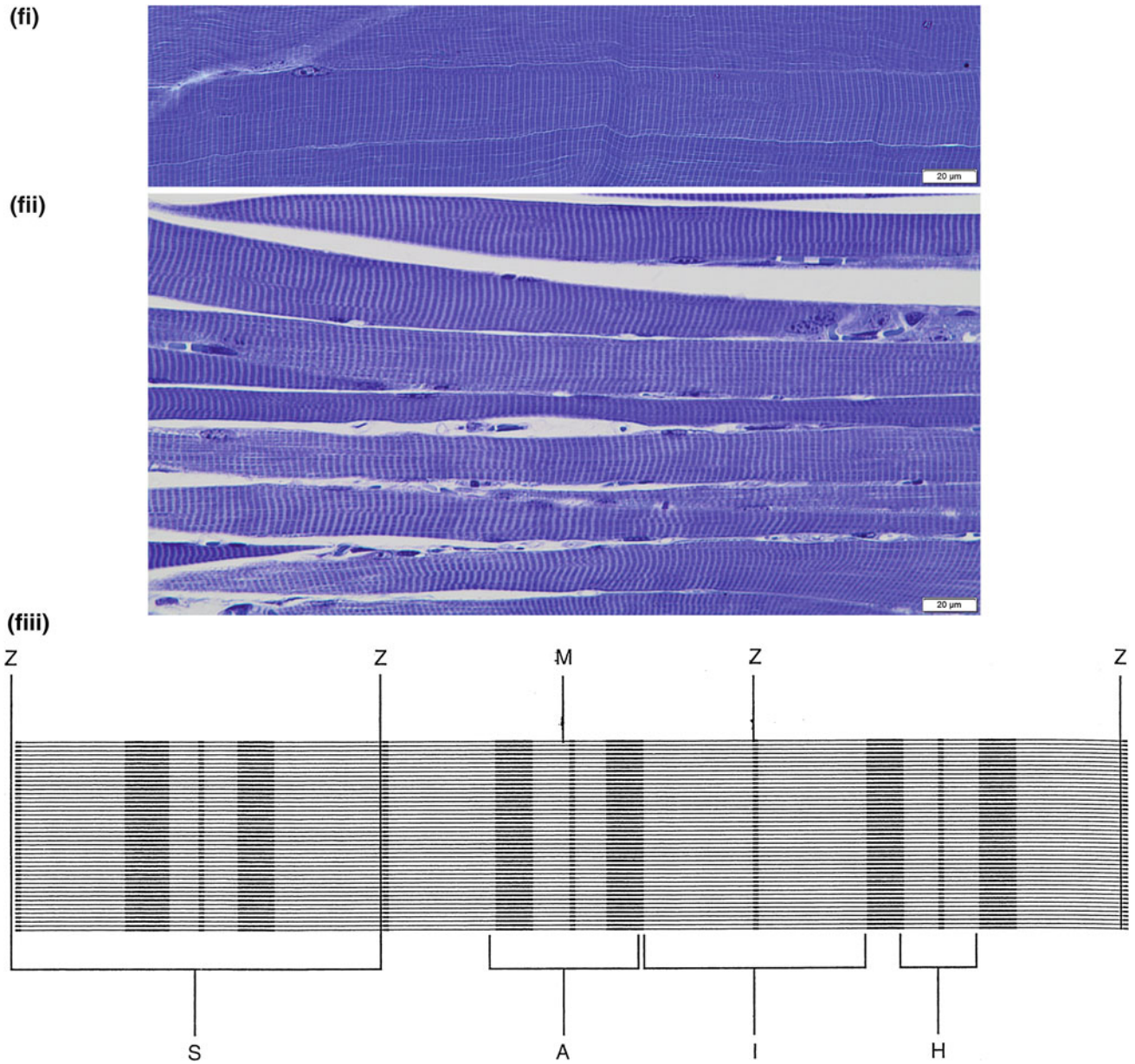


Fig. 2.14 **a**, **b** Outlines of development and differentiation in muscle are shown [260]. (Reprinted with permission from Charge and Rudnicki, Cellular and molecular regulation of muscle regeneration. Physiol Rev 2004;84:209–238. Copyright 2004 The American Physiological Society). **c** A more detailed outline of the timing and transcription factor activity in myogenesis is shown [258]. (Reprinted with permission from Bentzinger et al. Building muscle: molecular regulation of myogenesis. Cold Spring Harb Perspect Biol 2012;4:a008342. Copyright 2012 Cold Spring Harbor Laboratory Press). **d(i)** and **(ii)** The hierarchical structure of a muscle is illustrated in cross-section. The interconnected fibrous tissue covering and intramuscular distributions are similar to those seen in the tendon. **e** The position of the satellite cell is shown [258]. **f(i)** and **(ii)** The characteristic cross-banding pattern of muscle is illustrated. **(i)** and **(ii)** Show mouse skeletal muscle sectioned along the long axis. The nuclei of muscle and satellite cells are on the periphery. **f(iii)** a schematic outline of the banding pattern of muscle is shown. The functional unit or sarcomeres of the muscle passes from Z-line to Z-line. The crossbanding pattern develops based on the position of the parallel alignment of the actin (*thin*) and myosin (*thick*) fibril within each fiber

myocytes and the formation of myotubes are controlled by MyoG (myogenin) and MRF4 (Fig. 2.14c). The myoblast contains intracytoplasmic myosin and actin filaments and has the capacity to fuse with other myoblasts to form syncytial primary myotubes which are multinucleated cells with a cylindrical geometry (Fig. 2.14b). Sarcomere structure develops along the length of the myotube, beginning peripherally, with the nuclei initially arranged centrally in

the myotube in a myofibril-free zone. The sarcolemma (the outer cell membrane of the striated muscle cell) contains abundant membrane receptor protein for acetyl-choline (ACh) at the time of innervation of the myotube. Surface expression of this receptor, the nicotinic acetyl-choline receptor (AChR), appears to be necessary for the process of innervation. When the growth cone of the motor axon forms a junction with the muscle fiber, a motor end plate is developed and the AChR proteins become concentrated at this neuromuscular junction and disappear from the surface of the fiber elsewhere. The nuclei move to the perimeter of the developing myocytes, and regular arrays of myofibrils, the contractile elements of myocytes, are concentrated in parallel longitudinally oriented arrays as the myotube becomes a mature myofiber. Muscle fibers therefore are syncytial cells containing several hundred nuclei with continuous cytoplasm [256].

Individual myocytes are bounded by a basal lamina composed of laminins. The basal lamina is smooth and closely applied to the cell membrane, or sarcolemma. Membrane stability is provided by molecules of the dystrophin family which completely line the inner cell membrane of individual skeletal muscle cells. It is the molecular abnormality of dystrophin that underlies the most severe of the muscular dystrophies, Duchenne. Another group of molecules, sarcoglycans (α, β, γ, deta and zeta) also stabilize the cell membrane by connecting the muscle fiber cytoskeleton to the extracellular matrix by transmembrane action. Abnormalities in this group (currently comprising α, β, γ, and deta sarcoglycans) lead to the limb girdle muscular dystrophies. Variability in thickness and regularity of the cell membrane, or redundancy and reduplication, are commonly seen in hypercontracted fibers, near the motor end plate. The myocyte has peripheral nuclei and a small amount of cell cytoplasm just beneath the sarcoplasmic membrane. Occasional mononuclear cells are present between the basal lamina that surrounds each myocyte (muscle fiber) and the plasma membrane of the myocyte (muscle fiber). These are satellite cells and are estimated to comprise 10 % of nuclei at birth and 2.5–6 % of all nuclei in each muscle fiber in adults. These satellite cells are the cells primarily responsible for skeletal muscle regeneration [256].

The cytoplasm beneath the sarcolemma and adjacent to the nucleus contains granular glycogen and mitochondria as seen by electron microscopy. The entire central portion of each myocyte beneath this cytoplasm is composed of intracytoplasmic bundles of contractile elements known as myofibrils. Each myofibril is surrounded by a small amount of cytoplasm containing granular glycogen and occasionally mitochondria, which creates a reticular pattern in cross section.

A complex system of invaginations from the surface cell membrane is also present in myocytes. It is composed of both sarcoplasmic reticulum and a system of tubules, and arises at the surface of the myocyte from where it extends into the cytoplasm between myofibrils. The T tubules penetrate the interior of the cell, running parallel to the Z-disks, and are accompanied by two cisterns of endoplasmic (sarcoplasmic) reticulum on either side. This T tubular system, or triad, is composed of a centrally placed T tubule with two adjacent cisterns of sarcoplasmic reticulum and is frequently encountered between adjacent myofibrils.

Muscle also has a markedly hierarchical structure from individual fibrils to complete organ [Fig. 2.14d(i, ii), e, f(i–iii)]. Although the myofibrils are separated from each other by cytoplasm, they remain in register with each other to form the striations that extend across the diameter of the myocyte (Fig. 2.14f). The Z-disk is a disk into which the actin filaments insert and which has been used to define the beginning structure of the repeating unit, the sarcomere. Thin myofilaments are predominantly composed of actin and originate from the Z-disk. At some distance from the Z-disk, the thin filaments interdigitate with thick filaments, predominantly composed of myosin. This repeating sarcomeric structure is seen as alternating dark and light regions, and is the basis of the striations seen by light microscopy. The dark regions, containing the thick myosin filaments, interfere with the passage of polarized light and are referred to as anisotropic, or A-bands. The light regions, containing the thin actin filaments, allow the passage of polarized light and are isotropic, or I-bands. With higher resolution light microscopy [Fig. 2.14f(i, ii)] or with electron microscopy, a finer level of regular structures is apparent. The I-bands contain thin filaments and the narrow dark Z-disk, which contains alpha-actinin, in the center. Therefore, the I-band crosses two sarcomeres and includes the Z-disk at its center and the thin filament regions on either side. The A-band corresponds to the length of the thick myosin filaments. In the denser areas of the A-band, the thick filaments are overlapping with the thin filaments, and the paler areas correspond to the portions of the thick filaments that do not overlap with the thin filaments. Within the A-band is a paler region called the H-zone (H) composed of thick filaments alone. Inside the H-zone is a thin M-line formed by connecting components of the cytoplasm.

The cytoplasm between individual myofibrils contains loops of the T system, smooth endoplasmic (sarcoplasmic) reticulum, along with other components of cell cytoplasm, most visibly granular glycogen and mitochondria. The mitochondria are especially notable by electron micro-scopy and may be small and round, or long and branching. Fat globules are found predominantly within the cyto-plasm immediately beneath the sarcoplasm, but may also be located between myofibrils.

The compartments and fibrous enclosures of muscle are well defined [Fig. 2.14d(i, ii)]. Skeletal muscle is composed

of bundles (fascicles) of longitudinally oriented muscle cells that run the length of the muscle from origin to insertion. These fascicles, which can be appreciated grossly as the tiny strands of muscle, are separated from each other by a collagenous connective tissue layer, the perimysium, which encircles each fascicle. Groups of fascicles are bound together by a denser collagenous sheath, the epimysium. By light microscopy, individual muscle fibers are located within the fascicles, surrounded by perimysium, and located within a compartment known as the endomysium. Most of the endomysium is composed of individual myocytes, but there is a delicate connective tissue investment of basal lamina and scanty collagen that surrounds each myocyte. Capillaries and nerve fibers are located within this endomysial connective tissue. However, the amount of endomysial connective tissue, including basal lamina, collagen, fibroblasts, capillaries, and nerve fibers, is so scant that the myocytes appear to be almost immediately adjacent to each other. Muscle spindles may also be found within some fascicles and have a distinctive appearance. They are surrounded by concentric layers of fibroblasts that separate them from the adjacent endomysium. The myocytes in the muscle spindle are known as intrafusal muscle fibers, and their nuclei may be located in a central position.

2.21.1 Normal Muscle Structure Defined by Muscle Biopsy

Frozen sections of skeletal muscle provide important additional information. Cross sections allow for assessment of fiber size and distribution. Staining of muscle with hematoxylin and eosin (H&E) shows that muscle fibers are polygonal in shape and relatively uniform in diameter. Proteins tend to stain pink on H&E, and the central portion of the myocyte is largely pink, but it may have small blue particles distributed through the cytoplasm. The nuclei, which stain blue on H&E, are located predominantly at the periphery of the fiber, with less than 3 % of nuclei within the center of the normal myocyte. The size of the myocytes varies with age. In newborn infants, the normal mean diameter is approximately 15 μm. There is rapid growth during the first years of life, and the average size levels off in adolescence near the adult size of 60–80 μm (Figs. 2.4 and 2.3). Fiber atrophy is defined as a mean fiber size significantly less than the expected mean for age. Myocytes have a rounder cross-sectional profile in infancy, becoming more polygonal by age 5 years. Muscle spindles and nerve bundles are more frequently encountered in muscle biopsy specimens from infants, and should not be mistaken for an abnormality.

In normal muscle, the endomysial connective tissue is so delicate that it is difficult to appreciate on H&E sections, creating an appearance of muscle fibers that are immediately apposed to each other. Although endomysial capillaries may sometimes be visible, their number is greatly underestimated from H&E sections. The cytoplasm of individual myocytes has a slightly speckled appearance, created by the distribution of mitochondria and other cytoplasmic constituents around the myofibrils.

The modified Gomori trichrome stain is one of the most useful stains in muscle histology. Connective tissue is stained green, and the contractile apparatus is also stained a slightly darker green, discernible from the adjacent connective tissue but similar in hue. In contrast, mitochondria stain red-purple; this staining pattern highlights the fine even stippling of red particles (mitochondria) throughout the fiber with a slight accentuation beneath the sareolemma. Nuclei are stained blue and are clearly highlighted from both the mitochondria and from the contractile apparatus.

The delicate endomysial connective tissue is highlighted on the modified Gomori trichrome stain by its lighter shade of green surrounding each myocyte. The cytoplasm is normally devoid of deposits or vacuolcs.

The motor unit is the functional unit of the neuromuscular system and is defined by the motor neuron. Each motor unit is composed of an anterior horn cell within the spinal cord (or a motor neuron within the cranial nerve motor nuclei of the brainstem), its axon and axon terminal arborizations, and all of the muscle fibers innervated by the axon terminal. Muscles with highly refined movements, like the extrinsic muscles of the eye, have a higher ratio of motor neurons to muscle fibers, with approximately 10 muscle fibers in each motor unit. In contrast, those with relatively coarse movements, like the calf muscles, have as many as 2000 muscle fibers per motor unit. The entire motor unit contracts when the motor axon depolarizes, and with increasing voluntary effort, more of the individual units contract.

All of the muscle fibers within one motor unit belong to one of two major types of muscle fiber, defined physiologically as type 1 (“slow-twitch”) or type 2 (“fast-twitch”) fibers. Type 1 fibers tend to be involved in slow, sustained contractions and are resistant to fatigue. They derive most of their energy from the breakdown of lipid through aerobic oxidation. They contain more abundant mitochondria, oxidative enzymes, and lipid than do type 2 fibers. Type 2 fibers are “fast-twitch” fibers physiologically and may be subtyped into types 2A, 2B, and 2C. Type 2B fibers tend to be involved in strong contractions of short duration. They have a fast-twitch speed, fatigue easily, and derive most of their energy from glycogen breakdown. As a result, they tend to have abundant gylcogen and glycolytic enzymes but fewer mitochondria, oxidative enzymes, and lipid than type 1 fibers. Type 2A fibers have some characteristics of both type 1 and type 2B fibers. They are fast-twitch fibers but are relatively fatigue resistant compared with type 2B fibers. They also contain more oxidative capacity than type 2B

fibers and more glycolytic capacity than type 1 fibers. Type 2C fibers, although recognized by histochemical stains, are a less abundant fiber type.

2.22 Muscle Tissue Repair

Skeletal muscle tissue postnatally when intact sustains itself by its satellite cells which serve as the undifferentiated progenitor cells (Fig. 2.14e). Muscle tissue damaged by cutting or separation however has a marked tendency to be repaired only by fibrous scar tissue. Muscle regeneration in higher vertebrates depends on the injured tissue retaining an extracellular matrix scaffolding that serves as a template for the formation of muscle fibers [257, 258]. In those situations skeletal muscle has the ability to initiate a rapid, extensive repair process to maintain skeletal muscle mass. There are considerable similarities in structural and molecular pathways between developmental and reparative myogenesis. Necrosis of tissue is followed by an inflammatory response followed by activation of myogenic cells to proliferate, differentiate, and fuse leading to new myofiber formation and reconstitution of the contractile apparatus. Activation of adult muscle satellite cells is a key element since these are the undifferentiated progenitor cells available to muscle for its repair. Following muscle necrosis and degeneration the repair process is activated. Cellular proliferation occurs involving myogenic cells which differentiate and fuse to existing damaged fibers for repair to one another for new myofiber formation. Under normal conditions, regenerated muscle is morphologically and functionally indistinguishable from undamaged muscle.

Human muscle satellite cells. Muscle satellite cells are a population of myoblasts distinct from embryonic and fetal myoblasts. By electron microscopy they are seen between the plasma membrane of the muscle fiber and the basement membrane. They have an increased nuclear to cytoplasmic ratio and a reduced organelle content, indicative of being relatively quiescent. Extensive work is done to identify molecular markers specific to this cell to aid in studying its effect in regeneration. The overall satellite cell number appears to decrease as a function of age. Satellite cells depend on the same genetic hierarchy that governs embryonic myogenesis. Extensive efforts are underway to stimulate undifferentiated satellite cells of normal muscle by molecular means to differentiate to functional myoblasts. While the satellite cell has been known for several decades to be the latent quiescent stem progenitor cell for postnatal muscle repair it has certain qualities that have made it very difficult for muscle researchers to harness it for augmented repair. Stem cells in any organ reside in compartments referred to as the "stem cell niche" that supports self-renewal of the cells while preventing them from differentiating prematurely. Satellite cells are closely apposed to the myofiber and are covered by the extracellular matrix of the basement membrane. The problem for stem cell therapy is that the satellite cells cannot be isolated and expanded in vitro because they rapidly differentiate into myoblasts, a more committed muscle precursor with irreversible expression of *Myf5, MyoD, and Myogenin* [258, 259]. Autologous grafting is also limited by the small amount of satellite cells that can be obtained from a muscle biopsy and the difficulty of grafting large numbers of muscles (for systemic disease) or large areas (for more localized or post-traumatic disorders).

At the molecular level it has been shown that *Pax3* promotes myogenesis in the lateral myotome and *Pax3* expression in precursor cells contributes to myogenic cell expansion [260]. Satellite cells express *Pax7* at all times and *Wnt* proteins are crucial regulators of satellite cell commitment and self-renewal in postnatal myogenesis. *Wnt 3a* signaling is needed for myoblast differentiation and muscle regeneration while *Wnt 7a* mediated expansion of the satellite stem cell pool dramatically enhances regenerative capacity of muscle following injury.

2.22.1 Muscle Satellite Cells in Muscle Repair

Quiescent satellite cells have no detectable myogenic regulatory factors (MRFs) but with the injury the cells are activated, begin proliferating (myogenic precursor cells/mpc) and show rapid upregulation of 2 MRFS, *Myf5* and *MyoD* [260, 261]. Activation of the satellite cells activates the myogenic program leading to myonuclei fusion and myofiber formation. The mpc fuse to each other to form syncytial muscle fibers. Some satellite cells remain quiescent to help maintain the satellite cell pool by the process of asymmetric division. There is also evidence that the muscle satellite cells under certain conditions can differentiate along an osteoblast or adipogenic (fat) cell line. Several growth factors have been identified with muscle repair via satellite cells including Notch, Wnt hepatic growth factor (HGF), several fibroblast growth factors (FGFs), IGF-I and IFG-II, TGF-β family (β1, β2, β3) and the IL-6 family of cytokines. Muscle resident and non-muscle derived stem cells other than muscle satellite cells are also being investigated.

2.23 Peripheral Nerve Structure, Injury, and Repair

2.23.1 Anatomy of a Peripheral Nerve

The cell body for motor neurons is in the anterior horn of the spinal cord and for sensory nerves in the dorsal root ganglia immediately outside the spinal canal [262, 263]. The cell body of the presynaptic sympathetic nerve fibers also lies in the anterior horn. A peripheral nerve is composed of motor, sensory, and sympathetic nerve fibers. Individual axons carry products synthesized in the cell body to the neuromuscular junctions in the muscle (motor nerves) and free nerve endings in the skin or specialized receptors (sensory nerves). Nerve fibers are either myelinated (covered by myelin) or unmyelinated. Sensory and motor nerves contain both myelinated and unmyelinated fibers. Unmyelinated fibers have several axons individually wrapped in a single Schwann cell; the Schwann cell forms the multilaminated myelin sheath. The endoneurial sheath is the basil lamina outside the Schwann cell. Along the length of a myelinated nerve fiber the axon will relate to many Schwann cells. The length of the axon that a single Schwann cell relates to is called the internode. Between the internodes the axon is not myelinated and that region is the node of Ranvier. The collagenous endoneurium surrounds individual myelinated nerve fibers or groups of unmyelinated nerve fibers. The axons myelinated nerve fibers are also covered individually by single Schwann cells. Several axons are then bundled together into fascicles bound by the next level of fibrous tissue support, the perineurium, a connective tissue sheath consisting of several layers of perineurial cells. Groups of fascicles are bound together loosely by the fibrous interstitial epineurium and all the fascicles are wrapped in a fibrous circumferential epineurium (Fig. 2.15a). More than 50 % of the bulk of a peripheral nerve can actually be its connective tissue support system. The blood supply is longitudinal within the epineurium, perineurium and endoneurium with collaterals entering through a vasa vasorum. Intraneural communications are numerous. Fascicles within major peripheral nerves repeatedly divide and reunite to form fascicular plexuses [262].

2.23.2 Damage to Peripheral Nerves

Most damage to peripheral nerves which can be repaired is due to trauma. The repair situation with best success is where end-to-end primary repair can be done without excess tension. Short gaps can be repaired with epineural suturing. When primary repair cannot be done, nerve autografts are used to provide regenerating axons from the injured nerve proximally with a natural guidance channel populated with viable Schwann cells surrounded by their basal lamina. For wider nerves several autograft segments stacked side by side (nerve cable autografts) are used. Allografts are infrequently used today. An alternative to bridging relatively short nerve defects, which is currently the focus of extensive research, is the use of natural or artificial conduits referred to as tubulization techniques.

Seddon classified nerve injuries into three major groups: neurapraxia, axonotmesis, and neurotmesis [264]. Sunderlund augmented the classification to 5 types, subclassifying axonotmesis into 3 categories based on the extent to which the connective tissue is damaged [265, 266] (Fig. 2.15b) and some have increased the gradations to 6 [267].

2.23.2.1 Neurapraxia

Neurapraxia is the mildest form of peripheral nerve damage [264]. Neurapraxia involves a local conduction block at a discrete area along the nerve. The nerve is in continuity and there is no Wallerian degeneration. The disorder is due to extrinsic crush or localized pressure such as with a tourniquet palsy, localized pressure palsy or early entrapment problem. There is local myelin damage but axon continuity is preserved. Recovery is complete taking from a few minutes to several weeks but rarely longer than 12 weeks. These are sometimes referred to as first degree injuries. There is no permanent structural damage or transection.

2.23.2.2 Axonotmesis

The axons are disrupted by a stretch mechanism but the fibrous tissues of the sheath remain intact. This is a Sutherland type 2 injury. Recovery of function tends to occur over a several month period. The axonal damage leads to Wallerian degeneration distal to the site of injury. Proximally the injury incites axon sprouting and regeneration. Recovery is slow at a rate of 1–1.5 mm/day and is noted clinically proximal to distal. The endoneurium is not injured so axonal regeneration has a clear path for repair. The Schwann cells of the endoneurial tubes play a limited role in repair. Full motor and sensory function should be restored. Realization of whether an injury is first degree or second degree is made retrospectively; relatively quick recovery within 12 weeks implies a neurapraxia while slower repair at the 1–1.5 mm/day rate points to more severe damage with axontomesis.

2.23.2.3 Third Degree Injury

This is also a stretch injury with the perineurium and epineurium intact but the endoneurium is disrupted to a variable extent and the scarring involved in its repair may block some axonal regeneration. This is the Sutherland type 3 injury. The basal lamina of the Schwann cell which synthesizes the endoneurium is injured and if the axon has both sensory and motor fibers there may be some mismatching with repair

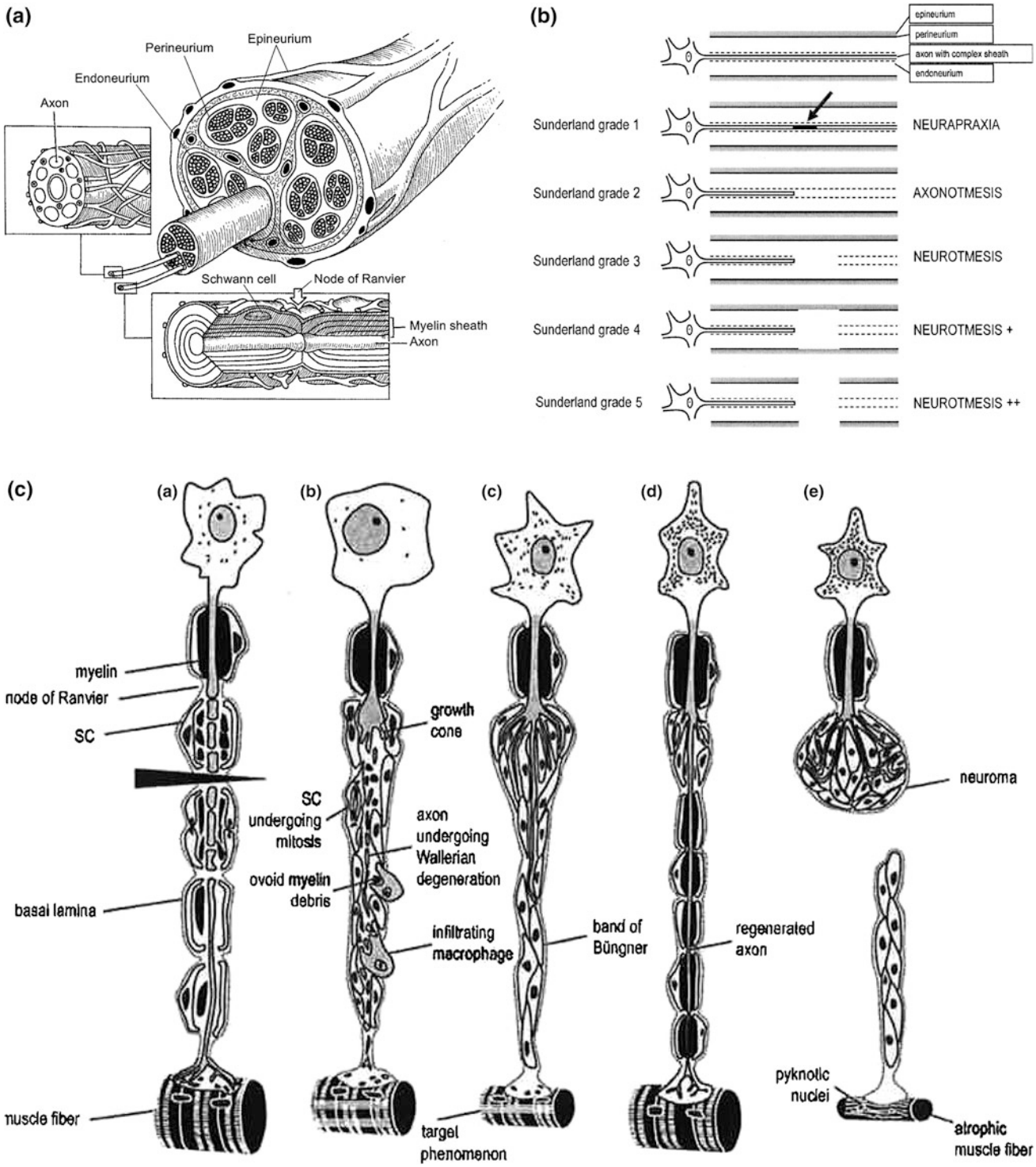


Fig. 2.15 (continued)

through scarred tissue. The potential for excellent repair still exists since the perineurium is intact. If there is entirely motor or sensory nerve fibers in the segment injured the potential for recovery is greater with a mixture making full recovery more problematic. Unlike the Sutherland type 2 injury, axonotmesis, full recovery is unlikely and the third degree injury has the greatest variability in response from almost full to almost no recovery.

2.23.2.4 Fourth Degree Injury

In these disorders the nerve is intact but non-functional since the continuity is maintained only with the intact epineurium

(d)

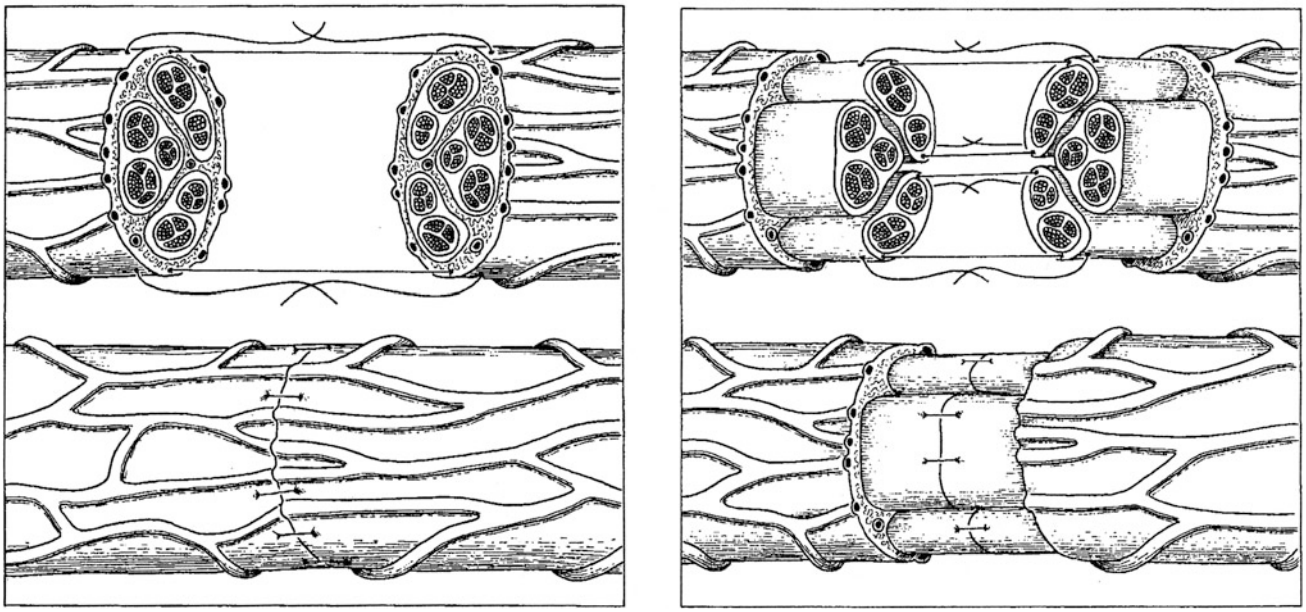


Fig. 2.15 **a** The hierarchical structure of a peripheral nerve is shown. The fibrous tissue positioning is similar to that seen in muscle and tendon [262]. (Reprinted with permission from Lee and Wolfe, Peripheral nerve injury and repair. J Am Acad Orthop Surg. 2000;8:243–252. Copyright 2000 Wolters Kluwer Health). **b** The 5 degrees of nerve injury according to Sunderland are shown [266]. (Reprinted with permission from Deumens et al. Repairing injured peripheral nerves. Prog Neurobiol 2010;92:245–276. Copyright 2010 Elsevier). **c** The sequence of cellular events triggered by transection of a myelinated axon is shown [269]. **d** Alternate methods of suturing a peripheral nerve transection are shown [262]. At left, the epineurium of the 2 fragments is sutured while at right, individual fascicles are sutured using the perineurium

forming with a bridge of scar tissue. This is the Sutherland type 4 injury. Wallerian degeneration occurs distal to the injury while proximal regeneration of the nerve is bound down in the scar and cannot unite with the distal components. There is no clinical evidence of repair even beyond 3 months and eventual surgical intervention will be needed for nerve repair, nerve grafting or a nerve conduit technique. This type of injury is the basis for the 3 month plus wait prior to surgical intervention since the first, second, or third degree injuries will have fully or partially repaired by then.

2.23.2.5 Neurotmesis. Fifth Degree Injury

Neurotmesis is the most severe injury causing disruption of the entire nerve which often is a complete transection of the peripheral nerve. Early surgical repair is warranted.

2.23.2.6 Neuroma-in-Continuity. Sixth Degree Injury

This type of injury combines some or all of the previous 5 types of injury. The mixed pattern presents as a neuroma-in-continuity. It was defined by Mackinnon [267]. The pattern of recovery is mixed but careful clinical assessment will indicate some fascicles and their functional sites showing no repair (4th, 5th degree). These are the segments that could benefit from surgical repair. Nerve degeneration and regeneration have been illustrated well by Hall [269] [Fig. 2.15c(i)] and Deumens et al. [266] [Fig. 2.15c(ii)].

2.23.3 Patterns of Nerve Degeneration

Wallerian Degeneration. After sectioning of a peripheral nerve antegrade (or forward, distal moving) degeneration occurs at the distal stump beginning within 24–48 h post-injury [268]. Wallerian degeneration refers to changes in the myelinated fibers in the distal nerve. Distal degeneration of thin fibers occurs at a rate of 250 mm/day and thick fibers at 45 mm/day. Myelin sheath destruction follows degeneration [262, 266, 268–270] (Fig. 2.15c).

Traumatic Degeneration. Retrograde (backward or proximal moving) degeneration occurs after sectioning of the nerve to the first node of Ranvier (although it may pass even more proximally) and demarcates the proximal nerve stump. While similar to Wallerian it is called “traumatic degeneration” [262, 266, 269].

Schwann cells proliferate along longitudinally oriented columns to demarcate the distal stump. Proximal stump regeneration composed of axonal sprouts (growth bulb)

starts at 10–21 days. For successful regeneration, the axonal sprouts from the growth bulb must pass distally guided by the longitudinal Schwann cell columns to traverse the gap between the two separated nerve stumps. The regenerating units are initially unmyelinated and a single axon produces multiple axons. With time, the fibers become myelinated and decrease, presumably to those making successful distal target organ contact.

Wallerian degeneration was described by Waller in 1850 in the frog with experiments on the glossopharyngeal and hypoglossal nerves [268]. After injury the Schwann cells proliferate and become phagocytic. Myelin and axonal degeneration occur and are removed by phagocytosis. Ultrastructurally, both neurotubules and neurofilaments become disarrayed and axonal contour becomes irregular. By 48–46 h post-injury axonal continuity is lost and there is no conduction of impulses. Myelin disintegration lags slightly behind that of axons but is well advanced by 36–48 h [270]. The regenerating unit, surrounded by the fibrous perineurium, shows myelinated and unmyelinated fibers. Regeneration and degeneration occur simultaneously in the distal stump. The endoneurial tubes (basal lamina of Schwann cells) collapse due to the phagocytosis within. As the Schwann cell returns to its proliferative phase it reforms the basil lamina and it is into the endoneurial tube that the new axons pass. Wallerian degeneration also occurs after nerve repair but in a much better aligned fashion.

2.23.4 Nerve Regeneration

After Wallerian degeneration the Schwann cell lamina persist and the Schwann cells align themselves longitudinally in what are referred to as Bungner bands [266], [271]. These provide direction and the molecular microenvironment for regenerating axons. At the tip of the regenerating axon is the growth cone composed on flattened cellular outshoots (lamellipodia) from which multiple finger-like projections (filopodia) extend to explore the microenvironment. The cone releases proteases to clear a path for axonal elongation to the target organ. The growth cone responds to 4 classes of factors: neurotrophic factors, neurite-promoting factors, matrix-forming precursors, and metabolic and other factors.

Following axonal transection, Lee and Wolfe have pointed out that the nerve cell body swells and undergoes chomatolysis in which the Nissl granules (the basophilic neurotransmitter synthetic machiney) disperse and the cell body becomes eosinphilic on histologic preparations (hematoxylin and eosin) reflecting the change from producing materials for structural axon repair [262]. The Nissl body granules are rough endoplasmic reticulum (as seen by electron microscopy) and are the site of protein synthesis.

Hall further outlined the response of the entire nerve to injury, including the neuronal cell body in spinal cord and ganglia and synaptic reorganization even in the cortex of the brain [269]. Some axonotomized neurons die after severe peripheral nerve injury. Persisting neurons switch to a 'survivor phenotype' expressing hundreds of genes designed to compensate for the loss of neurotrophic factors and to help regenerate axons for growth across the injury site back into the periphery. The neuron with its supporting Schwann cells undergoes activation of intracellular signaling mechanisms into a regenerative and proliferative state.

Axonal sprouts and Schwann cells in the proximal nerve stump start to bud from the damaged axons at their sealed tips and are compartmentalized by fibroblasts and perineural cells derived from the inner layers of the perineurium. There is increased expression of s-lamina and of desert hedgehog (dhh) a signaling molecule involved in normal Schwann cell-perineural cell signaling. The effectiveness of repair is based on the passage of axons across the defect into fibrous tubes to allow for distal growth reestablishment to the target organ. The mechanism by which axonal growth cones select Schwann tubes is not yet established. Repair in mixed sensory and motor nerves can be problematic due to the apparent need for modality specific tubes. In the normal state the body can provide this direction. Axons grow slowly at 1 mm/day and distance may defeat reinnervation even with axons in their appropriate Schwann tubes if the target muscle has succumbed to effects of chronic denervation.

2.23.5 Molecular Aspects of Nerve Degeneration and Regeneration

Molecular events accompanying the structural events listed above are being outlined. Successful axonal repair requires signaling and membrane trafficking in both directions from the site of injury. First, axonally transported vesicles accumulate while others are synthesized at the cut end to restore a barrier to the cut axon. Then, retrograde transport of vesicles along microtubules informs the cell body that injury has occurred distally. Finally, membrane addition to the newly forming growth cone is needed to promote axonal regrowth and elongation [262, 269]. Tuck and Cavalli [272] and Makwana and Raivich [273] have outlined the molecular activation sequences involved in these processes. The timeline of major events in nerve regeneration is outlined by Svennigsen and Dahlin [271].

Even more molecular information is provided by a proteomics approach to decipher the activities of both neuronal regeneration and degeneration [274]. Groups of molecules underlying the degenerative mechanism are concentrated into oxidative stress, dysfunctions of axonal transport,

mitochondria, chaperones and the ubiquitin-proteosome systems while those associated with regeneration include axonal transport, cytoskeleton, chaperones, and changes in signaling pathways.

2.23.6 Surgery on Nerves

2.23.6.1 Primary Repair of Transected Nerves

If a peripheral nerve is cut primary repair by suturing is the recommended treatment. This is often referred to as primary nerve coaptation or neurorrhaphy. For several decades repair tended to be done 3 weeks after injury to let Wallerian degeneration finish or at least be well underway but more recently immediate primary repair has produced better results. In one approach the repair is done by suturing the peripheral epineurium of the 2 fragments preferably using 9-0 nylon while an alternative approach sutures individual fascicles of the 2 segments using the perineurium (Fig. 2.15d). There are advocates of both approaches. A direct repair under slight tension is preferable to a tension-free repair [262].

Studies continue to be done concerning the timing of peripheral nerve repair. Jonsson et al. [275] have recently studied the timing of surgery in a rat sciatic nerve transection model. Repair with a nerve graft was done immediately and with 1, 3, or 6 months delay. A dramatic decline in the number of regenerating motoneurons and myelinated axons in the distal nerve stump was observed in the 3 and 6 month delayed groups. There was a progressive increase in fibrosis and proteoglycan scar markers in the distal nerve with increased delayed repair time. The critical time point after which the outcome of regeneration becomes too poor appears to be 3 months. There was also a decline in Schwann cell numbers in the distal stumps after 3 months.

2.23.6.2 Nerve Grafting

Nerve grafting plays a primary role in trauma where primary repair cannot be done due to excess tension and in developmental deformity, for example in relation to Erb's palsy cases, where some categories benefit from sural nerve grafting after resection of damaged segments. The most commonly used technique is the sural nerve autograft [262]. The 3 major types of autograft are the cable graft (where multiple small-caliber nerve grafts aligned in parallel span a gap between fasicular groups), trunk grafts (mixed motor-sensory whole-nerve grafts) or (infrequently) vascularized nerve grafts. The graft is generally replaced in reverse orientation to decrease the chance of axonal dispersion through distal nerve branches.

Allografts from banked material have been used with variable effects but most current research for grafts other than autografts is in development of artificial conduits using a tissue engineering approach. The approaches involve pharmacologic agents immune system modulators to decrease fibrosis, enhancing factors, and the conduits (tubulation chambers) [269].

Hall has outlined the criteria needed for the ideal artificial conduit (nerve-guidance channel) [269]. These are: a biodegradable and porous channel wall, the ability to deliver bioactive growth factors, the incorporation of an internal oriented matrix to support cell migration, intraluminal channels to mimic the structure of nerve fascicles, and transmission of electrical activity.

2.23.6.3 Nerve Conduits

Biological or polymeric nerve conduits have been developed to reconstruct long segments of damaged peripheral nerves. These are designed to serve as alternatives for the nerve autograft technique which is currently used to bridge nerve defects with gaps larger than 30 mm [269]. No ideal material has yet been found. Lee et al. recently reported on a synthetic collagen nerve conduit filled with collagen-glycosaminoglycan matrix in nerve repair in a rat model [276]. While the reversed autograft gave the best results in the 10 mm sciatic nerve repair model, the collagen-GAG matrix was almost as good and was much better than an empty conduit or one filled with collagen alone. The collagen conduits were made from highly purified type I collagen derived from bovine deep flexor tendon cross linked by formaldehyde. The inner diameter was 1.5 mm and the collagen layers were arranged in a loosely packed laminar fashion. The pore channels in the collagen-GAG matrix filling the collagen tubes are axially aligned to mimic the Schwann cell basal lamina as a mechanism to support axonal bridging across the gap. The conduits are bioabsorbable. Silicon tubes have also been used with good results.

2.23.6.4 Nerve Transfers

This repair technique refers to the method where less important nerve fascicles from a donor nerve are transected, intraneurally dissected, and attached to a functionally more important injured distal nerve segment [277]. It is primarily used for brachial plexus injuries.

Peripheral nerve surgery has reached an impasse. Repair of severed mixed motor and sensory nerves, such as ulnar or median, yields less than perfect results. Repair of nerves distant from their target such as the lower trunk of the brachial plexus is unlikely to restore useful function. Longer nerve gaps have less likely surgical repair success than shorter gaps. Results over the past few decades in peripheral nerve repair have not shown huge improvement leading to efforts to revisit many aspects of the approaches taken [278].

2.23.6.5 Overview of Techniques of Peripheral Nerve Repair

The technique of peripheral nerve repair includes four important steps outlined by Dahlin: preparation of nerve end, approximation, coaptation, and maintenance [279]. Nerves are usually repaired primarily with sutures applied in different tissue components. Nerve grafts and nerve transfers are needed where injury leaves a nerve defect. An early repair is preferable for neurobiological reasons. Neurobiological responses in neurons and Schwann cells trigger the peripheral nervous system into a reparative state. After nerve transection, calcium-dependent proteases are activated in the axon distally causing the axon to disintegrate and the Schwann cells to lose their myelin sheath. Macrophages remove both the Schwann cells and the remaining axon. Specific intracellular pathways are initiated post-injury to enhance regeneration.

A primary nerve repair is preferred after a nerve transection, done immediately or at least within 2 days. The nerve ends are prepared, removing necrotic material. They are then approximated and moved into coaptation. Any gap is filled with blood clot and a fibrin matrix. Schwann cells migrate in the fibrin matrix linking one fragment to the other, and originating from proximal and distal nerve segments. Axons from the proximal nerve grow in unison with the Schwann cells. The repair is maintained by 9-0 or 10-0 nylon inserted into the epineurium. Efforts are made to maintain normal pre-injury rotation, aided by lining up longitudinal intraneural blood vessels, and to repair individual fascicular groups. Where a defect needs to be bridged by a nerve graft after resection of badly crushed or necrotic nerve, sensory nerves the commonest of which is the sural, are preferred. It can be harvested from the level of the lateral malleolus to just below the knee. The autologous nerve graft is still the favored approach by most. The nerve graft is usually oriented in reverse. Multiple cables of the nerve are applied without tension and fibrin glue often supplements suture repair.

2.23.7 Nerve Pressure Release

Nerve pressure release is often curative. It can involve lysis of perineural adhesions or tight fibrous compartments, transfer of nerve to relieve extrinsic pressure, or release of extrinsic pressure to relieve a nerve. Examples of release of extrinsic pressure include: (i) an exostosis of the proximal fibula which can stretch the peroneal nerve, decreasing its function while removal of the exostosis can relax the nerve and allow it to regain full function; (ii) nerve roots can be stretched by protruding intervertebral discs or compressed by spinal stenosis but treatment of the primary deformity can allow normal nerve function to return; and (iii) spinal cord compression can be induced by thoracic kyphosis due to congenital vertebral body fusion and relieved by surgical correction of the spinal deformity.

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Skeletal Dysplasias

3

3.1 Terminology

The skeletal dysplasias are developmental disorders of the bones and encompass a large number of conditions most of which are genetic in origin. They can lead to such features as: disproportionate short stature; angular deformities of the long bones; joint surface irregularity; joint contractures or instability; lower extremity length discrepancies; increases or decreases of bone density; and axial deformities including cervical vertebral abnormalities, thoracolumbar scoliosis and kyphosis, spinal stenosis, and cranial bone malformations such as craniosynostosis and foramen magnum stenosis. Many terms have been used to refer to this large group of heterogeneous disorders including chondrodysplasia, because the large majority of disorders are due to primary defects of cartilage, and osteochondrodysplasia, referring to abnormalities of both cartilage and bone, but the more general term of skeletal dysplasia is used increasingly.

Dysostoses are localized malformations of single bones alone or in combination such as (i) localized disorders with predominant cranial and facial involvement (e.g., craniosynostosis), (ii) localized disorders with predominant axial involvement (e.g., spondylocostal dysplasia–congenital scoliosis), and (iii) localized disorders with predominant involvement of the extremities (e.g., symphalangism, foot or hand synostoses).

3.2 Classification Approaches

Classification criteria for the skeletal dysplasias can be defined into three broad groups: clinical, radiographic, and molecular. Some conditions are so characteristic such as achondroplasia or diastrophic dysplasia that they were defined initially and accurately by clinical appearances; some, such as the multiple epiphyseal dysplasias, spondyloepiphyseal dysplasias, or metaphyseal dysplasias, were most clearly defined, named, and categorized by characteristic radiographic findings; and some, such as the mucopolysaccharidoses (which according to radiologic criteria are spondyloepiphyseal dysplasias), have come to be defined by biochemical abnormalities. It is expected that all of the skeletal dysplasias are due to mutations in genes involved in skeletal development, many of which have been defined over the past two decades. Although the need to catalog clinical and radiographic variations among these disorders is evident, a deeper biologic understanding is being provided by elucidation of underlying gene and molecular defects in relation to collagen, glycoprotein, proteoglycan, fibroblast growth factor receptors, and other molecular components of developing limb buds, axial structures, epiphyseal cartilage, growth plate cartilage, and bone. Histology, histochemistry, and transmission electron microscopy frequently reveal structural abnormalities of physeal and epiphyseal cartilage and bone, although morphologic changes alone are rarely pathognomonic of specific diseases.

The term skeletal dysplasia does not refer to all short stature syndromes but only to those where the shape and structure of the bones are abnormal. One of the earliest distinctions made in relation to short stature syndromes was by Parrot in 1878 who used the term “achondroplasia” to distinguish disproportionate from proportionate short stature [1]. It soon came to be recognized that the former was due to primary inherited skeletal abnormalities while in the latter the bones were short secondary to systemic causes often acquired such as endocrine, metabolic, renal, hepatic, cardiac, or other disorders. By the late 1920s distinctions within the disproportionate group delineated short-limb dysplasias with limb shortening greater than truncal/axial shortening from short-trunk dysplasias with truncal/axial shortening greater than limb shortening. The prototypic short-limb disproportionate dwarfism is achondroplasia and short-trunk disproportionate dwarfism is Morquio’s disease (mucopolysaccharidosis IV). Further subdivision has followed but these basic outlines remain valuable. Many of the skeletal dysplasia syndromes were initially described and referred to as dwarfisms, dysostoses, or dystrophies but the modifying term dysplasia is used increasingly.

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Over 400 developmental disorders of the skeletal system have been described, many with several subtypes further increasing the number of entities. (Table 3.1; see also Tables 1.3 and 1.6a Chap. 1) [2–6]. The large number of disorders, the variable clinical and radiological appearance within individual disorders, the rarity of most of the defined

Table 3.1 Classification of osteochondrodysplasias/genetic skeletal dysplasias

Skeletal dysplasia groups	Gene/protein involved	Inheritance
1. Achondroplasia group		
Thanatophoric dysplasia, type I	FGFR3	AD
Thanatophoric dysplasia-type II	FGFR3	AD
Achondroplasia	FGFR3	AD
Hypochondroplasia	FGFR3	AD
Other FGFR3 disorders		
2. Spondylodysplastic and other perinatally lethal groups		
Lethal platyspondylic skeletal dysplasias (Torrance, Luton)		
Achondrogenesis type IA		
3. Metatropic dysplasia group		
Fibrochondrogenesis	COL 11A1	AR
Schneckenbecken dysplasia	SLC35D1; Lethal neonatal with snail-shaped pelvis, flat vertebral bodies, short ribs	AR
Metatropic dysplasia (various types)	TRPV4	AD
4. Short rib dysplasia (SRPS) (with/without polydactyly) group		
SRS Type I Saldino-Noonan	DYNC2H1	AR
SRS Type II Majewski	NEKI	AR
SRS Type III Verma-Naumoff	IFT80	AR
SRS Type IV Beemer-Langer		AR
Asphyxiating Thoracic Dysplasia (Jeune)	DYNC2H1, IFT80	AR
Chondroectodermal dysplasia (Ellis-van Creveld Dysplasia)	EVC 1, EVC 2	AR
5. Atelosteogenesis–omodysplasia group		
Atelosteogenesis type I and III	FLNB (filamin B), includes boomerang dysplasia	
Atelosteogenesis type II	DTDST	Sp
Omodysplasia I (Maroteaux)	Severe shortening of limbs especially rhizomelic (humerus, femur); dislocation of radial head; facial abnormalities	AD
Omodysplasia II (Borochowitz)		AR
Oto-palato-digital syndrome type II		XLR
6. Diastrophic dysplasia group		
Diastrophic dysplasia	DTDST	AR
Achondrogenesis IB	DTDST, lethal neonatal	AR
Atelosteogenesis type II	DTDST, lethal neonatal	AR
7. Dyssegmental dysplasia group		
Dyssegmental dysplasia(Silverman-Handmaker type)	Perlecan mutations; PLC(HSPG2)	AR
Dyssegmental dysplasia (Rolland-Desbuquois type)	Perlecan mutations; PLC(HSPG2)	AR
8. Type II collagenopathies		
Achondrogenesis II (Langer-Saldino)	COL2A1	AD
Hypochondrogenesis	COL2A1	AD

(continued)

Table 3.1 (continued)

Skeletal dysplasia groups	Gene/protein involved	Inheritance
Kniest dysplasia	COL2A1	AD
Spondyloepiphyseal dysplasia congenita (SED)	COL2A1	AD
Spondyloepimetaphyseal dysplasia (SEMD) Strudwick type	COL2A1	AD
SED with brachydactyly		AD
Mild SED with premature onset arthrosis	COL2A1	AD
Stickler dysplasia type 1 (heterogeneous, some linked to COL2A1)		AD
9. Type XI collagenopathies		
Stickler dysplasia type II (heterogeneous)	COL11A1	AD
Otospondylomegaepiphyseal dysplasia (OSMED)	COL11A1	
10. Other spondyloepi-(meta)-physeal [SE (M) D] dysplasias		
X-linked spondyloepiphyseal dysplasia tarda	SEDL (sedlin)	XLD
Other late onset spondyloepi-(meta)-physeal dysplasias (i.e., Namaqualand d., Irapa D.)		
Progressive pseudorheumatoid dysplasia		AR
Dyggve-Melchior-Clausen dysplasia	DYM (dymeclin)	AR
Wolcott-Rallison dysplasia		AR
Immunoosseous dysplasia Schimke	SMARCAL1	AR
Opsismodysplasia		AR
Chondrodystrophic myotonia (Schwartz Jampel), type I, type II		AR
Spondyloepiphyseal dysplasia with joint laxity		AR
Sponastrime dysplasia		AR
SEMD short limb—abnormal calcification		AR
11. Multiple Epiphyseal Dysplasias and Pseudoachondroplasia		
Pseudoachondroplasia	COMP	
Multiple epiphyseal dysplasia (MED)		AD
MED 1 (or EDM1)	COMP	
MED 2 (or EDM2)	COL9A2	
MED 3 (or EDM3)	COL9A3	
MED 5 (or EDM5)	MATN3	
MED 6 (or EDM6)	COL9A1	
12. Chondrodysplasia punctata (stippled epiphyses group)		
Rhizomelic type		AR
Zellweger syndrome (several types)		AR
Conradi-Hüunermann type	EBP	XLD
X-linked recessive type	ARSE (arylsulfatase E)	XLR
Brachytelephalangic type		XLR
Tibial-metacarpal type		AD
Vitamin K-dependent coagulations defect		AR
Other acquired and genetic disorders including Warfarin embryopathy,		

(continued)

Table 3.1 (continued)

Skeletal dysplasia groups	Gene/protein involved	Inheritance
13. Metaphyseal dysplasias		
Jansen type	PTHR1	AD
Schmid type	COL10A1	AD
McKusick type (cartilage-hair hypoplasia)	RMRP	AR
Metaphyseal anadysplasia	Type I MMP13, Type II MMP9	AD/AR
Metaphyseal dysplasia with pancreatic insufficiency and cyclic neutropenia (Shwachman-Diamond)	SBDS	
Metaphyseal chondrodysplasia Spahr type		AR
Acroscyphodysplasia (various types)		AR
14. Spondylometaphyseal dysplasias (SMD)		
Spondylometaphyseal dysplasia (Kozlowski type)	TRPV4	AD
Spondylometaphyseal dysplasia (Sutcliffe type)		AD
SMD with severe genu valgum (includes Schmidt and Algerian types)		AD
SMD Sedaghatian type	SBDS	AR
Mild SMD (various types)		
15. Brachyolmia spondylodysplasias		
Hobaek (includes Toledo type)		AR
Maroteaux type		AR
Autosomal dominant type		AD
16. Mesomelic dysplasias		
Dyschondrosteosis (Leri-Weill)	SHOX	AD
Langer type (homozygous dyschondrosteosis)	SHOX	AR
Nievergelt type		AD
Kozlowski-Reardon type		AR
Reinhardt-Pfeiffer type		AD
Werner type		AD
Robinow type, dominant		AD
Robinow type, recessive	ROR2	AR
Mesomelic dysplasia with synostes	SULF1 and SLCO5A1	AD
17. Acromelic and acromesomelic dysplasias		
Acromicric dysplasia		AD
Geleophysic dysplasia		AR
Weill-Marchesani dysplasia		AR
Cranioectodermal dysplasia		AR
Tricho-rhino-phalangeal dysplasia type I	TRPS1	AD
Tricho-rhino-phalangeal dysplasia type II (Langer-Giedion)	TRPS1, EXT1	AD
Tricho-rhino-phalangeal dysplasia type III	TRPS1	AD
Grebe dysplasia	GDF5	AR
Hunter-Thompson dysplasia		AR
Brachydactyly types A1–A4, B, C, D, and E		AD

(continued)

Table 3.1 (continued)

Skeletal dysplasia groups	Gene/protein involved	Inheritance
Pseudohypoparathyroidism (Albright hereditary osteodystrophy)		
Acrodyostosis		
Saldino-Mainzer dysplasia		AR
Brachydactyly-hypertension dysplasia		AD
Craniofacial conodysplasia		AD
Angel shaped phalango-epiphyseal dysplasia (ASPED)		AD
Acromesomelic dysplasia type Maroteaux (AMDM)	NPR2	AR
18. Dysplasias with prominent membraneous bone involvement		
Cleidocranial dysplasia	RUNX2	AD
Osteodysplasty, Melnick-Needles		XLD
Precocious osteodysplasty (terHaar dysplasia)		AR
Yunis-Varon dysplasia		AR
19. Bent bone dysplasia group		
Campomelic dysplasia	SOX9	AD
Kyphomelic dysplasia		?AR
Stüve-Wiedemann dysplasia		AR
20. Multiple dislocations with dysplasias		
Larsen syndrome	FLNB (filamin B)	AD
Larsen-like syndromes (chondrodysplaisa With congenital joint dislocations)	CHST3	AR
Desbuquois dysplasia	CANT1	AR
Pseudodiastrophic dysplasia		AR
21. Dysostosis multiplex group		
Mucopolysaccharidosis I-H	IDA	AR
Mucopolysaccharidosis I-S	IDA	AR
Mucopolysaccharidosis II	IDS	XLR
Mucopolysaccharidosis III-A	HSS	AR
III-B	NAGLU	AR
III-C	HSGNAT	AR
III-D	GNS	AR
Mucopolysaccharidosis IV-A	GALNS	AR
Mucopolysaccharidosis IV-B	GLBI	AR
Mucopolysaccharidosis VI	ARSB	AR
Mucopolysaccharidosis VII	GUSB	AR
Fucosidosis	FUCA	AR
α-Mannosidosis	MANA	AR
β-Mannosidosis	MANB	AR
Aspartylglucoasminuria	AGA	AR
gM1 Gangliosidosis, several forms	GLB1	AR
Sialidosis, several forms	NEU1	AR
Sialic storage disease	SLC17A5	AR

(continued)

Table 3.1 (continued)

Skeletal dysplasia groups	Gene/protein involved	Inheritance
Galactosialidosis, several forms	PPGB	AR
Multiple sulfatase deficiency	SUMF1	AR
Mucolipidosis II	GNPTAB	AR
Mucolipidosis III	GNPTAB	AR
22. Osteodysplastic slender bone group		
Type 1 osteodysplastic dysplasia		AR
Type 2 osteodysplastic dysplasia		AR
Microcephalic osteodysplastic dysplasia		AR
23. Dysplasias with decreased bone density		
Osteogenesis Imperfecta I	COL1A1, COL1A2	AD
Osteogenesis Imperfecta II	Lethal perinatal COL1A1, COL1A2, CRTAP, LEPRE 1, PPIB	AD/AR
Osteogenesis Imperfecta III	COL1A1, COL1A2, CRTAP, LEPRE 1, PPIB, FKBP10, SERPINHI	AD/AR
Osteogenesis Imperfecta IV	COL1A1, COL1A2, CRTAP, FKBP10, SP7	AD
Cole-Carpenter dysplasia Bruck syndrome	Type I FKBP10, type II PLOD2	AR
Singleton-Merten syndrome		AR
Osteopenia with radiolucent lesions of mandible		AD
Osteoporosis/pseudoglioma dysplasia		AR
Geroderma osteodysplasticum	GORAB	AR
Hyper IGE syndrome with osteopenia		AR
Idiopathic juvenile osteoporosis		Sp
24. Dysplasias with defective mineralization		
Hypophosphatasia-perinatal lethal and infantile forms	ALPL (alkaline phosphatase, tissue non-specific)	AR
Hypophosphatasia adult form	ALPL	AD
Hypophosphatemic rickets	X-linked-PHEX	XLD
	Autosomal dominant-FGF23	AD
Hypophosphatemic rickets–autosomal recessive, type 1	DMP1	AR
Hypophosphatemic rickets–autosomal recessive rickets, type 2	ENPP1	AR
Neonatal hyperparathyroidism	CASR	AR
Transient neonatal hyperparathyroidism with hypocalciuric hypercalcemia	ANKH	AD
25. Increased bone density without modification of bone shape		
Osteopetrosis		
(a) infantile type	OSTMI, RANK	AR
(b) delayed late-onset type	Type 1LRP5, type 2 CLCN7	AD
(c) intermediate type	CLCN7, PLEKHM1, RANKL	AR
(d) with renal tubular acidosis	CA2	AR
Axial osteosclerosis		
(a) Osteomesopycnosia		AD
(b) with Bamboo hair (Netherton syndrome)		AR
Pycnodysostosis	CTSK	AR
Osteosclerosis-Stanescu type		AD
Osteopathia striata		

(continued)

Table 3.1 (continued)

Skeletal dysplasia groups	Gene/protein involved	Inheritance
(a) isolated		SP
(b) with cranial sclerosis	WTX	XLD
Sponastrime dysplasia		AR
Melorheostosis	LEMD3	Sp
Osteopoikilosis	LEMD3	AD
Mixed sclerosing bone dysplasia		Sp
26. Increased bone density with diaphyseal involvement		
Diaphyseal dysplasia, Camurati-Engelmann	TGFβ-1	AD
Craniometaphyseal dysplasia	ANKH	AD
Lenz-Majewski dysplasia		Sp
Endosteal hyperostosis		
(a) van Buchem type	SOST (sclerostin)	AR
(b) Worth disease	SOST (sclerostin)	AD
(c) Sclerosteosis		AR
(d) with cerebellar hypoplasia		AR
Kenny Caffey dysplasia	TBCE	AD/AR
Osteoectasia with hyperphophatasia (juvenile Pagets) OPG		AR
Diaphyseal dysplasia with anemia		AR
Diaphyseal medullary stenosis with bone malignancy (Hardcastle)		AD
27. Increased bone density with metaphyseal involvement		
Pyle dysplasia		AR
Craniometaphyseal dysplasia	ANKH	AD
(a) severe type		AR
(b) mild type		AD
Fronto-metaphyseal dysplasia		XLR
Dysosteosclerosis		AR/XLR
Oculo-dento-osseous dysplasia		AD/AR
Trichodentoosseous dysplasia		AD
28. Neonatal severe osteosclerotic dysplasias		
Blomstrand dysplasia	PTHR1	AR
Raine dysplasia	FAM20C	AR
Prenatal onset Caffey disease		AR
29. Lethal chondrodysplasias with fragmented bones		
Greenberg dysplasia		AR
Dappled diaphyseal dysplasia		AR
Astley-Kendall dysplasia		AR
30. Disorganized development of cartilaginous and fibrous components of the skeleton		
Dysplasia epiphysealis hemimelica		Sp
Multiple cartilaginous exostoses (2 types)	EXT1, EXT 2	AD
Enchondromatosis (Ollier)		Sp
Enchondromatosis with hemangiomata (Maffucci)		Sp
Spondyloendochondromatosis		AR

(continued)

Table 3.1 (continued)

Skeletal dysplasia groups	Gene/protein involved	Inheritance
Spondyloendochondromatosis with basal ganglia calcification		AR
Dysspondyloenchondromatosis		
Metachondromatosis	PTPN11	AD
Osteoglophonic dysplasia	FGFR1	AD
Genochondromatosis		AD
Carpotarsal osteochondromatosis		AD
Fibrous dysplasia (Jaffe-Campanucci)		Sp
Fibrous dysplasia (McCune-Albright)		
Fibrodysplasia ossificans progressiva	ACVR1 (Activin A receptor)	AD
Cherubism	SH3BP2	AD
Cherubism with gingival fibromatosis		AR
31. Osteolyses		
Multicentric predominantly carpal and tarsal		
(a) multicentric carpal-tarsal osteolysis with and without nephropathy		AD
(b) Shinohara carpal-tarsal osteolysis		
Multicentric predominantly carpal, tarsal, and interphalangeal		
(a) Francois syndrome		AR
(b) Winchester syndrome	MMP2	AR
(c) Torg syndrome	MMP2	AR
Whyte Hemingway carpal-tarsal phalangeal osteolyses		AD
Predominantly distal phalanges		
(a) Hadju-Cheney syndrome		AD
(b) Giacci familial neurogenic acroosteolysis		AR
(c) Mandibulo acral syndrome	Type A: LMNA, Type B: ZMPSTE24	AR
Predominantly involving diaphyses and metaphyses		
(a) familial expansile osteolysis	RANK	AD
(b) juvenile hyaline fibromatosis		AR
32. Patella dysplasias		
Nail patella dysplasia	LMX1B	AD
Scypho-patellar dysplasia		AD
33. Craniosynostosis syndromes		
Pleiffer syndrome	FGFR1	AD
	FGFR2	AD
Apert Syndrome	FGFR2	AD
Crouzon Syndrome	FGFR2	AD
Craniosynostosis, Muenke	FGFR3	AD
Craniosynostosis, Boston	MSX2	AD
34. Dysotoses with predominant vertebral ± rib involvement		
Spondylocostal dysostosis Type 1	DLL3	AR
Spondylocostal dysostosis Type 2	MESP2	AR

(continued)

Table 3.1 (continued)

Skeletal dysplasia groups	Gene/protein involved	Inheritance
Spondylocostal dysostosis Type 3	LFNG (lunatic fringe)	AR
Spondylocostal dysostosis Type 4	HES7	AR
Klippel-Feil	GDF6	AD
35. Other Disorders with musculoskeletal components		
Marfan syndrome	FBN1	AD
Rubinstein-Taybi syndrome	CREBBP	AD
	EP300	AD
Progeria (Hutchinson-Guilford)	LMNA (lamin A/C)	AD
Ehlers-Danlos syndrome (progeroid form)	B4GALT7	AR
Ehlers-Danlos syndrome (musculo-skeletal variant)	CHST14	AR

Modified from International nomenclature and classification of the osteochondrodysplasias (1997). Am J Med Genet 79:376–382, 1998 and Warman ML et al. Nosology and classification of genetic skeletal disorders: 2010 revision. Am J Med Genet A 2011;155A:943–968
AR autosomal recessive, *AD* autosomal dominant, *XLD* linked dominant, *XLR* X-linked recessive, *Sp* sporadic

disorders, and the fact that many patients with a skeletal dysplasia still cannot be classified definitively even with detailed and conscientious efforts has made it difficult for understanding these disorders. It became evident early in the era of mutational analysis that a wide spectrum of clinical involvement even within a single entity such as osteogenesis imperfecta was due to the fact that virtually no two patients have the same molecular abnormality of collagen with more than 200 different mutations found by 1991 [7]. Similar situations occur with some of the other skeletal dysplasias. The subdivision of multiple epiphyseal dysplasias into 10–15 subtypes or spondyloepiphyseal dysplasia into even more subtypes based on clinical and radiographic variability [8] is almost certainly reflective of varying molecular abnormalities, many as yet undefined, and of varying degrees of penetrance and expressivity. Relatively broad groupings at a clinical–radiographic level are rapidly being correlated with gene–molecular abnormalities [5, 6].

Multiple systems of classification have evolved over time but no universal, accurate system exists. The earliest attempts at classification were hindered by the fact that many disorders currently appreciated were not even known owing to their rarity and in some instances variable geographic locations. The medical discipline of those describing the disorders has always played a role in defining how the patients are described. Early clinical observers defined proportionate and disproportionate syndromes; clinical geneticists elucidated autosomal dominant or recessive and sex-linked disorders; radiologists favored descriptions noting epiphyseal, metaphyseal, or diaphyseal localization; orthopedic surgeons distinguished between syndromes with and without spinal involvement, neurologic sequelae, angular limb deformity, and articular surface irregularity; and molecular biologists now define gene and molecular abnormalities. While these findings interdigitate to a significant extent there is not a complete fit between groupings. A relatively small number of entities characterize the large majority of patients with skeletal dysplasias such that reasonably accurate categorization in most patients is achievable.

Rubin reviewed the several classification systems which had evolved for the bone dysplasias by the 1970s [9]. Murk Jansen was the first to focus on description of the skeletal abnormality based on the region of the bone which was most deformed and his basic classification defined epiphyseal dysostosis, metaphyseal dysostosis, and diaphyseal dysostosis [9, 10]. This remains a valuable way to assess radiographs initially. Brailsford wrote on developmental bone disorders recognizing that the dysplasias are variable in degree and severity with many "transitional" forms which made classification difficult [5, 9]. He divided the disorders into three groups: (1) defective ossification of the whole skeleton which was either osteopenic involving osteogenesis imperfecta or radio-dense involving osteopetrosis; (2) abnormal metaphyseal growth in which he placed the achondroplasia disorder and chondro-osteodystrophy; and (3) proliferation of mesoblastic cells in which he defined four disorders only one of which, melorheostosis, could be clearly recognized by most today [11]. Fairbank in his "Atlas of General Affections of the Skeleton" reviewed several syndromes [12]. Although seven categories of general affections of the skeleton were listed the major value of the book rests on his description of specific entities rather than at attempts to force them into specific groupings. Even in the earliest of classifications difficulties are apparent owing to the mixing of clinically recognizable syndromes such as achondroplasia with those defined not by the clinical appearance of the individual but rather by the specific

radiologic abnormalities. Further difficulties developed by mixing the bases of the classifications even further by defining variables such as tissue of origin, cartilage, or bone, often in the absence of any convincing histopathologic correlation. With each year more detailed radiographic and clinical information accumulated leading to additional syndromes and classification systems. The uncovering of gene and molecular abnormalities is a welcome addition to the field but delineation of these abnormalities into molecular families does not totally clarify the situation because considerable areas of molecular overlap between seemingly disparate clinical disorders are being found.

Rubin provided an interesting approach to assessing the skeletal dysplasias based on the dynamics of bone development and the specific regions which were deformed [9]. These observations, made initially by Jansen and confirmed by many other studies, clearly show a regional or localizing tendency for abnormal structure in many dysplasias such that they can be defined adequately although not completely by these localizations as seen radiographically. Rubin's dynamic classification of bone dysplasias described (i) epiphyseal dysplasias (by which he meant dysplasias of the articular cartilage and secondary ossification centers); (ii) physeal dysplasias; (iii) metaphyseal dysplasias; and (iv) diaphyseal dysplasias. The dynamic nature of his classification is accompanied by detailed reviews of bone morphogenesis and development involving synthesis and resorptive aspects. He stressed the modeling of the various regions with growth, characterizing epiphyseal enlargement as a hemispherization process; physeal function as involving growth; metaphyseal development as a funnelization process; and diaphyseal development as a cylindrization process. Abnormal bone modeling was a process characterized by: (i) amplification, in which "the bone showing the greatest growth potential will show the greatest change, since it will magnify the same defect to a greater degree;" (ii) polarity, which defines the maximal direction of longitudinal growth since tubular bones grow in a differential pattern, one end predominating over the other; and (iii) changes which occur over time. The development of changes with time was delineated clinically by congenita and tarda variants.

A difficulty in radiologic categorization is that many disorders defined by regional terms affect adjacent areas radiographically and that other disorders, even if not apparent radiographically, must affect adjacent areas nevertheless. For example, disorders defined as metaphyseal dysplasias must affect the physes if they are short stature syndromes. Efforts to encompass epiphyseal and metaphyseal involvement utilize terms such as spondyloepimetaphyseal dysplasias, although the disorder pseudoachondroplasia also involves each of the three areas. It appears that the limits of radiographic nosology have been reached and could actually benefit from simplification although observations of extent and position of involvement in any individual case are essential.

Bailey approached the classification of short stature conditions by using clinical anatomic features [8]. Group 1 was disproportionate, absolutely short patients; group 2 was a spectrum group with a wide range of variability in stature and body proportions; and group 3 included proportionate short stature patients, the vast majority of which represent primary non-osseous problems with the bones shortened secondarily due to systemic growth failure.

Efforts then switched to constructing an all-inclusive classification system. The International Classification of Osteochondrodysplasias was outlined initially by a working group on bone dysplasias in 1972 with periodic revisions published in 1992 [2], 1998 [3], 2002 [4], 2007 [5], and 2011 [6]. This classification seeks to define disorders where the skeletal system is either primarily or at least extensively involved. The osteochondrodysplasias were divided into three groups in the 1992 classification: group A, defects of the tubular (and flat) bones and/or axial skeleton, 24 sections; group B, disorganized development of cartilaginous and fibrous components of the skeleton; and group C, idiopathic osteolyses. In the 1997–1998 version the overall alignment of groups was retained but the A, B, and C subdivisions were eliminated. In 2002, the categorization included 33 groups of osteochondrodysplasias along with 3 groups of genetically determined dysostoses. The dysostoses included those with predominant cranial and facial involvement (such as the craniosynostoses as a result of fibroblast growth factor receptor (FGFR) mutations), those with predominant axial involvement (such as the vertebral segmentation defects), and those with predominant extremity involvement (such as the ectrodactylys and Fanconi syndrome groups) including some subtypes, which are listed. In the next revision "Nosology and Classification of Genetic Skeletal Disorders," published in 2007, 37 groups and 372 different conditions are categorized along with updates on mode of inheritance (autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive, or sporadic), chromosome locus, gene mutation, gene product, and OMIM (Online Mendelian Inheritance in Man) syndrome number and gene protein number [5, 13]. In the 2010 revision [6] 456 conditions were included and placed in 40 groups defined by molecular, biochemical, and/or radiographic criteria. Cohen has also detailed molecular, pathologic, and clinical correlations in skeletal disorders [14, 15].

Bone, joint, and limb malformations are present in an even larger number of developmental abnormality syndromes [16]. "Smith's Recognizable Patterns of Human Malformation" lists essentially all dysmorphic syndromes including chromosomal abnormality syndromes listing over 300, many not referred to in the genetic skeletal disorders classification yet also with minimal to severe skeletal involvement such as

facial bone abnormalities, hand and foot abnormalities, limb length alterations, vertebral structural defects with or without kyphoscoliosis, and joint region malformations such as hip dislocation, club feet, and elbow contractures [17]. Elucidation of the underlying chromosome, gene, and molecular abnormalities leads to more biological definition of skeletal dysplasia and multiorgan dysmorphic disorders and thus to an evolving change in classification. Any classification using solitary criteria, by which is meant clinical or radiographic or even molecular–genetic findings, invariably seems to lump diverse entities together or place similar entities in differing groups. Our approach considers several general criteria to be of importance in assessing a patient with a skeletal dysplasia (Table 3.2).

Table 3.2 Basic considerations in assessment of a skeletal dysplasia patient

1. Short stature	May not be fully established by reference to growth charts until 1 year of age
	Absolute: below 3rd percentile
	<5 feet male and <4 feet 10 inches female at maturity
	Relative: low normal range but < familial range determined by 1 year of age
	Growth will continue along same percentile, but some have premature growth cessation
	Not all skeletal dysplasia syndromes have short stature
2. Disproportion	
(a) Disproportionate short stature re extremity-trunk relationship	Most skeletal dysplasias are disproportionate; most "medical" short stature disorders are proportionate (chronic renal, hepatic, pulmonary or cardiac disease)
	Short-limb dysplasia: outstretched fingers reach to hip area only
	Short-trunk dysplasia: outstretched fingers reach to knee area
(b) Disproportionate involvement within an extremity	Micromelia-entire extremity length shorter than normal
	Rhizomelic-proximal extremity regions most affected: arm (humerus) and thigh (femur)
	Mesomelic-mid extremity regions most affected: forearm (radius, ulna) and leg (tibia, fibula)
	Acromelic—distal extremity most affected: wrist and hand (carpals, metacarpals, phalanges) and ankle and foot (tarsals, metatarsals, phalanges)
3. Lethal/nonlethal	Lethal disorders: generally detectable in 2nd trimester by ultrasonography. Three commonest types are thanatophoric dysplasia, osteogenesis imperfecta type II (OIC A), and achondrogenesis
	Nonlethal disorders: some are diagnosable at birth but others do not show clinically or radiographically for a few years
4. Classification criteria	
(a) Clinical criteria	Syndrome recognition by clinical examination: achondroplasia and diastrophic dysplasia (recognizable at birth); hereditary multiple exostoses (usually not identifiable clinically until 3+ years of age)
(b) Radiographic criteria	
	(i) Region primarily affected: *epiphyseal* involvement-abnormal shape; irregular time of appearance and configuration of secondary ossification center; growth plate wider, narrower, irregular or with premature closure; *metaphyseal* involvement-widening, ± exostoses, physeal-metaphyseal irregularity; *diaphyseal* involvement-localized thickening
	(ii) Bone density: ↓ density (osteopenia) and ↑ density (osteopetrosis)
	(iii) Structural irregularities: upper and lower extremity bones, face and skull, spine and pelvis
(c) Gene-molecular criteria	Several gene mutation families; more discoveries to follow
(d) Histopathologic criteria	Light and electron microscopic abnormalities of cartilage/bone; immunocyto-chemical findings
5. Orthopaedic considerations	Areas of abnormality differ in varying syndromes. Regions and types of common abnormalities are listed below
(a) Spinal deformity	Spinal shortening (platyspondyly)
	Cervical: C1–C2 subluxation with odontoid hypoplasia and ligamentous laxity, kyphosis, spina bifida
	Thoracic and thoracolumbar: kyphosis, scoliosis, kyphoscoliosis
	Lumbar: spinal stenosis, lordosis

(continued)

Table 3.2 (continued)

(b) Neurologic sequelae of spinal deformity	Treatable surgically
	C1–C2 abnormalities, cervical kyphosis, foramen magnum and cervical canal stenosis
	Localized thoracic or thoracolumbar kyphosis
	Progressive kyphoscoliosis, scoliosis deformity
	Lumbar spinal stenosis with disc protrusion
(c) Upper/lower extremity deformity	Angular bone deformity—physeal/metaphyseal site, correctable
	Joint surface irregularity—predisposes to osteoarthritis, not currently amenable to therapy
	Forearm and leg deformity secondary to unequal involvement of radius/ulna and tibia/fibula
	Joint contractures
	Joint instability
	Exostoses
	Syndromes amenable to limb lengthening: normal articular shape and surfaces, no angular deformity, joint stability, no contractures
(d) Short stature	Syndromes more difficult to lengthen: abnormally shaped articular surfaces, angular deformity, instability, contractures

3.3 Prevalence of Skeletal Dysplasias

In spite of the fact that several dysplastic syndromes have been identified, relatively few of the disorders still account for the majority of cases. These will differ in various areas throughout the world including whether lethal dysplasias are tabulated in surveys, but data from Europe, North America, and South Africa are roughly comparable. A study by Wynne-Davies and Gormley assessed 4,383 individuals with skeletal dysplasias in Scotland, England, and Wales over a 30-year period [18]. The commonest disorder was osteogenesis imperfecta involving 859 patients (19.6 %) followed by multiple epiphyseal dysplasias, 588 patients (13.4 %); hereditary multiple extososis (diaphyseal aclasis), 452 (10.3 %); spondyloepiphyseal dysplasia tarda, 406 (9.3 %); achondroplasia, 226 (5.2 %); pseudoachondroplasia, 226 (5.2 %); spondyloepiphyseal dysplasia congenita, 181 (4.1 %); dyschondrosteosis, 181 (4.1 %); and metaphyseal and spondylochondrodysplasias 181 (4.1 %). These nine disorders represented 75.3 % of the diagnosed skeletal dysplasias.

In South Africa a national skeletal dysplasia registry documented 1,270 chondrodysplasias [19] . The commonest group encompassing almost 27 % of all disorders was osteogenesis imperfecta with most of these being type I or type III and a relatively small number of type II patients. The next most common groups involved those with achondroplasia, 8.6 % of all patients (109 with achondroplasia, 21 with hypochondroplasia, and 15 with thanatophoric dysplasia), cleidocranial dysplasia 4.3 %, sclerosteosis 6.4 %, SED congenita 3.7 %, pseudoachondroplasia 3.6 %, and multiple epiphyseal dysplasias 3.3 %. In Finland, the most common skeletal dysplasia is diastrophic dysplasia [20].

Studies of the frequency of occurrence of skeletal dysplasias based on pre-natal ultrasound studies are skewed toward the severe lethal dysplasias but even within this group relatively few disorders predominate. Schramm et al. reviewing their series of 162 fetuses with skeletal dysplasias found that 52 % of all cases pre-natally were thanatophoric dysplasia (TD), osteogenesis imperfecta (OI), and achondrogenesis. In other studies these three disorders comprised 48, 65, 64, and 53 % of all cases, with most of these being TD or OI. Achondroplasia was the most frequent dysplasia of the survivor group diagnosed pre-natally-primarily because most skeletal dysplasias do not become apparent until the post-natal time frame. In the one-third to one-half of pre-natal cases diagnosed by ultrasound, a similar pattern predominated including lethal variants such as short-rib dysplasia, Ellis–van Creveld disease, campomelic dysplasia, and Jeune asphyxiating thoracic dystrophy [21].

3.4 Diagnosis of Skeletal Dysplasias

3.4.1 Overview

There are both lethal and non-lethal types of skeletal dysplasias. Many of the disorders can now be diagnosed pre-natally by ultrasonography. All of the lethal disorders reach clinical awareness in the perinatal period. Some non-lethal conditions can be diagnosed clinically and radiographically at birth, whereas others do not manifest

themselves for several months or years [22]. Conditions that can be diagnosed at birth include achondroplasia, diastrophic dysplasia, Kniest syndrome, spondyloepiphyseal dysplasia congenita, cleidocranial dysplasia, chondrodysplasia punctata, metatropic dysplasia, mesomelic dysplasia, acromesomelic dysplasia, the various acrodysplasia syndromes, osteogenesis imperfecta types II and (usually) III, and osteopetrosis (malignant recessive variant) [23]. Those that tend to become identifiable with time are the metaphyseal dysplasias, spondylometaphyseal dysplasia, pseudoachondroplasia, multiple epiphyseal dysplasias, Morquio's disease, spondyloepiphyseal dysplasia tarda, hereditary multiple exostoses, hypochondroplasia, osteogenesis imperfecta type I, and benign autosomal dominant osteopetrosis.

3.4.2 Pre-natal Assessment

Ultrasonography has allowed increasingly accurate diagnosis of skeletal dysplasias in utero. Linear array real-time (rapid B-scan) ultrasonography has established normal ranges for the length of fetal limbs (Fig. 3.1), and several of the lethal and even non-lethal dysplasias can now be diagnosed in the second trimester. Reports of the ability to diagnose skeletal dysplasia by ultrasound began appearing in the late 1970s and much experience has accumulated showing the value of this technique. The diagnosis is based primarily on measurement of femoral long bone length from metaphysis to metaphysis and comparison of the lengths obtained to normal values. Other abnormalities detected often specific to particular dysplasias involve decreased bone brightness, angular deformity of the shaft of the long bones, head shape, and fractures of the long bones. Measurement of the diaphyseal–metaphyseal lengths of the fetal long bones was established from 13 weeks of gestational age for the humerus, radius, and ulna and from 14 weeks of gestational age for femur, tibia, and fibula by Jeanty and Romero [24]. Normal standards for lengths of these bones were also established by Elejalde and Elejalde [25]. Percentiles from the third to the ninety-seventh were calculated for each of the long bones in 102 pregnancies with values listed from 10 to 40 weeks of gestation. The long bones were measured from metaphyseal bone proximally to metaphyseal bone distally with the maximum distances recorded. Larger studies using more sensitive equipment have recently been published documenting femoral length in cross-sectional studies. Chitty et al. measured femoral length in 649 fetuses of 12–42 weeks of gestation and Lessoway et al. measured 790 femurs from 12 to 42 weeks of gestation [26, 27]. Both groups published centile charts and tables. There were no significant differences between male and female fetuses. Reference values for fetal limb biometry at 10–14 weeks of gestation have been published for humerus, ulna, femur, tibia, and foot lengths in relation to the crown-rump lengths [28].

Several studies have documented the accuracy of ultrasonographic determinations. The lethal perinatal type II osteogenesis imperfecta has been diagnosed sonographically between 16 and 19 weeks of pregnancy. Kurtz and Wapner reported 16 pregnancies in 15 women at high genetic risk for having fetuses with skeletal dysplasias, in whom ultrasound examinations were performed during the second trimester [29]. Eleven of 16 fetuses were normal and 5 were abnormal. At birth all 11 ultrasonographically determined normal fetuses were normal and at birth or elective termination of pregnancy the other 5 were abnormal. Hobbins et al. reported on ultrasound investigations of 66 women at risk for fetal skeletal dysplasia using femoral and humeral measurements [30]. A positive diagnosis of dysplasia was made in five of seven second trimester fetuses while in two others subsequently born with dysplasia the overlap with normal did not allow for definitive diagnosis. All other fetuses were normal at birth following normal ultrasound evaluation. Filly et al. indicated that prenatal diagnosis of short-limb dwarfs could be accomplished readily by the ultrasound technique and Kurtz et al. pointed out the range of femoral measurements by ultrasound in achondroplasia [31, 32]. Gordienko detected 30 of 39 prenatally diagnosed skeletal dysplasias (77 %) in the first and second trimester including 46 % before the 24th week [33]. In those instances where a conclusive post-natal diagnosis was made the ultrasonographic accuracy in terms of specific syndromes was reasonably high at 73 %. The other fetuses had a skeletal dysplasia although definitive verification was not present. There were three instances of OI type II A with gestation diagnosis at 20, 20, and 22 weeks; OI type II B, three cases correctly diagnosed at 19, 19, and 24 weeks; OI type II C, 2 cases at 23 and 25 weeks; achondroplasia with correct diagnoses at 26 and 34 weeks; hypochondrogenesis diagnosed at 23 and 24 weeks; Saldino–Noonan short polydactyly syndrome diagnosed at 19 and 24 weeks; thanatophoric dysplasia at 26 weeks; metatropic dysplasia at 11, 17, and 25 weeks; achondrogenesis type I at 10 and 20 weeks and type II at 23 weeks; polycampomelic syndrome at 32 weeks; diastrophic dysplasia at 22 weeks; chondroectodermal dysplasia at 24 weeks and asphyxiating thoracic dysplasia at 22 weeks.

Relatively few cases are diagnosed before 15 weeks of gestational age. The peak number of diagnostic studies occurs between 15 and 29 weeks with many cases of thanatophoric dysplasia, osteogenesis imperfecta, and achondrogenesis diagnosed in the 15–19½ week time period. Some large groups report a very high level of accuracy in diagnosing lethal dysplasia variants from 88 to 100 % of the time. In other series the lethal variants are the most accurate of the diagnoses made. In assessing the accuracy of diagnosis (by which is meant the first ultrasound compared to the

A

Week	Length of Humerus (mm)			Length of Ulna (mm)			Length of Radius (mm)		
	Percentile			Percentile			Percentile		
	5th	50th	95th	5th	50th	95th	5th	50th	95th
12	—	9	—	—	7	—	—	7	—
13	6	11	16	5	10	15	6	10	14
14	9	14	19	8	13	18	8	13	17
15	12	17	22	11	16	21	11	15	20
16	15	20	25	13	18	23	13	18	22
17	18	22	27	16	21	26	14	20	26
18	20	25	30	19	24	29	15	22	29
19	23	28	33	21	26	31	20	24	29
20	25	30	35	24	29	34	22	27	32
21	28	33	38	26	31	36	24	29	33
22	30	35	40	28	33	38	27	31	34
23	33	38	42	31	36	41	26	32	39
24	35	40	45	33	38	43	26	34	42
25	37	42	47	35	40	45	31	36	41
26	39	44	49	37	42	47	32	37	43
27	41	46	51	39	44	49	33	39	45
28	43	48	53	41	46	51	33	40	48
29	45	50	55	43	48	53	36	42	47
30	47	51	56	44	49	54	36	43	49
31	48	53	58	46	51	56	38	44	50
32	50	55	60	48	53	58	37	45	53
33	51	56	61	49	54	59	41	46	51
34	53	58	63	51	56	61	40	47	53
35	54	59	64	52	57	62	41	48	54
36	56	61	65	53	58	63	39	48	57
37	57	62	67	55	60	65	45	49	53
38	59	63	68	56	61	66	45	49	54
39	60	65	70	57	62	67	45	50	54
40	61	66	71	58	63	68	46	50	55

Fig. 3.1 (continued)

B

Week	Length of Tibia (mm)			Length of Fibula (mm)			Length of Femur (mm)		
	Percentile			Percentile			Percentile		
	5th	50th	95th	5th	50th	95th	5th	50th	95th
12	—	7	—	—	6	—	4	8	13
13	—	10	—	—	9	—	6	11	16
14	7	12	17	6	12	19	9	14	18
15	9	15	20	9	15	21	12	17	21
16	12	17	22	13	18	23	15	20	24
17	15	20	25	13	21	28	18	23	27
18	17	22	27	15	23	31	21	25	30
19	20	25	30	19	26	33	24	28	33
20	22	27	33	21	28	36	26	31	36
21	25	30	35	24	31	37	29	34	38
22	27	32	38	27	33	39	32	36	41
23	30	35	40	28	35	42	35	39	44
24	32	37	42	29	37	45	37	42	46
25	34	40	45	34	40	45	40	44	49
26	37	42	47	36	42	47	42	47	51
27	39	44	49	37	44	50	45	49	54
28	41	46	51	38	45	53	47	52	56
29	43	48	53	41	47	54	50	54	59
30	45	50	55	43	49	56	52	56	61
31	47	52	57	42	51	59	54	59	63
32	48	54	59	42	52	63	56	61	65
33	50	55	60	46	54	62	58	63	67
34	52	57	62	46	55	65	60	65	69
35	53	58	64	51	57	62	62	67	71
36	55	60	65	54	58	63	64	68	73
37	56	61	67	54	59	65	65	70	74
38	58	63	68	56	61	65	67	71	76
39	59	64	69	56	62	67	68	73	77
40	61	66	71	59	63	67	70	74	79

Fig. 3.1 Developing femoral and tibial lengths are listed as determined by ultrasound studies from 12 weeks to skeletal maturity. **a** *upper* extremity long bones (humerus, radius, ulna); **b** *lower* extremity long bones (femur, tibia, fibula). Measurements (in mm) include only the bony shaft (metaphysis—diaphysis—metaphysis) with the proximal and distal epiphyses not included. Values include 5th, 50th, and 95th percentile measurements. (Reprinted with permission from Hobbins and Benacerraf, Diagnosis and Therapy of Fetal Anomalies, 1989, Academic Press. Copyright 1989 Academic Press)

post-natal findings) the terms are "correct" (specific diagnosis confirmed) and "partially correct" (skeletal dysplasia present but different than the one indicated). A large study of 162 cases reported in 2009 found correct diagnoses in 68 % and showed a steady increase in accuracy from 35 % reported in 1993, three papers in 1998 with 44, 48, and 50 % accuracy and papers in 2000 and 2003 with 62 and 65 % accuracy. Most cases not correct are partially correct with fewer than 8 % false positive or false negative [21].

Most studies now correctly predict all or virtually all cases of lethal skeletal dysplasias. Parilla et al. noted the ability to predict lethality at 100 % in 16 cases [34]. The mean gestational age at diagnosis for the lethal dysplasias was 20.4 weeks. The diagnostic criteria favoring a lethal diagnosis were: early severe micromelic long bone shortening (13), hypoplastic thorax (10), marked long bone bowing or fractures (4), short ribs (4), caudal regression (1), and cloverleaf skull (1) [34]. Accurate antenatal diagnosis of the specific variant of dysplasia in 31 cases occurred in 20 (65 %). Witters et al. correctly identified all 27 cases of lethal variants in their series between 1996 and 2005 [35]. A correct antenatal diagnosis of the specific type of skeletal dysplasias was more difficult with 25 of 38 cases (65.8 %) correctly diagnosed.

A study by the International Skeletal Dysplasia Registry (ISDR) showed how far pre-natal ultrasound diagnostic accuracy has come, as well as the frequency of the more common disorders [36]. In a retrospective review of 1500 cases from 1990 to 2004, 70 % of cases were recognized in the second trimester, many prior to 20 weeks of gestation with 30 % showing recognition of the skeletal dysplasia after 24 weeks. The ultrasound diagnosis and final post-natal radiographic diagnoses were the same in 42 % of cases. In a prospective review of 500 cases from 2005 to 2009, the ultrasound diagnosis and postnatal radiographic diagnosis were the same in 78 % of the cases (compared with 42 % in the retrospective review). Lethality was accurately predicted in 96.8 % of cases. The final radiographic and histologic diagnoses showed a similar pattern in both groups. The three most common diagnoses were: osteogenesis imperfecta type 2 (20 and 16 %; retrospective/prospective), thanatophoric dysplasia (11 and 12 %), and achondrogenesis 2 (8 and 6 %). These three disorders accounted for almost 40 % of pre-natal–onset cases.

3.4.3 Clinical Examination

At birth, concern about a skeletal dysplasia is based on the presence of dysmorphic features, disproportion of limb–trunk relationships, orthopedic deformities, and abnormalities of bone length and shape. Patients who are being assessed in the neonatal period and within the first year of life may not demonstrate short stature based on clinical height measurement and reference to growth charts although the diagnosis of a skeletal dysplasia syndrome may be evident by clinical features and radiographic abnormalities. After one year of age the growth differential between normal and skeletally dysplastic children is sufficiently great that short stature can be diagnosed by using the growth charts.

When a child is suspected of having a skeletal dysplasia syndrome clinical examination helps to determine whether the relationship of the limbs to the trunk is proportionate or disproportionate. As a general rule the bone structure of persons with short stature due to skeletal dysplasia is disproportionate, whereas those with short stature due to systemic medical causes such as endocrine, renal, hepatic, or cardiac disorders are proportionate. In patients whose skeletal proportions are normal, the outstretched fingers reach the mid-thigh, a finding seen even in the neonatal period. In those whose skeletons are disproportionate, the fingers reach either the trochanteric region, as a result of short-limb dwarfism such as achondroplasia, or the knee region, as a result of short-spine dwarfism such as Morquio's spondyloepiphyseal dysplasia (mucopolysaccharidosis IV). In a short-limb dwarfism the extremities are more affected than the spine and in a short-trunk dwarfism the reverse is true. A second type of disproportion in many skeletal dysplasias is seen within each extremity with an abnormality in the normal length relationships of the proximal, middle, and distal segment bones. Micromelia refers to shortening of length of the entire extremity but this shortening is usually disproportionate; if the proximal (humeral–femoral) segment is most affected the shortening is referred to as rhizomelic (e.g. achondroplasia), if the middle segment (radius–ulna–tibia–fibula) is most affected the shortening is referred to as mesomelic (e.g. dyschondrosteosis), and if the distal segment (carpus, metacarpals, tarus, metatarsals, phalanges) is most affected the shortening is referred to as acromelic (e.g. Apert syndrome).

Although diagnoses of a skeletal dysplasia can be made frequently in the newborn period, there may actually be no short stature at that time but by one year of age the growth differential between the skeletal dysplastic child and a normal child becomes apparent and those with a skeletal dysplasia are either below the third percentile or in the lowest reaches of the normal range. After the first year of life however the child with a skeletal dysplasia will grow along the same established percentile. Some of the most severe dysplasias have premature growth plate closure around 10–12 years of age such as occurs in diastrophic dysplasia. In those children who are short because of a medical disorder the limbs and trunk are symmetrical or proportionate but there is almost always a continuing falloff in height percentile with time. Growth charts have been established for achondroplasia and diastrophic dysplasia, spondyloepiphyseal dysplasia

congenita, and pseudoachondroplasia [37, 38]. Scott has summarized the adult height ranges in several of the more common skeletal dysplasias [39].

Three characteristic clinical findings are seen in many types of skeletal dysplasia. The first is a depressed nasal bridge, since this area is formed initially in cartilage whereas the rest of the face and skull (excluding the skull base) develop from intramembranous bone which is not affected in chondrodysplasias. The second involves a lack of full extension of the elbows. This is usually a mild, non-progressive deformity of 10°–15° with little to no clinical significance. The third is a lumbar lordosis which can become rigid in the second decade but is relatively non-progressive.

3.4.4 Radiographic Examinations

Radiographs play a major role in diagnosing skeletal dysplasia syndromes, in following their development through time, and in assessing the need for surgical intervention to correct structural abnormalities (Table 3.2). A complete skeletal survey is warranted in the initial assessment. Views which are particularly helpful are antero-posterior and lateral skull; the cervical spine with antero-posterior, open mouth, and lateral views in flexion, neutral, and extension; postero-anterior views of the wrist and hand; antero-posterior and lateral projections of the elbows, hips, and knees; antero-posterior and lateral views of the thoraco-lumbar vertebrae and an antero-posterior view of the lumbar and sacral vertebrae.

The range of radiographic abnormalities is summarized in Table 3.2 and reviewed in detail for specific disorders in Sects. 3.7, 3.8, 3.10 and 3.11. Structural abnormalities of the skull and axial skeleton characterize many skeletal dysplasias and radiographs of these regions are an integral part of assessment.

Radiographic abnormalities of the long bones in the skeletal dysplasias can involve: shortening; irregularities of the secondary ossification centers; shaping abnormalities centered primarily in the epiphyses, metaphyses, or diaphyses; irregularity of the articular cartilage surface; angular deformity; and altered radiodensity. Most of the skeletal dysplasias will show radiographic evidence of abnormalities in the secondary ossification centers. This can involve fragmentation of the secondary center as is seen in multiple epiphyseal dysplasias in particular in the proximal femoral capital epiphysis or marked delay in appearance of the secondary center as occurs with spondyloepiphyseal dysplasia congenita in the proximal femoral capital epiphysis where it is absent as late as 7 or 8 years of age and in the knee region where the centers of the distal femur and proximal tibia are not present at birth whereas in normal individuals they are. Metaphyseal abnormalities are characterized by a broadening of the region owing to abnormalities in resorptive remodeling, and irregularities at the physeal–metaphyseal junction with cartilage persistence in the metaphysis, features seen with the metaphyseal or spondylometaphyseal dysplasias. There can also be prominent exostoses at the periphery of the metaphyseal area, for example in hereditary multiple exostoses. In rare diaphyseal dysplasias, which are not short stature syndromes, the epiphyseal and metaphyseal regions are usually structurally normal but there is widening of the diaphysis owing to increased periosteal new bone formation; this is seen in the progressive diaphyseal dysplasia syndrome of Camurati–Engelmann. The entire bone can be radio-dense as seen in osteopetrosis or radiolucent as seen in the inherited osteoporosis syndromes, the commonest of which is osteogenesis imperfecta.

If the patient has a short stature syndrome the epiphyseal region by definition must be abnormal although the structural irregularity shown on the plain radiograph may be present only in the metaphysis. The underlying biologic features of the abnormalities must be considered carefully in assessing the nature of a skeletal dysplasia since descriptive terms based on plain radiographs can be misleading. For example, groups of the skeletal dysplasias are referred to as metaphyseal dysplasias or metaphyseal dysostoses although clinical examination clearly indicates the presence of short stature and radiographs often show some physeal widening. The primary abnormality therefore must reside in the physis of the epiphysis even though the main structural or radiographic manifestation is metaphyseal.

Radiographic assessment of patients with skeletal dysplasia has two major values. The first is related to syndromal diagnosis and the second to orthopedic management. The current literature is weighted heavily to the diagnostic categorization side with numerous books and articles by radiologists and medical geneticists using the structural abnormalities detected on plain films to categorize patients and syndromes. There is a relative paucity of studies in the orthopedic literature which relates specific structural deformities to the degree of clinical symptoms on the one hand and to the need for and results of operative intervention on the other. There has also been relatively little reference to the changing patterns of radiographic abnormalities throughout the period of skeletal development in each of the various disorders. For example, long bone shape as seen on radiographs of a child with diastrophic dysplasia of 1 or 2 years of age may well be normal, even though by age 10 years the shortened stature, deformed epiphyses, and joint space narrowing will be well established. In other disorders such as metatropic dysplasia, the change in radiographic profile with time has been well documented. The clinical and

radiographic features have been well documented in such texts as Disproportionate Short Stature by Bailey [8]; Heritable Disorders of Connective Tissue by McKusick [40]; Inherited Disorders of the Skeleton by Beighton [41]; Les Maladies Osseuses De l'Enfant by Maroteaux [42]; and Bone Dysplasias-an Atlas of Constitutional Disorders of Skeletal Development by Spranger et al. [43].

3.4.5 Laboratory Studies

Some basic blood and urine studies are warranted in a skeletal dysplasia work-up. Phosphorus levels will be low in hypophosphatemic rickets which can mimic an osteochondrodystrophy. The alkaline phosphatase is elevated in osteogenesis imperfecta and markedly diminished in hypophosphatasia. Osteopetrosis can show anemia, granulocytopenia, and a diminished platelet count. Urinalysis is helpful in hypophosphatemic rickets (increased urinary phosphate), hypophosphatasia (decreased phosphoethanolamine), and the mucopolysaccharidoses (increased loss of heparan, dermatan, and keratan sulfate). Screening for mucopolysaccharides in urine is the simplest biochemical test for MPS [44]. If positive then leukocytes and cultured skin fibroblasts are assayed for specific enzyme activities. Skin biopsy for fibroblast culture and collagen typing was used initially for specific diagnosis in osteogenesis imperfecta but gene assessments by blood studies are increasingly done. The detection of molecular abnormalities in several of the skeletal dysplasia syndromes, as outlined in Sect. 3.6 below, is still done in most instances by specific research laboratories but many of these analyses are becoming available via commercial diagnostic laboratories.

3.5 Chromosome Abnormality Sites in Skeletal Dysplasias

Chromosome abnormality sites as well as the gene involved have been mapped in a large number of the skeletal dysplasias [45, 46]. These are listed in Table 3.3.

Table 3.3 Genetic skeletal disorders with chromosomal location and gene defect[a]

Gene symbol	Chromosomal location	Disorder	Gene defect
Chromosome 1			
AOM2	1p21	Arthroophthalmopathy, progressive, with deafness Stickler syndrome	Collagen type XI (COLIIA1)
EDM2	1p32	Multiple epiphyseal dysplasia, Fairbank type	Collagen type IX, alpha 2
EDS 6	1p36.3–P36.2	Ehlers-Danlos, type VI, ocular scoliotic form (PLOD deficiency)	Lysyl hydroxylase, protocollagen (PLOD) (putative)
HOPS1	1p36.1–p34	Hypophosphatasia, infantile	Alkaline phosphatase, liver, bone, kidney (ALPL)
PYCD	1q21	Pycnodysostosis	Cathepsin K, lysosomal (CTSK)
SJS	1p36.1–p34	Chondrodystrophic myotonia, Schwartz-Jampel syndrome	
Chromosome 2			
EDS3	2q31–q32.3	Ehlers-Danlos syndrome, type III, with joint hypermobility, minor hyperextensibility and softness of the skin	Collagen type III, alpha 1; (COL3A1)
EDSA4	2q31–q32.3	Ehlers-Danlos syndrome, type IV, arterial, dominant (COL3A1 defect)	Collagen type III, alpha 1; (COL3A1)
FN1	2q34	Ehlers-Danlos syndrome, type X	?fibronectin 1 (FBN1)
PSDY2	2q31	Polysyndactyly, type 2	Homeobox HOXD13
SHFM4	2q24–q31	Split hand and foot deformity, type 2, including syndactyly, brachysyndactyly, camptodactyly (?same gene as PSDY2)	
Chromosome 3			
ACAA	3p23–p22	Rhizomelic chondrodysplasia punctata	?acetyl-CoA acyltransferase (ACAA)
CDLSL	3q26.31–q27.3	Cornelia de Lange-like syndrome with dup (3q)	
CDMJ	3p22–p21.1	Metaphyseal chondrodysplasia, Jansen type	Parathyroid hormone, parathyroid hormone related peptide receptor (PTHR)

(continued)

Table 3.3 (continued)

Gene symbol	Chromosomal location	Disorder	Gene defect
FHH1	3q13.3–q21	Hypercalcemia hypocalciuric, familial, benign	Parathyroid calcium sensing receptor (PCAR1)
HPT2	3q13.3–q21	Hypoparathyroidism AD	Parathyroid calcium sensing receptor (PCAR1)
HYPOCA	3q13.3–q21	Mild hypocalcemia with hyperphosphatemia and normal PTH levels, autosomal dominant	Parathyroid calcium sensing receptor (PCAR1)
LRS1	3p21.1–p14.1	Larsen syndrome of multiple dislocations of large joints	
MFS2	3p25–p24.2	Marfan syndrome 2	
MMDL	3q22.3–q23	Mesomelic dwarfism, with hypoplastic ulna, fibula and mandible, Langer type	
MPS4B	3p21.33	Mucopolysaccharidosis, type IVB; Morquio disease B	Galactosidase, beta 1 (GLB1)
NSHPT	3q13.3–q21	Severe neonatal hyperparathyroidism	Parathyroid calcium sensing receptor (PCAR1)
Chromosome 4			
ACH	4p16.3	Achondroplasia, hypochondroplasia (FGFR3 defect)	Fibroblast growth factor receptor 3 (FGFR3)
CDPR	4p16–p14	Chondrodysplasia punctata, rhizomelic 1	
CRS5B	4p16.3	Crouzon syndrome with acanthosis nigricans	Fibroblast growth factor receptor 3 (FGFR3)
CRS7C	4p16.3	Pfeiffer syndrome	Fibroblast growth factor receptor 3 (FGFR3)
CRS8	4p16	Craniosynostosis, syndromatic 8, Adelaide type	
EVC	4p16	Ellis-van Creveld syndrome, chondroectodermal dysplasia	
GNPTA	4q21–q23	Mucolipidosis, type II, I cell disease; mucolipidosis type III, pseudo Hurler polydystrophy	*N*-acetyl-glucosamine (GNPTA) phosphotransferase
MPS1	4p16.3	Mucopolysaccharidosis, type I, Hurler, Scheie disease (IDUA deficiency)	Iduronidase, alpha-L (IDUA)
TNTP	4p16.3	Thanatophoric dysplasia, types 1 and 2	Fibroblast growth factor receptor 3 (FGFR3)
Chromosome 5			
ACG1B	5q31–q34	Achondrogenesis IB, Fraccaro type	Sulfate transporter (DTDST)
ATSG2	5q31–q34	Atelosteogenesis	Sulfate transporter (DTDST)
CCA	5q23–q31	Contractural arachnodactyly, congenital, Marfan-like disorder	Fibrillin 2 (FBN2)
CRS4	5q34–q35	Craniosynostosis, familial, primary, Boston type	Homeo domain encoding gene (MSX2)
DTD	5q31–q34	Diastrophic dysplasia	Sulfate transporter (DTDST)
MPS6	5p11–q13	Mucopolysaccharidosis, type VI, Maroteaux-Lamy disease (ARSB deficiency)	Aryl-sulfatase B (ARSB)
TCOF1	5q32–q33.1	Treacher Collins-Franceschetti syndrome	
Chromosome 6			
CCD2	6p21	Cleidocranial dysplasia 2	
CDMS	6q21–q22.3	Chondrodysplasia, metaphyseal, Schmid type	Collagen type X, alpha 1; (COL10A1)
OCDD	6p22–p21.3	Osteochondrodysplasia with mild spondyloepiphyseal dysplasia, osteoarthrosis, sensorineural deafness, dominant Stickler-like without eye involvement	Collagen type XI, chain (COL11A2)
OSMED	6p22–p21.3	Otospondylomegaepiphyseal dysplasia (chondrodystrophy with sensorineural deafness, Nance-Insley syndrome) (COL11A2 defect)	Collagen type X1, (COL11A2)

(continued)

Table 3.3 (continued)

Gene symbol	Chromosomal location	Disorder	Gene defect
Chromosome 7			
ACS3	7p21.2	Acrocephalosyndactyly III, Saethre-Chotzen syndrome with craniosynostosis	Helix loop, helix transcription factor (TWIST)
CRS1	7p22–p21	Craniosynostosis, syndromatic 1	
CRS2	7p15–p13	Craniosynostosis, syndromatic 2	
EDS7A2	7q21.3–q22.1	Ehlers-Danlos syndrome, type VIIA2	Collagen type I, alpha 2; (COL1A2)
GCPS	7p13	Greig cephalopolysyndactyly syndrome	Zinc finger protein (GLI3)
MFSV	7q21.3–q22.1	Marfan syndrome variant	Collagen type I, alpha 2; (COL1A2)
MPS7	7q11.21–q11	Mucopolysaccharidosis, type VII; Sly disease	Glucuronidase, beta (GUSB)
OI1B	7q21.3–q22.1	Osteogenesis imperfecta, types I & IA with dentinogenesis	Collagen type I, alpha 2; (COL1A2)
OI2B	7q21.3–q22.1	Osteogenesis imperfecta, type II congenital, lethal	Collagen type I, alpha 2; (COL1A2)
OI3B	7q21.3–q22.1	Osteogenesis imperfecta, type III, severe, nonlethal, dominant and recessive	Collagen type I, alpha 2; (COL1A2)
OI4B	7q21.3–q22.1	Osteogenesis imperfecta, type IV, moderately severe	Collagen type I, alpha 2; (COL1A2)
OPM	7q21.3–q22.1	Osteoporosis, postmenopausal (some cases)	Collagen type I, alpha 2; (COL1A2)
PPD2	7q36	Preaxial polydactyly type 2	
PSDY1	7q36	Polysyndactyly, complex, bilateral	
SHFM1	7q21.3–q22.1	Split hand and foot deformity, type 1, including some ectrodactyly, ectodermal dysplasia, cleft palate, EEC syndrome	
TPT	7q36	Triphalangeal thumb, opposable (?and nonopposable) type (same as PSDY1)	
Chromosome 8			
CA2	8q22	Osteopetrosis with renal tubular acidosis and cerebral calcifications	Carbonic anhydrase II, cytosolic, ubiquitous
CCD1	8q22	Cleidocranial dysplasia 1	
CPDD1	8q	Chondrocalcinosis 1 (calcium pyrophosphate-deposition disease) with early-onset osteoarthritis	
CRS7A	8p11.2–p11.1	Craniosynostosis syndromatic 7, with characteristic broad thumbs and big toes, Pfeiffer syndrome	Fibroblast growth factor receptor 1 (FGFR1)
EXT1	8q24.1	Exostoses, multiple, congenital 1	EXT1, tumor suppressor gene
LGCR	8q24.11–q24.13	Langer-Giedion syndrome, trichorhinophalangeal syndrome, may be associated with bilateral agenesis of tibia and first metatarsus (contiguous gene syndrome)	Contiguous gene with deletion of TRP1 and EXT1
SGM1	8q22–q22.3	Segmentation gene 1 (vertebral fusions with laryngeal abnormalities), Klippel-Feil syndrome	
TRP1	8q23.3–q24.13	Trichorhinophalangeal syndrome I	
Chromosome 9			
CHH	9p13	Cartilage hair hypoplasia	
NPS1	9q34.1	Nail patella syndrome 1	
Chromosome 10			
ACS1	10q26	Acrocephalosyndactyle type 1, Apert syndrome with craniosynostosis and syndactyly (FGFR2 defect)	Fibroblast growth factor receptor 2 (FGFR2)
CRS5A	10q26	Craniosynostosis, syndromatic 5, Crouzon syndrome with craniofacial dysostosis	Fibroblast growth factor receptor 2 (FGFR2)
CRS6	10q26	Craniosynostosis, syndromatic 6, Jackson-Weiss syndrome with foot anomalies and great phenotypic variability	Fibroblast growth factor receptor 2 (FGFR2)

(continued)

Table 3.3 (continued)

Gene symbol	Chromosomal location	Disorder	Gene defect
CRS7B	10q26	Craniosynostosis, syndromatic 7, Pfeiffer syndrome, with characteristic broad thumbs and big toes (FGFR2 defect)	Fibroblast growth factor receptor 2 (FGFR2)
CRS9	10q26	Craniosynostosis, syndromatic 9, Beare-Stevenson syndrome	Fibroblast growth factor receptor 2 (FGFR2)
Chromosome 11			
BWS	11p15.5	Beckwith-Wiedemann, exomphalos-macroglossia-gigantism syndrome	
EXT2	11p12–p11.12	Exostoses, multiple, congenital, 2, also associated with, craniosynostosis, mental retardation in a contiguous gene syndrome with 11p-deletions	
Chromosome 12			
ACG2	12q12–q13	Achondrogenesis II, Langer Saldino type	Collagen type II, alpha 1; (COL2A1)
AOM1	12q12–q13	Arthroophthalmopathy, progressive, with deafness, Stickler syndrome	Collagen type II, alpha 1; (COL2A1)
ATDJ	12p12.2–p11.21	Asphyxiating thoracic dystrophy of the newborn, Jeune syndrome	
HOS	12q23–q24.1	Holt-Oram syndrome excluding heart-hand syndrome, type III	T-box transcription factor (TBX5)
KND	12q12–q13	Kneist dysplasia	Collagen type II, alpha 1; (COL2A1)
MPS3D	12q14	Mucopolysaccharidosis, type III, Sanfilippo disease, type D	*N*-acetylglucosamine-6-sulfatesulfatase (GNS)
NSED	12q12–q13	Spondyloepiphyseal dysplasia, mild, Namaqualand type;	Collagen type II, alpha 1; (COL2A1)
OAP	12q12–q13	Osteoarthrosis, precocious	Collagen type II, alpha 1; (COL2A1)
PDDR	12q14	Pseudo-vitamin D dependency rickets, type I,	25-(OH)D3-1 alpha hydroxylase
SEDC	12q12–q13	Spondyloepiphyseal dysplasia, congenital	Collagen type II, alpha 1; (COL2A1)
SEMD	12q12–q13	Spondyloepimetaphyseal dysplasia congenita, Strudwick type	Collagen type II, alpha 1; (COL2A1)
VDR	12q13	Rickets, vitamin D-dependent, type II, with alopecia	Vitamin D receptor
Chromosome 13			
Chromosome 14			
Chromosome 15			
CRS3	15q15	Craniosynostosis, syndromatic 3	
MFS1	15q21.1	Marfan syndrome 1	Fibrillin (FBN1)
PHP1B	15q11–q13	Albright hereditary osteodystrophy 2, pseudo-hypoparathyroidism type IB	
SGS	15q21.1	Shphintzen-Goldberg syndrome marfanoid craniosynostosis	Fibrillin (FBN1)
Chromosome 16			
MPS4A	16q24.3	Mucopolysaccharidosis, type IVA; Morquio disease A)	Glactose-6-sulfatase (GALNS)
Chromosome 17			
AP1 J	17q21–q22	Symphalangism, proximal (ankylosis of the proximal interphalangeal joints, often associated with conductive deafness)	
CMPD1	17q24.3–q25.1	Campomelic dysplasia, 1 including mild campomelic	DNA binding protein SOX9
EDS7A1	17q21.31–q22.15	Ehlers-Danlos syndrome, type VIIA1	Collagen type I, alpha 1; (COL1A1)
MPS3A	17q25./3	Mucopolysaccharidosis IIIA, Sanfilippo disease type A	Sulfamidase (SPHM)
MPS3B	17q11–q21	Mucopolysaccharidosis, type IIIB, Sanfilippo disease type B	Acetylglucosaminidase, alpha M (NAG)

(continued)

Table 3.3 (continued)

Gene symbol	Chromosomal location	Disorder	Gene defect
OI1A	17q21.31–q22.15	Osteogenesis imperfecta, types I and IA with dentinogenesis imperfecta	Collagen type I, alpha 1; (COL1A1)
OI2A	17q21.31–q22.15	Osteogenesis imperfecta, type II, congenital, lethal	Collagen type I, alpha 1; (COL1A1)
OI3A	17q21.31–q22.15	Osteogenesis imperfecta, type III, severe, nonlethal, dominant and recessive	Collagen type I, alpha 1; (COL1A1)
OI4A	17q21.31–q22.15	Osteogenesis imperfecta, type IV	Collagen type I, alpha 1; (COL1A1)
SRS	17q25	Silver-Russell syndrome	
Chromosome 18			
Chromosome 19			
EDM1	19p13.1	Multiple epiphyseal dysplasia, Fairbank type, allelic to PSACH	Cartilage oligomeric matrix protein (COMP)
EXT3	19p	Exostoses, multiple, congenital, 3	
FHH2	19p13	Hypercalcemia hypocalciuric, familial, benign	
PSACH	19p13.1	Pseudo-achondroplasia	Cartilage oligomeric matrix protein (COMP)
Chromosome 20			
AMCD	20q11.2	Acromesomelic chondrodysplasia, Hunter-Thompson type	Cartilage derived morphogenetic protein (CDMP1)
MCAS	20q13.2	McCune-Albright polyostotic fibrous dysplasia with café au lait spots and endocrine dysfunction	Somatic mutation (GNAS1)
PHPIA	20q13.2	Albright hereditary osteodystrophy 1, pseudohypoparathyroidism type 1, A	Guanine nucleotide binding protein, alpha stimulating activity, polypeptide 1 (GNAS1)
Chromosome X			
CDPX1	Xp22.32	Chondrodysplasia punctata 1, recessive type	Arylsulfatase E (ARSE)
CDPX2	Xq27–q28	Chondrodysplasia punctata 2, dominant type	
CFND	Xpter–p22.2	Craniofrontonasal dysplasia	
HSH	Xp22.2	Hypomagnesemia with secondary hypocalcemia	
HYP1	Xp22.2–p22.1	Hypophosphatemia with vitamin D resistant rickets, excluding the gyromouse homologous type	Phosphate regulating gene (PEX)
HYP2	Xp11	Hypophosphatemia with vitamin D resistant rickets and hypercalcuria, gyromouse homolog, with inner ear abnormalities (allelism with HYP1, not definitely excluded)	
MPS2	Xq27.3–q28	Mucopolysaccharidosis, type II, Hunter disease	Iduronate 2-sulfatase (IDS)
OPD1	Xq26–q28	Otopalatodigital syndrome, type 1	
SEDL	Xp22.3–p21.3	Spondyloepiphyseal dysplasia tarda	
SHFM2	Xq26	Split hand and foot deformity	
XLRH	Xp11.22	X-linked recessive hypophosphatemic rickets, likely including Dent syndrome	Chloride voltage gated channel 5 (CLCN5)

[a]*Derived from* Frezal J, Le Mener M, Chauvet ML (reference #45) and Human Genetic Disorders chart 1997, Journal of NIH Research

3.6 Gene and Molecular Abnormalities in Skeletal Dysplasias

The vast majority of skeletal dysplasias are hereditary disorders caused by genetic abnormalities. The subsequent structural anatomic abnormality is dependent on the specific molecular abnormality and the role that molecule plays in the development or maintenance of the skeleton. There are several ways of assessing the gene and molecular abnormalities. These include (i) the mutation families into which the abnormalities are clustered; (ii) the type of molecular function defects; and (iii) the phase of the developmental pattern of skeletogenesis where the abnormality has its negative effect. The specific gene abnormalities are listed in Tables 3.3 and 3.4 in this chapter and in relation to the skeletal gene database presented in Chap. 1, Table 1.6a.

Abnormalities in processing the glycosaminoglycans were defined in the 1950s as the underlying causes of the mucopolysaccharidoses. That abnormalities relating to these molecules would lead to skeletal deformity was not surprising since proteoglycans are some of the most prominent and extensive components of the cartilage matrix. Processing abnormalities of each of the four major proteoglycans have been defined and six definitive syndromes are associated with these. In the most commonly occurring syndrome, Morquio's disease (MPS IV), the radiographic findings are those of a spondyloepiphyseal dysplasia but the identification of biochemical abnormalities allowed for classification under that terminology rather than under the radiographic pattern abnormality. There was a relative lack of additional molecular findings in other skeletal dysplasias over the subsequent decades in spite of extensive analyses performed but more recent identification of gene and molecular abnormalities has increased markedly.

With the increasing molecular definition of several types of collagen and recognition of the concentration of certain types in cartilage tissue, many skeletal dysplasias have now been defined as collagen abnormalities. Among the first to be defined was the lethal skeletal dysplasia achondrogenesis which was shown to be associated with deficient production of type II collagen with massive subsequent implications for cartilage model and skeletal formation. In hypochondrogenesis, another lethal chondrodysplasia, cultured chondrocytes at autopsy showed a type II collagen gene (COL2A1) mutation with a G – > A transition causing a glycine substitution at amino acid 574 of the pro (II) collagen triple helical domain [47]. Other studies have indicated abnormal synthesis of type II collagen in the spondyloepiphyseal dysplasia congenita syndromes, but problems remain in interpretation of the information [48, 49]. Although the hip is almost invariably abnormal in SEDC having a coxa vara deformity and the spine also has abnormalities in the anterior portion of the cartilage model of the vertebral bodies, there is generally a normal appearance of other major joints such as the knee and ankle. Since an abnormality in type II collagen COL2A1 should affect that molecule throughout the body, it remains unclear how the currently defined abnormality can translate on the one hand into major structural abnormalities of the vertebrae and proximal femur while leaving the distal femur, proximal tibia, and other regions structurally unaffected.

Several reviews of molecular defects have been presented [3–6, 50–57].

3.6.1 Mutation Families

Several syndromes have now been identified in relation to the chromosomal abnormality, the gene locus, and in many instances the specific mutation. All chromosomes except 13, Y and the mitochondrial chromosome have been defined as the site of gene mutation responsible for at least one of the skeletal dysplasias. Mapping studies of the skeletal dysplasias have uncovered considerable heterogeneity within individual disorders, for example in hereditary multiple exostoses (with three types defined), chondrodysplasia punctata, multiple epiphyseal dysplasias, and the several variants of osteogenesis imperfecta. Another finding is that clinically separate disorders are the result of mutations in the same gene. These disorders are now described as belonging to mutation groups or mutation families relating to allelic mutations of the same gene (Table 3.4). Spranger introduced the concept of bone dysplasia families in which disorders of

Table 3.4 Commoner skeletal dysplasia mutation groups

1. Fibroblast growth factor receptor
(FGFR) mutation group
(a) *FGFR 3*
Thanatophoric dysplasia
Achondroplasia
Hypochondroplasia

(continued)

Table 3.4 (continued)

(b) *FGFR 2*
Crouzon syndrome
Apert syndrome
Jackson-Weiss syndrome
Pfeiffer syndrome
(c) *FGFR 1*
Pfeiffer syndrome
2. Collagen mutation group
(a) Type I collagen
COL1A1
COL1A2
Osteogenesis imperfecta
(b) Type II collagen
COL2A1
Achondrogenesis type II
Hypochondrogenesis
SED congenita
Kniest dysplasia
Stickler dysplasia
Strudwick dysplasia
SED tarda
(c) Type IX collagen
COL9A2
Multiple epiphyseal dysplasia type 2
(EDM2)
COL9A3
Multiple epiphyseal dysplasia
(d) Type X collagen
COL10A1
Schmid metaphyseal dysplasia
(e) Type XI collagen
COL11A2
Stickler-like, mild SED
Fibrochondrogenesis
3.Diastrophic Dysplasia Sulfate Transporter mutation group (Sulfation Disorders Group)
DTDST
Achondrogenesis type IB
Atelosteogenesis type 2
Diastrophic dysplasia
4. Arylsulfatase gene mutation family
ARSE
Chondrodysplasia punctata, X-linked recessive
5. Lysosomal enzyme gene mutation family (lysosomal storage diseases)
Mucopolysaccharidoses
Mucolipidoses

(continued)

Table 3.4 (continued)

6. Cartilage Oligomeric Matrix Protein mutation group
COMP
Multiple epiphyseal dysplasia, type 1
(EDM 1)
Pseudoachondroplasia
7. Parathyroid Hormone–Parathyroid Hormone
Related peptide receptor mutation group
PTHrPR
Jansen metaphyseal dysplasia
8. SOX mutation family
SOX 9
Campomelic dysplasia
9. Short stature homeobox-containing mutation family
SHOX
Leri-Weil dyschondrosteosis
Langer Mesomelic dysplasia
10. Alteration of synthesis of cell surface heparan sulfate glycosaminoglycan
EXT1
EXT2
Hereditary multiple exostoses
11. Mutations involving transcription factor CBFA1
CBFA1/RUNX2
Cleidocranial dysostosis
12. Alkaline phosphatase, tissue non-specific
ALPL
Hypophosphatasia
13. Delta-like 3, Mesoderm posterior 2, lunatic fringe
DLL3, MESP2, LFNG
Spondylocostal dysostosis (congenital vertebral ± rib abnormalities)
14. Perlecan group
PLC (HSPG2)
Dyssegmental dysplasia
Schwartz-Jampel syndrome
15. Natriuretic peptide receptor 2
NPR2
Acromesomelic dysplasia type
Maroteaux (AMDM)
16. Chloride channel 7 disorders
CLCN7
Osteopetrosis (severe neonatal, infantile, intermediate and late onset forms)
17. Filamin group
FLNA, FLNB
Frontometaphyseal dysplasia (FLNA)
Atelosteogenesis I and III (FLNB)
Larsen syndrome (FLNB)

differing severity would be grouped on the basis of common gene and molecular abnormalities with different specific mutations within the gene [58]. Superti-Furga et al. also attempted to classify disorders by pathogenetic–molecular mechanisms while recognizing the difficulty of such an approach [56].

3.6.1.1 Fibroblast Growth Factor Receptor (FGFR) Mutation Group

The fibroblast growth factors and their receptors (FGFRs) help regulate bone growth and there are many interactions between FGFs and FGFRs in skeletal development and growth which are both temporally and spatially variable. Mutations in FGFRs 1, 2, and 3 have been shown to occur in many skeletal dysplasias [14, 59–61]. (a) FGFR3. The fibroblast growth factor receptor 3 mutation group includes three separate disorders: the lethal thanatophoric dysplasia; the commonest skeletal dysplasia, achondroplasia; and the mild variant hypochondroplasia [62–65]. (b) FGFR2. The FGFR 2 group has shown mutations with Crouzon syndrome (craniofacial dysostosis), Apert syndrome, Jackson–Weiss syndrome, and Pfeiffer syndrome [59, 60]. (c) FGFR1. The FGFR 1 group is also seen in some cases of Pfeiffer syndrome.

3.6.1.2 Collagen Mutation Family

The main structural collagen in bone, tendon, ligament, and dermis is type I collagen. There are four main collagens present in cartilage, type II, IX, X, and XI and each type has been shown to have mutations associated with specific skeletal dysplasias.

Type I collagen. Mutations in type I collagen, COL1A1 and COL1A2, are associated with osteogenesis imperfecta. This disorder is reviewed extensively in Sect. 3.12.30.

Type II collagen. COL2A1. Mutations of the type II collagen gene are associated with many skeletal dysplasias especially since type II collagen is a primary matrix protein of physeal and epiphyseal cartilage [47, 53, 66, 67]. All mutations have involved only one of the two COL2A1 alleles and map to the triple helical domain. Most involve the substitution of glycine residues critical to assembly of the triple helix. This group encompasses achondrogenesis type II, hypochondrogenesis, SED congenita, SED tarda, Kniest dysplasia, Stickler dysplasia, and spondyloepimetaphyseal (Strudwick) dysplasia [48, 68–77].

Type IX collagen. COL9A2. A large family with multiple epiphyseal dysplasias always affecting the knee joints and often other more peripheral upper and lower extremity joints but never affecting the shoulder or hip joints has been found with mutations in the COL9A2 gene. This is currently referred to as MED type 2 (or EDM 2).

COL9A3. Paassilta et al. and Bonnemann et al. described families with MED also with invariable knee involvement with a mutation in the COL9A3 gene [78, 79]. There was also a mild proximal myopathy detected in the cases studied by Bonnemann et al. [78].

Type X collagen. COL10A1. Schmid metaphyseal dysplasia has been associated with a mutation causing a 13 base pair deletion in one type X collagen allele [80, 81]. The mutations map to the region of the gene that encodes the C-propeptide. The subsequent disruption of helix formation prevents half of the type X collagen chains from entering into molecule formation diminishing the number of molecules by half.

Type XI collagen. COL11A2. A Stickler-like syndrome with mild spondyloepiphyseal dysplasia, osteoarthritis, sensorineural hearing loss but no eye involvement has been linked with mutations of type XI collagen, COL11A2 [82, 83].

3.6.1.3 Diastrophic Dysplasia Sulfate Transporter (DTDST) Mutation Family

These disorders are related to the diastrophic dysplasia sulfate transporter gene which was found to be the causative gene abnormality in diastrophic dysplasia, but is also the gene mutation site for achondrogenesis type 1B (Fraccaro type) and atelosteogenesis type II [84–90]. Several different mutations have been found in each of the three disorders. Older reports of lethal diastrophic dysplasia are now defined as atelosteogenesis II.

3.6.1.4 Cartilage Oligomeric Matrix Protein (COMP) Mutation Family

These disorders result from mutations from the gene for cartilage oligomeric matrix protein which now includes pseudoachondroplasia and some forms of multiple epiphyseal dysplasias [91–96]. MED type 1 (EDM1) is characterized by relatively severe joint involvement in particular of hips, knees, and ankles.

3.6.1.5 Parathyroid Hormone-Related Peptide Receptor (PTHrPR) Mutation Family

Mutations of the gene encoding a G-protein transmembrane spanning receptor for parathyroid hormone-related peptide have been found in Jansen metaphyseal dysplasia [97].

3.6.1.6 SOX9 Mutation Family

SOX9 is a member of a family of transcription-factor genes structurally related to the sex determining region Y genes. SOX9 transcripts have been seen in growth plate chondrocytes. Mutations of SOX9 have been reported in several patients with campomelic dysplasia, a usually lethal skeletal dysplasia with bony malformation and sex reversal.

3.6.1.7 Short Stature Homeobox-Containing (SHOX) Mutation Family

Mutations (deletions) have been identified in the SHOX gene in patients with Leri–Weil dyschondrosteosis and Langer mesomelic dwarfism [98, 99].

3.6.1.8 Arylsulfatase Gene (ARSE) Mutation Family

The arylsulfatase gene ARSE has been found with mutations in some patients with X-linked recessive chondrodysplasia punctata.

3.6.1.9 Lysosomal Enzyme Mutation Family

Abnormalities of specific lysosomal enzymes lead to the mucopolysaccharidoses and mucolipidoses [100].

3.6.1.10 Cell Surface Heparan Sulfate Proteoglycan Mutation Group

Three genes are associated with hereditary multiple exostoses referred to as EXT1 on 8q24.1, EXT2 on 11p11–13, and EXT3 on 19p. EXT1 and EXT2 have been found to be proteins with glycosyltransferase activities required for the synthesis of the glycosaminoglycan heparan sulfate. These two members of the EXT family of tumor suppressors are involved in heparan sulfate biosynthesis. Heparan sulfate proteoglycans are present both on cell surfaces and in the extracellular matrix.

3.6.1.11 Mutations Involving the Thyroid Hormone Receptor Interactor 11 Gene (Trip 11)

Mutations in the thyroid hormone receptor interactor gene (Trip 11) have been found to cause achondrogenesis type 1A [101]. Trip 11 encodes the Golgi microtubule-associated protein 210 (GMAP-210), which is missing with the TRIP 11 mutation and thus causes interference with the function of the Golgi apparatus, an integral part of the intracellular protein synthesis pathway.

3.6.1.12 Mutations Involving Transcription Factor CBFA1

Mutations in CBFA1, a transcription factor essential for osteoblast differentiation, have been found associated with cleidocranial dysplasia (Table 3.3 and Chap. 1, Table 1.6a) [102].

The collagen II and FGFR3 chondrodysplasias are caused by dominant mutations but the DTDST chondrodysplasias are recessive. Some disorders previously grouped together on a radiologic basis as metaphyseal dysplasias are now separated on the basis of differing gene abnormalities. It is becoming evident that while molecular classification brings us closer to a clarification of the causation of disorders in some instances it further complicates the matter of classification. Previously attempts were made to classify disorders based on radiographic structural similarities which seemed to make good sense. As the metaphyseal chondrodysplasia group shows, disorders with similar radiographic appearances can be caused by different gene and molecular abnormalities while disorders from the same gene frequently cause markedly varying dysplasias, for example thanatophoric dysplasia which is lethal and hypochondroplasia which is extremely mild and in many instances undetectable other than by slight short stature.

3.6.2 Molecular Function Defects

Another approach to interpreting gene and molecular information is to attempt to classify the disorders based on general categories defining the functions of the abnormal genes and molecules. Rimoin has categorized these defects into: (a) defects in structural proteins of cartilage; (b) inborn errors of cartilage metabolism; (c) local regulators of cartilage growth; and (d) systemic defects influencing cartilage development [52]. He has also suggested additional categories for genes which have been identified with skeletal dysplasias but where molecular abnormalities are unknown and other disorders in which a gene location has been mapped but no further information is available. His categorization is utilized and expanded upon below.

3.6.2.1 Defects in Structural Proteins of Cartilage

These disorders involve abnormalities of type II, type IX, type X, and type XI collagen and of the cartilage oligomeric matrix protein (COMP). The disorders of the type II collagen gene (COL2A1), referred to as type II collagenopathies, are responsible for achondrogenesis type II, hypochondrogenesis, and some cases of spondyloepiphyseal dysplasia, spondyloepimetaphyseal dysplasia, Stickler dysplasia, and Kniest dysplasia.

Type II collagenopathies. Type II collagen is the major collagen of cartilage and consists of three identical polypeptide alpha 1(2) chains encoded by the COL2A1 gene located on chromosome 1. Mutations in the COL2A1 gene give rise to a spectrum of clinical phenotypes varying from lethal to mild arthropathy only. Since type II collagen is found in cartilage, the vitreous humor of the eye and the intervertebral disks there is a relatively high association of ocular problems such as myopia and retinal detachment and vertebral abnormalities in these dysplasias. These disorders include achondrogenesis II/hypochondrogenesis. The most severe form of achondrogenesis has a striking micromelia, a hydropic appearance, and death in utero or in the early hours of life. Hypochondrogenesis is characterized by a very short stature and hydrops at birth with a flat face, widely spaced

eyes, and small rib cage also leading to death within hours or weeks. The skeleton is less severely affected. The vertebral bodies are ossified and the tubular bones are longer. In both types there are single amino acid substitutions for a glycine residue, all clustered near the carboxy-terminal end. Hypochondrogenesis however is a type II collagenopathy caused by heterozygous substitution mutations of glycine interrupting the obligatory gly-x-y repeat of the triple helical domain of 1(2) chain. The mutations result in cartilage matrix with a reduced amount of type II collagen with increased levels of post-translational modifications. The marked diminution of type II collagen leads to predominately type I and III collagen in the cartilage matrix and minor amounts of type XI. Even the small amounts of type II collagen produced were post-translationally overmodified and remained intracellular. Bones were formed however suggesting that cartilage formation and bone development can take place in the absence of type II collagen.

Over 50 mutations have been found at the type II collagen gene locus (COL2A1). If one considers that the collagen 2A1 molecule involves the triple helical region, the amino propeptide end and the amino telopeptide as well as the carboxy telopeptide and carboxy propeptide end all mutations found so far have been in the triple helical domain. The abnormalities vary from lethal perinatal types involving achondrogenesis type II, and hypochondrogenesis, to those of intermediate severity involving SED congenita and Kniest dysplasia, to the mildest forms involving SED tarda with early osteoarthritis. The SED variants have shown a variety of single nucleotide substitutions throughout the molecule as well as deletions and insertions. Kniest dysplasia has exon-skipping mutations clustered around the amino-terminal end of the molecule. Stickler dysplasia also is present. Most of the disorders other than Stickler are felt to disrupt the formation of the type II collagen triple helix leading either to the abnormally deformed molecules that are degraded prematurely or are incorporated in an imperfect fashion into the extracellular fibrillar network. Rimoin et al. found a direct correlation in type II collagenopathy skeletal dysplasias between the ratio of type I to type II collagen in cartilage and clinical severity. The most severe lethal achondrogenesis II disorder only type I collagen is present in cartilage. Normally type I collagen is not found in cartilage. In the slightly less severe hypochondrogenesis there is both type I and post-translationally overmodified type II collagen while in SED, type I is not present and type II is both normal and overmodified.

Type IX collagen abnormalities (COL9A2 and COL9A3) have been found in some families with multiple epiphyseal dysplasias. Both linkage and mutational changes have been noted. Multiple epiphyseal dysplasia cases have also been defined in relation to abnormalities of the cartilage oligomeric matrix protein (COMP) as well although these so far are phenotypically similar to the type IX variants.

Heterozygous mutations in type X collagen (COL10A1) have been defined in Schmid-type metaphyseal dysplasia in the region of the gene which holds the carboxyl-terminal chain domain and presumably leads to a reduced amount of type X collagen in the matrix.

Mutations in type XI collagen (COL11A2) have been described in a family with Stickler syndrome. Mutations of the COL11A2 gene encoding the alpha II chain of type XI collagen have been described in families with Stickler dysplasia-like phenotypes presenting with mild spondyloepiphyseal dysplasia, precocious osteoarthritis, and sensorineural hearing loss although they lack the eye abnormalities typical of the syndrome. Other types of the Stickler syndrome have resulted from type II collagen defects. It is in the collagen type II disorder that the families have severe myopia and vitreoretinal degeneration.

The other structural cartilage protein defect identified so far is in the cartilage oligomeric matrix protein (COMP) present in the short arm of chromosome 19. COMP is a member of the thrombospondin family of proteins found in the extracellular matrix of cartilage. Abnormalities of this gene have been detected in pseudoachondroplasia as well as multiple epiphyseal dysplasias (Fairbank type). Some types of MEDs and pseudoachondroplasias are thus allelic and appear to share common pathogenetic features. Pseudoachondroplasia is a genetically distinct autosomal dominant condition in which heterozygous mutations in the cartilage oligomeric matrix protein (COMP) gene have been identified. Several cases of PSACH have been studied in which COMP mutations have been found. Several differing mutations have been found within the COMP region.

3.6.2.2 Inborn Errors of Cartilage Metabolism

There are three disorders involving the diastrophic dysplasia sulfate transporter (DTDST) group found in the long arm of chromosome 5q. Abnormalities of the gene lead to reduced sulfate transport which has a major affect on the sulfation of chondroitin sulfate containing proteoglycans and on type IX collagen which has a proteoglycan component. Mutations in the DTST gene have been described in diastrophic dysplasia, in a more severe disorder achondrogenesis 1B, and in a third disorder, atelosteogenesis type II. The DTDST mutations identified in each of these conditions demonstrate a series of allelic phenotypes of variable severity.

The other two defects in this category involve enzymes of sulfate metabolism and degradation, respectively. The first group includes mutations of genes encoding for enzymes of sulfate metabolism such as arylsulfatase (ARSE) which are associated with chondrodysplasia punctata and lysosomal enzymes, abnormalities of which lead to the mucopolysaccharidoses and mucolipidoses. The mucopolysaccharidoses (MPS) are a heterogeneous group of disorders that result from inherited deficiencies of enzymes involved in the

degradation of proteoglycans. They are classified into seven types based on clinical features and specific enzyme defects. Genetic abnormalities of specific enzymes lead to an intralysosomal accumulation of glycosaminoglycans followed by excess excretion of these substances in the urine.

3.6.2.3 Local Regulators of Cartilage Growth

Early linking studies placed the achondroplasia gene on the short arm of human chromosome 4. The particular region of the chromosome affected was known to be the position where the gene for fibroblast growth factor receptor 3 (FGFR3) was present. This protein spans the cell membrane and consists of three extracellular immunoglobulin-light domains, a lipophilic transmembrane domain, and intracellular torroisin domains. FGFR3 is expressed in cartilage and brain and studies in the mouse showed that it was able to mediate the effect of fibroblast growth factor on chondrocytes. The role of FGFR3 is particularly strong in the growth plate, although it appears to involve negative regulation of intrinsic growth rates with the mutation causing the receptor to become constitutively active. Two groups reported analysis of the FGFR3 gene in achondroplastic individuals with both groups finding an FGFR3 mutation in the DNA from affected persons. No such mutations were found in DNA from unaffected persons. Unlike some other skeletal disorders both groups found that mutations were at exactly the same nucleotide of the transmembrane domain of the FGFR3 gene. Shiang et al. found that 15 of 16 achondroplasia mutations had a guanine-to-adenine transition at nucleotide 1138 and the 16th had a guanine-to-cytosine transition at the same nucleotide [65]. Both mutations resulted in the substitution of arginine for glycine at amino acid 380 of the protein. Rousseau et al. found that all 23 achondroplasia mutations in their patients resulted in the same substitution at the same amino acid of the transmembrane domain at FGFR3 protein [64]. Mutations at the same site (codon 380) have now been found in several hundred patients—the normal glycine residue replaced by an arginine residue, Gly380Arg [63]. The high proportion of identical mutations, which is 100 % for the amino acid change, helps explain the consistency of the phenotype in achondroplasia. Prenatal diagnosis of achondroplasia, homozygous achondroplasia, and the unaffected state is now possible.

Hypochondroplasia, a mild autosomal dominant skeletal disorder with clinical similarities to achondroplasia, is also linked to the FGFR3 locus on chromosome 4. FGFR3 mutations have been identified and cluster to amino acid residue 540 (N540K) where asparagine is replaced by lysine [103, 104]. Unlike achondroplasia however, hypochondroplasia shows heterogeneity since not all patients have the FGFR3 mutation [105]. Rousseau et al. detected the mutation in 21 of 29 cases while Prinster et al. found it only in 9 of 18 cases [106, 107]. Both studies found the mutation in those with relative macrocephaly and Prinster et al. felt that the mutation was found in the more definitive cases with unchanged/narrowed lumbar interpedicular distances and fibulas longer than the tibia.

The fibroblast growth factor receptor 3 (FGFR3) family of disorders involves achondroplasia, hypochondroplasia, and thanatophoric dysplasia [108, 109]. In the FGFR3 gene abnormality family almost complete homogeneity leading to achondroplasia has been demonstrated. Initially the two separate papers by Shiang and Rousseau indicated that 37 of 39 achondroplastic alleles carried the same mutation a G to A transition at nucleotide 1138 and that the remaining two alleles had a G to C transversion at the same nuclear sites thus leading to substitution of glycine to an arginine residue at position 380 (gly380Arg) of the protein. Further genetic homogeneity was demonstrated by Bellus et al. who found the gly380Arg mutation in 153 of 154 achondroplastic alleles [63]. Further studies have indicated that 192 of 194 achondroplastic alleles carried the gly380Arg mutation of which over 95 % are due to the G to A mutation.

In thanatophoric dysplasia (TD) heterozygous mutations were found to cluster mainly to four locations in the FGFR3 gene. Those with thanatophoric dysplasia type I with straight femurs and the severe cloverleaf skull deformity all have the same mutation with an Lys650Glu substitution in the intracellular tyrosine kinase domain of the receptor. In thanatophoric dysplasia type I with curved femurs with or without the cloverleaf skull, most of the mutations were found in the extracellular domain sharing a substitution of cysteine for another amino acid. Nerlich et al. defined two cases similar to thanatophoric dysplasia where molecular analysis disclosed distinct mutations of the FGFR-3 gene which were identical to those previously found in other cases of TD but there were slightly differing clinical manifestations indicating that other factors than the mutation itself appear to modulate the phenotypic expression of the disease [110]. The achondroplasia mutations map to the transmembrane domain of the mature protein, hypochondroplasia mutations to the proximal tyrosine kinase domain, thanatophoric dysplasia I to the immunoglobulin domains, and TD II to the distal tyrosine kinase domain.

3.6.2.4 Systemic Defects Influencing Cartilage Development

Genes that switch undifferentiated mesenchymal cells to specific tissue lines are beginning to be defined. The Y-linked test is the determining factor, S1-y, starts male gonadal development and chondrocyte differentiation. Mutations in the S1-y related gene SOX9 occur in campomelic dysplasia which has severe bowing and angulation of long bones, small scapulae, deformed pelvis and spine, and missing ribs. Other factors in cartilage development involve peroxisomal defects such as are found in the

rhizomelic form of chondrodysplasia punctata with a deficiency of the peroxisomal enzymes. Other rare disorders involve adenosine deaminase deficiency (ADA) which can lead to metaphyseal dysplastic changes.

Abnormal genes have been identified in some disorders although the actual protein affected has not yet been revealed. Hereditary multiple exostoses are an autosomal dominant disorder, which has now been shown to be heterogeneous with different chromosomal locations at chromosomes 8, 11, and 19. On chromosome 8 the trichorhinophalangeal syndrome type II is contiguous to the multiple extososes gene.

This work in relation to gene and molecular abnormalities is beginning to indicate that the number of genes that harbor chondrodysplasia mutations may not be as large as previously suspected. Well over half of all humans with chondrodysplasias so far have been defined to mutations at 1 of 2 loci; COL2A1 or FGFR3. Chondrodysplasia families are now being recognized at the molecular level with the two largest families of COL2A1 representing spondyloepiphyseal dysplasias and FGFR3 representing achondroplasia families. Mutations of COL2A1 tend to be dispersed throughout the gene. Mutations in genes whose products interact functionally with type II collagen such as COL11A2 cause similar phenotypes. SED phenotypes have wide variability resulting from dysfunction of collagen fibrils containing type II, IX, and XI collagen. On the other hand, mutations of FGFR3 are different showing clustering to a few codons. These result in abnormal signaling disorders and relatively subtle differences in the dose signals generated by the receptors lead to different degree of deformity depending on the specific mutation.

Mutations in several genes in mice have been noted to be associated with abnormal bone and cartilage development and similar abnormalities almost certainly underlie several of the human osteochondrodysplasias. Mutations have been noted in oncogenes c-src and c-fos, homeodomain genes involved in pattern formation such as pax 1 and pax 3, zinc finger genes, and growth factor genes such as TGF β I.

A few years later, as even more molecular abnormalities were detected, Superti-Furga et al. expanded on the earlier approach attempting to correlate the molecular–pathogenetic approaches to the clinical syndromes [56]. Seven groups of molecular defects were outlined: defects in extracellular structural proteins, defects in metabolic pathways (enzymes, ion channels, transporters), defects in folding and degradation of macromolecules, defects in hormones and signal transduction mechanisms, defects in nuclear proteins and transcription factors, defects in oncogenes and tumor suppressor genes, and defects in RNA and DNA processing and metabolism. Specific disorders were placed into the various groups based on the mutations detected. They found that many disorders fit well into individual groups but others could be in two or more while for some the biologic mechanism of action was not clear.

3.6.3 Phase of the Developmental Cycle Where Abnormality Has Its Negative Effect

Another approach to understanding how specific mutations lead to skeletal dysplasias is to assess skeletal development from the embryonic period on showing how specific molecules in the developmental cascade appear and how if they are mutated abnormalities follow. Mundlos and Olsen have described heritable disorders of the skeleton using this framework [54, 55]. Their approach includes: disorders associated with abnormal mesenchymal condensation or differentiation. These early disorders of regional patterning lead to early inappropriate model formation following which skeletal development would of necessity be abnormal; disorders associated with abnormal proliferation or maturation of cartilage by which abnormality of the endochondral ossification sequence was established; abnormalities of intramembranous bone formation; disorders associated with defects in collagenous extracellular matrix components; defects associated with non-collagenous matrix components; abnormalities of sulfate transport and metabolism; and disorders associated with abnormal matrix homeostasis. Each of the mutation families in Sect. 3.1 above and of the specific functional defects in Sect. 3.2 above can also be slotted into the framework outlined in this latter approach. This approach is helpful however in relation to the earliest phases of embryonic bone formation where mesenchymal condensation and differentiation lead to pattern formation with involvement of the homeobox transcription factor family or HOX genes, the paired-box PAX genes affecting segmentation and neurogenesis and the bone morphogenetic proteins (BMPs) which are signaling molecules influencing the size and shape of skeletal elements. Surprisingly perhaps relatively few abnormalities of the HOX genes have been discovered in human abnormalities even though they represent extremely numerous and intricate series of patterning molecules. One such disorder however has been the syndrome referred to the synpolydactyly in which in humans expansions of a polyalanine stretch within the amino-terminal non-DNA-binding region of HOXD-13 have been shown to cause synpolydactyly characterized by insertion of an extra digit between digits 3 and 4 and variable syndactyly. In the group defined as disorders associated with abnormal proliferation or maturation of cartilage it is the FGFR group that has been implicated in disorders. These involve abnormalities of growth plate function in the achondroplasia–hypochondroplasia–thanatophoric dysplasia disorders. Along with signaling disorders related to

mutations in the parathyroid hormone-related peptide (PTHrP) known now to be associated with the Jansen-type metaphyseal dysplasia. Analogous to the FGFR3 abnormality in causing physeal problems are those of FGFR1 and 2 which have a major negative effect on cranial sutures which form by the intramembranous bone mechanism. Mutations here cause varying degrees of craniosynostosis or premature fusion of the cranial sutures alone with abnormalities of the fingers and toes and on occasion tarsal and metatarsal bones. Mutations in these acrocephalosyndactyly syndromes are associated with the major role of fibroblast growth factor genes in limb development many of which are expressed in the apical ectodermal ridge where proximo-distal growth in the developing limb bud is controlled.

Following the synthesis of models of the developing bone by the processes of mesenchymal condensation and then cartilage or intramembranous bone model formation, the growth and development is then dependent on the presence of normal amounts and types of matrix proteins and their appropriate processing. Abnormalities therefore of collagen, non-collagenous proteins such as COMP, and abnormal sulfate processing can lead to major deformations as outlined previously with the DTDST family of mutations. FGFR abnormalities also cause premature cranial suture fusion leading to several craniosynostosis syndromes. The craniosynostosis in Crouzon syndrome is due to mutations in FGFR2. Apert, Jackson–Weiss, and Pfeiffer syndromes have limb defects as well as craniosynostosis and show mutations in FGFR2 and (Pfeiffer) FGFR1. The latter three are sometimes referred to as acrocephalosyndactyly syndromes. All have craniosynostosis plus limb abnormalities ranging from complete syndactyly (bone and/or skin fusion of the digits) of hands and feet in Apert syndrome, broad big toes with tarsal–metatarsal fusion in Jackson–Weiss syndrome, to broadening and deviation of thumbs and big toes without syndactyly in Pfeiffer syndrome.

The other local cartilage regulator disorder affects the parathyroid hormone-related peptide receptor (PTHrPR). A mutation in this receptor leads to the Jansen-type metaphyseal chondrodysplasia. The mutation was a histidine-to-arginine substitution at position 223 in the receptor protein. The functional abnormality relates to alterations in signaling and signal transduction between growth plate chondrocytes.

3.7 Lethal Perinatal Skeletal Dysplasias

3.7.1 Diagnostic Profile

Some skeletal dysplasias are lethal in the perinatal period, primarily because they have caused severe underdevelopment of the skeletal system in general and the ribs and thorax in particular. The disorders in this group are disproportionate short-limb disorders. They appear to occur in 1–2 per 10,000 newborns. The commonest among these include achondrogenesis, thanatophoric dwarfism, homozygous achondroplasia, short-rib syndromes with or without polydactyly, chondrodysplasia punctata (rhizomelic recessive type), campomelic dysplasia, osteogenesis imperfecta type II, and most types of asphyxiating thoracic dystrophy (Jeune's syndrome). Less common conditions are fibrochondrogenesis, hypochondrogenesis, and atelosteogenesis. A detailed list of lethal disorders is presented in Table 3.5. The disorders have been reviewed in detail by Spranger et al. [43], Maroteaux [42], and Tretter et al. [111]. Orthopedic

Table 3.5 Classifications of the Lethal Osteochondrodysplasias (LOC)/Lethal Skeletal Dysplasias (LSD)[a]

(1) Hypophosphastasia and morphologically similar disorders
Hypophosphastasia Congenita
Lethal metaphyseal dysplasia
(2) LSD with Spotted Calcifications
Lethal Conradi-Hünermann disease
Rhizomelic chondrodysplasia punctata
Greenberg dysplasia (hydrops-ectopic calcification)
(3) Achondrogenesis and Related Disorders
Achondrogenesis I-A (Houston-Harris)
Achondrogenesis I-B (Fraccaro)
Achondrogenesis II (Langer-Saldino)
Hypochondrogenesis
(4) Thanatophoric Dysplasia and Related Disorders
Thanatophoric dysplasia type I

(continued)

Table 3.5 (continued)

Thanatophoric dysplasia type II
Homozygous achondroplasia
(5) Platyspondylic LSD
Luton type
Torrance type
Shiraz type
Opsismodysplasia
(6) Lethal Metatropic Dysplasia and Related Disorders
Lethal metatropic dysplasia
Fibrochondrogenesis
Schneckenbecken dysplasia (severe spondylodysplastic dysplasia)
(7) Kniest-Like LSD
Dyssegmental dysplasia, Silverman type
Dyssegmental dysplasia, Rolland-Desbuquois type
Lethal Kniest disease
Blomstrand dysplasia
(8) Short Rib Polydactyly Syndromes
Asphyxiating thoracic dysplasia-Jeune type
Saldino-Noonan type
Verma-Naumoff type
Yang type
Le Marec type
Majewski type
Beemer type
(9) LSD with Prominent Diaphyseal Abnormalities
Campomelic syndrome
Boomerang dysplasia
Atelosteogenesis
De la Chapelle dysplasia
McAlister dysplasia
Pseudodiastrophic dysplasia
(10) Osteogenesis Imperfecta
Osteogenesis imperfecta type II
(11) Osteoporosis neonatal lethal variant

[a]*Modified and updated from* Spranger J, Maroteaux P (1990) Adv Hum Genet 19:1–103

management is rarely indicated owing to the extremely short life span.

Large studies of lethal skeletal dysplasias have noted similar findings concerning the incidence of the specific disorders. The studies by Tretter et al. (29 patients) [111], Rasmussen et al. (35 patients) [112], and Sharony et al. (134 patients) [113] each find thanatophoric dysplasia to be the commonest (48, 34, and 24 %, respectively). The next most common disorder is osteogenesis imperfecta type II (21, 26, and 26 %), followed by achondrogenesis (7, 3, and 13 %), short-rib syndromes (10, 6, and 8 %), campomelic dysplasia (7, 11, and 10 %), and atelosteogenesis (3.5, 0, and 2 %). Approximately two-thirds of all lethal skeletal dysplasias are thanatophoric dysplasia, osteogenesis imperfecta type II, and achondrogenesis. Other rarer lethal skeletal dysplasias included anywhere from 0 to 20 % of involved cases. In the Maryland study, 20 out of 27 pregnancies were terminated with an average age at detection of 21.6 weeks

while 7 pregnancies proceeded to birth at an average at detection of 29.2 weeks. Almost 60 % of cases therefore were diagnosed prior to 22 weeks of gestation corresponding to the typical timing of mid-second trimester screening sonography. The major diagnostic finding by ultrasound was short limbs in 88 %. Almost 80–90 % of lethal skeletal dysplasias were currently being detected in pregnancies receiving prenatal care which was indicative not only of the frequency of sonography but also of its increasing accuracy. In spite of this, however, although a lethal skeletal dysplasia syndrome could be diagnosed with great accuracy a specific antenatal diagnosis was made in only 48 %. This was almost identical to the 45 and 50 % accuracy rates from two other major studies. Currently, lethality is diagnosed almost 100 % of the time while overall diagnostic accuracy has increased to the 65–78 % range.

In a large retrospective study the most common disorders diagnosed in a large series of 226 fetuses and stillborns included osteogenesis imperfecta type II (18 %), thanatophoric dysplasia (14 %), campomelic dysplasia (6 %), and achondrogenesis (5 %). Brief summaries of ultrasound findings in 22 skeletal dysplasias were given [114].

3.7.2 Thanatophoric Dysplasia

Thanatophoric dysplasia is the most common lethal skeletal dysplasia. It was first diagnosed by Maroteaux et al. in 1967 [115]. It is commonly diagnosed by ultrasonography in the second trimester. It is the most severe variant of the FGFR3 molecular abnormality group which also includes the non-lethal conditions achondroplasia and hypochondroplasia. It is characterized by polyhydramnios, hypotonia, feeble fetal activity, extremely short ribs, narrow thorax, and a relatively large head [116, 117]. Occasional long-term survivors are reported with severe involvement and foramen magnum stenosis. Affected individuals are usually stillborn or die in the neonatal period due to respiratory failure or compression of the brainstem due to severe foramen magnum stenosis. The clinical appearance is characteristic of a skeletal dysplasia in general and achondroplasia in particular with short limbs, a prominent forehead, a depressed nasal bridge, and narrow thorax [41]. Two types have been recognized [117, 118]. In TDI the femurs are relatively short and curved and there may or may not be a cloverleaf skull deformity (Fig. 3.2ai); in TDII the femurs are straight and relatively longer but the cloverleaf skull is common (Fig. 3.2aii). The characteristic and pathognomonic radiographic finding in TDI is in the femurs which are short and remarkably curved leading to the older "telephone receiver" terminology regarding configuration (Fig. 3.2ai). There are also characteristic H-shaped vertebrae on antero-posterior radiographs, narrowed lumbar interpedicular distances caudally, a narrow sacrosciatic notch, and horizontal acetabulum. Every case of 91 cases of TD examined had an identifiable FGFR3 mutation [119]. For TD 1 a series of missense mutations have been defined [119] but for TD II a single point mutation (Lys 650 Glu) appears to predominate [120].

3.7.3 Homozygous Achondroplasia

Since achondroplasia is by far the most common of the disproportionate short stature skeletal dysplasias, there have been marriages between two affected individuals. Any child born to two affected parents has a one in four chance of inheriting two faulty genes causing an even more severe dwarfism called homozygous achondroplasia. Those affected look clinically like achondroplasts but radiographic changes are more marked and respiratory death usually occurs within weeks after birth although some have survived beyond early infancy to 29–37 months. The acetabulae are horizontal as in achondroplasia but the limbs are proportionally even more shortened [121]. Many lethal cases, but not all, are associated with severe stenosis of the foramen magnum with ventriculomegaly and cervical myopathy. Surgical decompression has been performed but remains problematic with questions arising from its safety, effectiveness and the question of whether this anatomic site is the sole cause of lethality.

3.7.4 Osteogenesis Imperfecta

Lethal perinatal Sillence type II OI, OI congenita A. These severe variants of OI are almost invariably lethal although the affected individual may be stillborn, die in the first few hours after birth, or live for several weeks to months and even occasionally into the second year [122, 123]. The disorder is considered in detail in the section on osteogenesis imperfecta below. A radiographic example is shown in Fig. 3.2b.

3.7.5 Achondrogenesis

Achondrogenesis is a lethal newborn dwarfing syndrome in which the limbs are extremely short and the head disproportionately large. It is currently classified into two main types, achondrogenesis type I (Parenti–Fraccaro variant) and achondrogenesis type II (Langer–Saldino variant) (Fig. 3.2c) [68, 124]. Type I exhibits defective ossification of endochondral and membrane bones and is further subdivided into 1A and 1B groups. Type IA is caused by a mutation in Trip 11 which encodes the Golgi microtubule-associated protein

210 (GMAP-210) [101]. Type IB is caused by a mutation in the diastrophic dysplasia sulfate transporter gene [89]. Type II is caused by non-expression of type II collagen with a mutation in the COL2A1 gene [68]. Type IA is characterized by multiple rib fractures, proximal femurs with metaphyseal spikes, a partially membranous bone cranial vault, pedicles ossified in the cervical and upper thoracic region only, and no vertebral body ossification. Type IB has no rib fractures and distal femoral metaphyseal irregularities, an ossified cranial vault, and ossified pedicles throughout the entire spine. In Type II, membrane bone formation appears to be normal. There is normal cranial ossification but severe underossification of the axial skeleton. The pedicles are ossified but vertebral body ossification is variable. The ribs are short but without fracture. Radiographs of achondrogenesis II show clavicles and bones of the cranial vault to be normal while the ribs are slightly short and without fractures. The maxilla and other facial bones are diminutive; the mandible is more nearly normal but still slender and pointed at the symphysis. The tubular bones are extremely short, appearing somewhat cupped at their ends, but the intrinsic trabecular pattern is normal. The extremities are extremely short; the hands and feet are very small with short bones and there is very little ossification of the middle and distal phalanges. The bones of the spine consist of tiny ossification centers, paired in the thoracic and lumbar area, and somewhat larger in the upper cervical region. The vertebral canal is narrow with the spinal cord fitted snugly within it. No ossification centers are visible in the sacrum or sternum. The iliac bones are small and crescent-shaped with a convex border superiorly and a concave border inferiorly. It is difficult to identify acetabula on radiographs as there is no ossification of pubis or ischial bones; however, the hips are not dislocated.

In both types, infants are often stillborn, premature or die soon after birth and demonstrate pulmonary hypoplasia and diminutive thoracic volume. (These cases are distinct from the nonlethal Grebe–Quelce–Salgado disorder termed achondrogenesis II in some older reviews; hence, the variable nomenclature.) In utero diagnosis by ultrasound has been reported. The disorder is due to non-expression of type II collagen [68].

3.7.6 Hypochondrogenesis

This lethal dysplasia is similar to but structurally a little milder than achondrogenesis II (Langer–Saldino). There is extreme short stature, hydrops at birth, oval flat face with widely spaced eyes, often cleft palate, and relatively longer tubular bones (compared with achondrogenesis II) [124].

3.7.7 Atelosteogenesis

This lethal neonatal dysplasia shows a micromelic dwarfism, bowed lower extremities, club feet, dislocated elbows, and often a cleft palate. The vertebral bodies are poorly ossified. The disorder can be considered as a severe variant of the diastrophic dysplasia sulfate transporter (DDST) mutation family [125]. Further characterization shows a large degree of variability leading to categorization as atelosteogenesis type I (AOI) which includes the previously described boomerang dysplasia, atelosteogenesis type II (AOII) which includes the previously described de le Chapelle dysplasia, and AO III. Atelosteogenesis I and III (AOI, AOIII) are caused by mutations in two regions of the ubiquitous filamin B gene FLNB. The majority of mutations are in exons 2 and 3 with the others in exons 28 and 29. The filamins are a family of cytoplasmic proteins that bind to and organize actin filaments and provide a scaffolding for signaling molecules [126]. Filamin B is expressed in human growth plate chondrocytes and in the developing mouse vertebrae [127]. Mutations of FLNB have also been found in Larsen syndrome and spondylocarpaltarsal syndrome [127]. Target areas of marked abnormality are the humerus and femur, pelvis, fibula, calcaneus, vertebral bodies, and hand and foot phalanges. The humeral bone can be absent, oval shaped, round, distally hypoplastic, and tapered or distally bifurcated. The femur can be boomerang shaped, oval, rectangular, or distally tapered. The fibula is often non-ossified and the tibia is bowed. The calcaneus is often non-ossified. The lumbar vertebral bodies show coronal clefting in their mid-region on lateral radiographs. The proximal and middle phalanges can be non-ossified while the distal phalanges are ossified. The ilia are misshapen while their lower one-third plus pubis and ischium are often non-ossified.

3.7.8 Chondrodysplasia Punctata, Rhizomelic Form

This represents a form of stippled epiphysis which in its characteristic pattern is almost invariably lethal but it must be distinguished from benign forms of stippled epiphysis included in the Conradi–Hünermann diagnostic category and from stippling of epiphyses accompanying other skeletal disorders such as some variants of multiple epiphyseal dysplasias [128]. The characteristic radiographic finding of rhizomelic chondrodysplasia punctata (RCP) is punctate radiodensities of the epiphyseal cartilage present occasionally in single joints but usually involving several including the larger ones. The calcifications are not limited to the central epiphyses but include the entire epiphyseal and often peri-epiphyseal regions (Fig. 3.2d). The most common

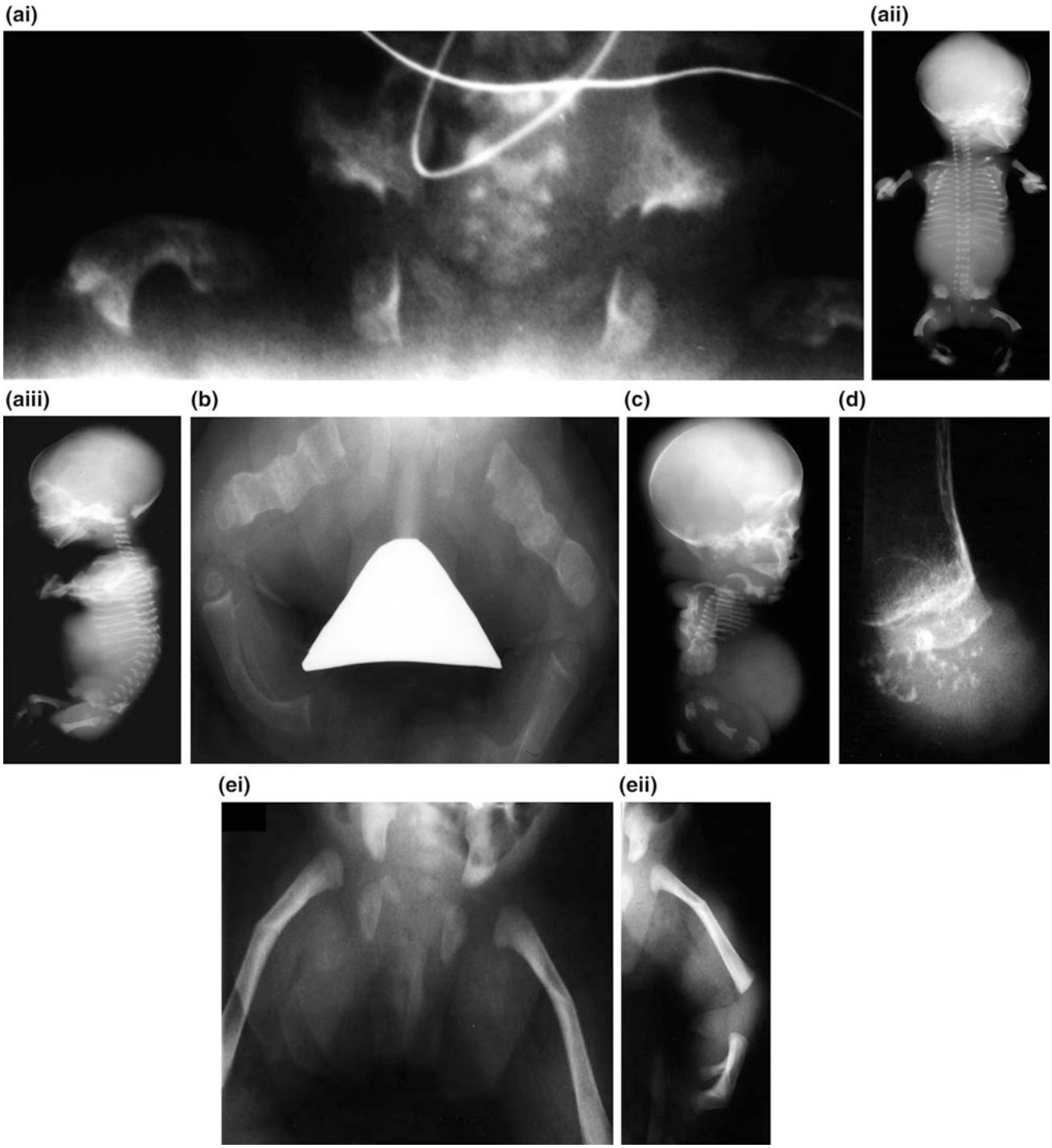


Fig. 3.2 Radiographic examples of several cases of lethal skeletal dysplasia are shown. **a** Thanatophoric dysplasia. **i** In TD type I there are short, curved femurs with the characteristic "C" or "telephone receiver" shape. The acetabulae are horizontal and there is a small sciatic notch. The latter 2 radiographic findings are also characteristic of achondroplasia. **ii** In TD type II (seen in anteroposterior full-body radiograph) the femurs are slightly longer and less curved but pelvic findings are the same as in type I. **iii** Lateral view of **ii** is shown. **b** The lethal perinatal variant of osteogenesis imperfecta (Sillence type 2, OI congenita A) is characterized by short, broad, and crumpled femurs along with deformed tibias with extensive diaphyseal bending. Multiply fractured and broadened ribs and a wormian bone skull deformation are characteristic. **c** Langer-Saldino achondrogenesis is characterized by a disproportionately large head, a shortened trunk, and even more shortened *upper* and *lower* extremities. The head can make up as much as 40–50 % of entire body length. There is marked under ossification of the axial skeleton in particular of the *lower* thoracic, lumbar, and sacral regions. The cervical and upper thoracic pedicles are almost always present but there is variable and diminishing mineralization of the vertebral bodies. Long bone formation is markedly abnormal with the bones shortened and often lacking any of the characteristic shapes. **d** Specimen radiograph of chondrodysplasia punctata shows characteristic punctate radiodensities in the distal femoral epiphysis. The calcification is present throughout the epiphyseal region and not simply in that area which would ultimately undergo secondary ossification center formation. **e** Radiograph of a newborn with campomelic dysplasia shows the characteristic diaphyseal bending of both femurs (**i**) and femur and tibia on one side (**ii**)

variant, type I, RCPI is due to a disorder of peroxisome function associated with PEX7 receptor defect [129]. Death usually occurs within the first year of life but a review of 35 previously unreported cases as well as 62 from the literature showed that survival was greater than previously reported with 90 % surviving up to one year and 50 % surviving up to 6 years [130]. Cause of death was usually respiratory. Previously it was thought that death from respiratory complications such as tracheal stenosis usually occurs in the neonatal period and almost all die within the first 10 months of life but some survive for 1–2 years. All infants with RCP had joint contractures, bilateral cataracts, and severe growth and psychomotor delays. Features of lethal and benign variants were outlined by Jeune et al. in 1953 [131]. The two general variants cannot necessarily be distinguished at birth so a careful follow-up is needed. In a study of 40 cases from the literature all lethal cases died before 10 months of age with all beyond that age being long-term survivors. This is an autosomal recessive rhizomelic form characterized by marked symmetrical rhizomelia (proximal limb shortening) with the most prominent areas of involvement being the humerus and femur. Femoral (thigh) shortening is greater than humeral and is usually asymmetric with one side more involved. Lenticular cataracts and dermal abnormalities are present in approximately two-thirds of cases. There is a tendency to have short digits with limited joint mobility. Mental deficiency is common. Spinal involvement is mild but vertebral body stippling can occur. RCP type 2 is caused by a deficiency of the peroxisomal enzyme dihydroxyacetone phosphate acyltransferase (DHAPAT) and RCP3 by a deficiency of the peroxisomal enzyme alkyldihydroxyacetone phosphate synthase (ADAPS).

3.7.9 Campomelic Dysplasia

The vast majority of patients with campomelic dysplasia are in the lethal category dying in the neonatal period because of respiratory deficiency. Those affected rarely live beyond 1 year of age and most are stillborn or die in the first few weeks of life. A few will survive but with feeding problems, failure to thrive, and serious central nervous symptom deficiency. The disorder is characterized by bending primarily the lower limbs with intrauterine bony curvature of the diaphyseal regions of the femurs, tibias, and fibulas particularly prominent (Fig. 3.2e). There is delayed osseous maturation in the fetal period. The head is large and there tends to be a large brain with hydrocephalus and gross cellular disorganization of the cerebral cortex and midbrain. Clubfeet are common. There is no ossification of the distal femoral and proximal tibial epiphyses in the newborn.

There is marked fibular and scapular hypoplasia, a tendency to calcaneal–valgus foot deformities, numerical rib defects, ossification defects of the vertebral bodies, flat face with ocular hypertelorism, micrognathia, and cleft palate. The most severe bowing is of the tibia usually present at the junction of the middle and distal thirds associated with a cutaneous dimple. Femoral bowing tends to be in the mid shaft and is often from 70° to 90°. Laterally dislocated hips in association with hypoplastic ilia are also seen. Respiratory difficulties are worsened by hypoplasia of the cartilage of the tracheal rings. Roth et al. described in detail a case of lethal campomelic dysplasia [132]. Multiple studies of the bent long bones led to the conclusion that the disorder was caused by an abnormality in the formation of the cartilage model of the long bones rather than being due to bony fracture, trauma, or pressure phenomena causing mechanical bending. The bone tissue itself appeared normal and was synthesized in the appropriate patterns and positions in relation to the marked angular diaphyseal deformity. The epiphyseal cartilage was entirely within normal limits. In relation to the endochondral sequences at the epiphyseal growth plates, each of the stages of cellular maturation was seen. The epiphyses had cartilage canals but there was clear delay in the formation of ossification centers of the distal femur and proximal tibia both of which should be present at birth. The anterior and lateral portions of the ring of Ranvier were within normal limits but posteriorly in the area of the concavity the ring was thicker than normal and the bone was reduplicated.

Three clinical types are recognized involving the long-limbed type, the short-limbed craniosynostotic type, and the short-limbed normocephalic type. It is those with the long-limbed variant that survive. In those few who survive the bowing is less marked and tends to correct with time [133, 134]. They are of markedly shortened stature and have considerable deformities of the cervical and thoracolumbar spines, generally necessitating spine fusion early in the first decade [133]. The upper extremities are only minimally affected by the bowing. The hands however have many shaping abnormalities. The ossific nuclei of the distal femur, proximal tibia, and usually talus are not generally present at birth in this dysplasia.

3.7.10 Hypophosphatasia

Hypophosphatasia is a rare but lethal skeletal dysplasia. It is autosomal recessive and characterized by small stature and poorly mineralized bone, in particular poorly and almost non-mineralized cranial bone. The long bones are extremely thin, hypoplastic, and fragile with a marked osteopenia. The ribs are short in association with a small thoracic cage. Death occurs secondary to respiratory insufficiency in the neonatal period but many are stillborn often with markedly premature birth. The disorder is characterized by severe deficiency of bony tissue, markedly lower levels of serum alkaline

phosphatase, and an excessive urinary excretion of phosphoethanolamine. The disorder is due to mutations in the gene ALPL, the gene encoding alkaline phosphatase [135]. Ultrasonography, prenatal radiographs, and demonstration of markedly lowered alkaline phosphatase levels in cultured amniotic fluid cells have aided intra-uterine diagnosis. The major differential diagnosis involves distinction from osteogenesis imperfecta type II. Several very rare milder variants occur, all characterized by low serum alkaline phosphatase.

3.7.11 Short-Rib Syndromes

The short-rib syndromes, also referred to as "short rib-polydactyly syndromes," are potentially lethal, in particular where thoracic constriction is prominent. Respiratory insufficiency and pulmonary hypoplasia contribute to death soon after birth in almost all cases. Three types are defined.

Type I. Saldino–Noonan. The entity shows micromelia, post-axial polydactyly, brachydactyly, thoracic narrowing, and abnormalities of the cardiovascular system and genitalia. Radiographically there are short horizontal ribs, small iliac bones, metaphyseal spurs on the tubular bones, and deficiency in ossification of the distal extremities.
Type II. Majewski. This variant has changes similar to those of the Saldino–Noonan form but there is super-added facial clefting and nose deformities. The pelvis is radiographically normal and the tibia is more involved being markedly shortened and ovoid.
Type III. Naumoff. Radiographic features are similar to those of types I and II but thoracic constriction is severe.

3.7.12 Asphyxiating Thoracic Dystrophy (Jeune)

On occasion, patients with this disorder live, but most die in particular those with marked pulmonary hypoplasia and pancreatic and hepatic fibrosis. There are short ribs, horizontal acetabular roofs, and early appearance of the proximal femoral capital epiphysis secondary ossification centers. In those who survive there is progressive improvement of lung function and often close to normal stature.

Table 3.6 lists the most prominent feature or features of these disorders, reference to which may be helpful in directing initial thoughts regarding diagnosis.

3.7.13 Metatropic Dysplasia Lethal Variants

Lethal metatropic dysplasia consists of three variants with a similar radiographic pattern but also other variants which are similar but more divergent from the basic pattern [136]. The three variants are (i) lethal hyperplastic metatropic dysplasia (type I), (ii) lethal metatropic dysplasia–hyperchondrogenesis (type II), and (iii) fibrochondrogenesis. These lethal disorders (stillborn or die in the first few days after birth) also include the Schneckenbecken dysplasia variant. The characteristic anomaly radiographically is shortened long bones with expanded mushroom shaped metaphyses and very short diaphyses leading to a dumbbell appearance. Other findings are a narrow chest, caudal appendage (tail) overlying the sacrum, long fingers and toes, wafer thin/widely spaced vertebral bodies, bulky pedicles with very narrow interpedicular distances, and crescent-shaped iliac bones with horizontal acetabula. The fibulae are

Table 3.6 Radiographic characteristics of lethal skeletal dysplasias

Thanatophoric dysplasia	**Short, c-shaped, "telephone-receiver" femurs**; horizontal acetabulae; narrow sacrosciatic notch; underformed "H-shaped" vertebrae
Osteogenesis imperfecta, lethal perinatal (Sillence II, OIC A)	**Short, broad crumpled femurs;** wormian skull bones; thickened ribs; short tibia with 45°–90° diaphyseal angulation; extremity thin to absent cortices
Achondrogenesis	**Disproportionately large head (approximately 40–50 % of total body length) with extremely short limbs**; severe underossification of axial skeleton, especially lower thoracic, lumbar, and sacral areas; pelvis, limb bones extremely short with little markedly abnormal shaping
Campomelic dysplasia	**Bent diaphyseal regions of femurs and tibias**
Hypophosphatasia	**Severe undermineralization of all bones with virtually no mineralization of calvarial bone; metaphyses are widened** with marked radiolucency and cupping
Short rib syndromes	**Thoracic narrowing with short horizontal ribs; polydactyly; micromelia;** cardiovascular and multi-system abnormalities
Chondrodysplasia punctata (rhizomelic type)	**Punctate calcifications in epiphyseal and peri-epiphyseal regions; rhizomelic shortening**
Atelosteogenesis	**Club feet, dislocated elbows, bowed lower extremities, abnormally shaped (oval, curved, bifurcated) and shortened humeri and femurs, coronal clefting of lumbar vertebral bodies;** lower pelvis, calcanei often not ossified

Further subcategorization of most of these syndromes is then possible

relatively long. These findings are best seen in the type II hyperchondrogenesis variant. In the more severe type I variant many of the ribs are wide, sclerotic, and covered by periosteal new bone. In fibrochondrogenesis the vertebrae differ from the above two groups: the vertebral bodies are rounded anteriorly, constricted posteriorly, flattened, absent ossification in the cervical spine, interpedicular distances widened, sagittal clefting in thoracic vertebrae, and coronal clefting in lumbar vertebrae.

Histology. In types I and II there is hyperplastic cartilage in the metaphyses, trachea, and bronchi. Growth plate hypertrophic chondrocytes are arranged in clusters with no columnation and above, premature vascularization leads to foci of calcification. In fibrochondrogensis there are fibrous strands in the cartilage matrix and the chondrocytes are elongated, resembling fibroblasts. Fibrous septa are present in the growth cartilage. O'Sullivan et al. describe a detailed autopsy of a stillborn with lethal metatropic dysplasia [137].

3.8 Microstructural–Morphologic Abnormalities of the Epiphyses and Metaphyses in Skeletal Dysplasias

3.8.1 General Considerations

Light microscopic and ultrastructural studies of epiphyseal cartilage, growth plate cartilage, and bone in the skeletal dysplasias show many structural abnormalities although these are rarely pathognomonic alone for any particular dysplasia. With the increasing discovery of molecular abnormalities and with refinements of structural techniques at both the light and electron microscopic levels, correlation between molecular abnormality and structural defect should play an increasing role in assessing the pathogenesis of deformity.

We propose a regional and hierarchical approach to structural descriptions of abnormal epiphyses and metaphyses in the skeletal dysplasias [138]. Although there have been a few attempts at coordinating descriptions of pathologic findings in the skeletal dysplasias, they have rarely been adhered to on a uniform basis. A systemic approach to tissue examination was provided by Yang et al. [139]. There are a relatively limited number of ways in which structural abnormalities of an affected physis, entire epiphysis, and adjacent metaphysis can be manifested. The purpose of this approach is not to list in detail the structural abnormalities described in the various skeletal dysplasias but rather to outline the broad categories of gross and microscopic structural abnormality that occur in the various dysplasias, so that organized assessments can begin to link molecular abnormalities with eventual structural consequences. The categorization is outlined in Table 3.7.

3.8.2 Histopathologic Classification of Skeletal Dysplasias

3.8.2.1 Shaping Abnormalities of the Epiphyses

The entire epiphysis including the articular surfaces can be abnormally shaped. The model of the epiphysis can be irregular from the embryonic period on but in other disorders the articular surface and epiphyseal mass can be normally

Table 3.7 Outline of structural morphologic abnormalities of the epiphyses in skeletal dysplasias

A regional-hierarchical approach
A. Shaping abnormalities
1. of epiphyses:
• embryonic-fetal (primary)
• Juvenile to adult (secondary)
2. of the periphery of the epiphyseal-metaphyseal junction
3. of the metaphyses
B. Physeal Abnormalities
4. Alterations in growth plate thickness
• thinner
• thicker
5. Change in proportional contribution of varying regions of the growth plate
6. Disorganization of the cytoarchitecture of growth plate
7. Premature closure of the growth plate
C. Epiphyseal and Physeal Abnormalities
8. Change in cellularity of epiphyseal and physeal cartilage

(continued)

Table 3.7 (continued)

A regional-hierarchical approach
• hypocellular
• hypercellular
9. Altered Vascularity (or cartilage canals) of the cartilaginous epiphyses
• hypervascular
• hypovascular
10. Altered appearance of the secondary ossification center
• timing
• uniformity of appearance
11. Stippling of the epiphyses
D. Abnormal cell and matrix appearances
12. Abnormal cell appearance at light microscopic level
13. Matrix abnormalities at the light microscopic level
14. Ultrastructural cell abnormalities
15. Ultrastructural matrix abnormalities
16. Abnormalities of the epiphyseal-metaphyseal junction

[a]Shapiro F (1998) Structural abnormalities of the epiphyses. In: Skeletal Growth and Development: Clinical issues and basic science advances. American Academy of Orthopedic Surgeons, Rosemont, IL (Ref. [138])

shaped at birth but become progressively deformed with time. An example of abnormal epiphyseal shaping dating from the embryonic period is epiphyseal dysplasia hemimelica or Trevor's disease in which part of an epiphysis is markedly and focally enlarged (Fig. 3.3a, b). The disorder, likened by some to an epiphyseal osteochondroma, is seen most commonly at distal tibia, distal femur, and distal radius. An example of a dysplasia in which the entire epiphyseal shape appears normal at birth and for the next few years prior to collapsing the articular surface is diastrophic dysplasia. The cumulative effects of abnormal cartilage synthesis, increased cartilage fibrosis, and continued weight bearing on imperfect structure lead to collapse of the articular surface and a lack of adjacent surface articular cartilage congruity (Fig. 3.3c). Many dysplasias have subtle articular surface shape irregularities which are not of clinical significance in the childhood years but lead to adult onset osteoarthritis, such as in multiple epiphyseal dysplasias.

3.8.2.2 Shaping Abnormalities of the Periphery of the Epiphyseal–Metaphyseal Junction

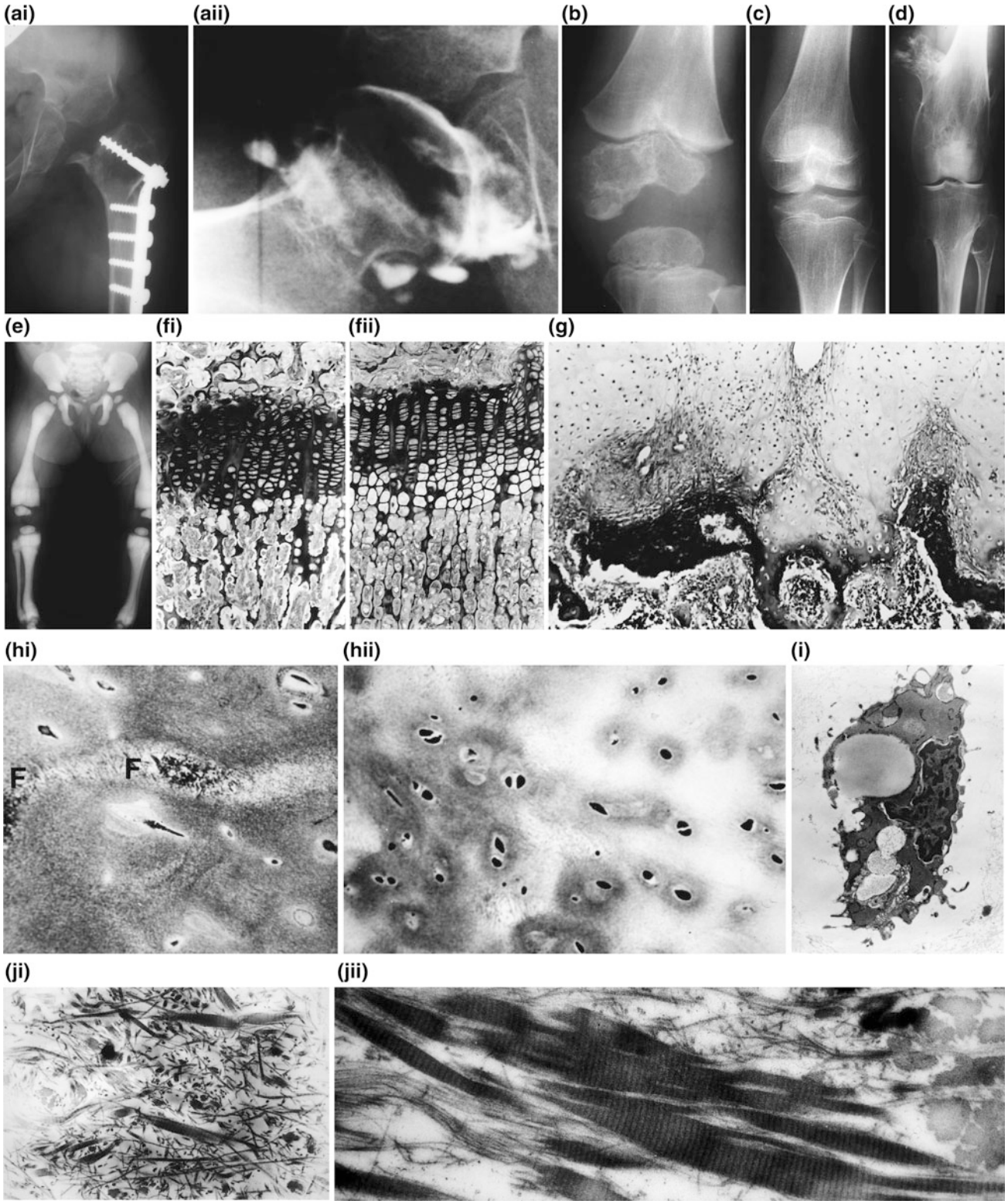
The tissues surrounding the growth plate and upper metaphysis are well organized into the perichondrial ossification groove of Ranvier. In hereditary multiple exostosis, abnormalities of differentiation in this tissue complex lead to irregular sites of cartilage and bone synthesis causing both widening of the physeal and metaphyseal regions by formation of cartilage outgrowths where normal periosteum should occur, and by absence of osteoclastic resorption (Fig. 3.3d). In other disorders, deposition of bone in the perichondrial ossification groove is greater than it should be, leading to a larger and more rigid perichondrial bony ring. This occurs in achondroplasia and was also shown in unnamed dysplasias and appears to result from a dissociation of the normal two patterns of growth since the intramembranous bone formation system which synthesizes the bony ring is functioning normally while the adjacent endochondral bone formation system is less effective than normal [140].

3.8.2.3 Shaping Abnormalities of the Metaphyses

The metaphyses are abnormally shaped in an entire subset of skeletal dysplasias referred to as the metaphyseal dysplasias or dysostoses. Since patients with this disorder are of short stature there must be physeal malfunction but the structural manifestation of the problem comes at the metaphyseal level. Widening of the metaphyses is also seen in osteopetrosis where the normal resorptive, funnelization process at the lower parts of the perichondrial groove complex is prevented by absent or non-functioning osteoclasts (Fig. 3.3e).

3.8.2.4 Variations in Growth Plate Thickness

The growth plate can be of the same thickness as the normal, thicker than normal, or thinner than normal. In many skeletal dysplasias, there is no change in the thickness as determined by qualitative assessments and on occasion by quantitative assessment. In those abnormalities associated with a defect of mineralization, the growth plate is thicker than normal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with persistence of cartilage in the hypertrophic zone and adjacent metaphysis where mineralization normally occurs. Thickened growth plates are the hallmark of rickets disorders, regardless of whether these are nutritional in nature or due to genetic disorders such as hypophosphatemic rickets. The physis can also be thicker in metaphyseal dysplasias although they tend to be so in irregular fashion with isolated areas of radiolucency in metaphyseal bone adjacent to the physis. The majority of skeletal dysplasias which show changes in physeal thickness have thinner growth plates. This is particularly true in the case of lethal chondrodystrophies where the cartilage tissue itself is markedly poor in formation and in diastrophic dysplasia toward the end of the first decade when premature growth plate closure further worsens prognosis.

3.8.2.5 Change in Proportional Contribution of Varying Regions of the Growth Plate

In addition to whether the growth plate is of normal thickness, thinner, or thicker, it is important to assess the relative contributions of the various cytologically specialized areas of the plate to its thickness. In certain disorders, there is an apparent normal progression from resting and germinal zones through the proliferating zone, but then a marked diminution in the height of the hypertrophic cell region. This is seen in particular in the cn/cn mouse which is a short stature naturally occurring mutant (Fig. 3.3f) [141]. In rickets disorders, on the other hand, the hypertrophic zone is markedly increased in height owing to the failure of mineralization of the cartilage cores which normally occurs as part of the endochondral developmental sequence. The unmineralized cartilage fails to trigger the normal resorptive response and persists, increasing the thickness of the physis.

3.8.2.6 Disorganization of the Cytoarchitecture of the Growth Plate

One of the most common findings in skeletal dysplasias is a disorganization in the cellular organization of the growth plate. It is important to recognize that columnation in the human is rarely as well organized as that demonstrated in animal studies from the rabbit, mouse, and rat. In some instances, therefore, cytologic human specimens reported as abnormal really vary little from samples in non-affected individuals. Disorganization, once present, however generally tends to be throughout the growth plate beginning in the resting and germinal zones and involving the proliferating as well as the hypertrophic zones. This is not surprising since growth plate cytologic structure represents a coordinated

◀ **Fig. 3.3** Radiographic and histopathologic abnormalities of the epiphyses and metaphyses that can occur in various skeletal dysplasia disorders are reviewed in this figure. **a** Delayed appearance of the secondary ossification center is characteristic of many of the skeletal dysplasias. It is particularly marked in the proximal femur in spondyloepiphyseal dysplasia congenita where it is often not seen as late as the end of the first decade. **i** Anteroposterior view of hip from a 7 year old female with spondyloepiphyseal dysplasia congenital (SEDC) with no proximal femoral secondary ossification center (s/p valgus osteotomy). **ii** Arthrogram of the opposite side hip in the patient with SEDC shows dye (*white*) outlining oval femoral head in acetabulum with no secondary ossification center. **b** A localized shaping abnormality of the epiphysis dating from the embryonic period is shown in this example of epiphyseal dysplasia hemimelica of the distal femur. Note the markedly enlarged medial femoral condyle. **c** Shaping abnormalities of the articular surface and subchondral bone region of the epiphysis are seen in many skeletal dysplasias. The articular cartilage shape can be normal in the newborn period but imperfect structure due to abnormal cartilage synthesis and increased cartilage fibrosis leads to progressive collapse of the articular surface with weight bearing and the lack of adjacent surface articular cartilage congruity. This example of malformation with flattening of the lateral femoral condyle is from a patient with multiple epiphyseal dysplasia. **d** The classic example of shaping abnormalities of the periphery of the epiphyseal-metaphyseal junction is that occurring in hereditary multiple exostosis. This radiograph shows characteristic widening of the metaphyses of the distal femur and proximal tibia plus prominent localized tissue outgrowths referred to as exostoses (*arrows*). **e** Shaping abnormalities of the metaphyses are seen in osteopetrosis owing to abnormal resorption of bone. This disorder which is mediated through imperfect osteoclast function leaves a widened metaphysis owing to failure of the normal resorptive-remodeling processes as well as dense bone in all bones due to absent marrow resorption. **f** There can be changes in proportional contributions of varying regions of the growth plate in certain skeletal dysplasias. **i** An example from a naturally occurring mutant cn/cn mouse is a marked diminution in the height of the hypertrophic cell region. **ii** In a normal mouse physis at *right* each of the appropriate zones is represented while in the mutant at *left* the germinal and proliferating zones are seen but there is an abrupt diminution of height in the hypertrophic zone adjacent to metaphyseal bone. The gene defect corresponds to the human short stature disorder Acromesomelic dysplasia Maroteaux type (AMDM). **g** Epiphyseal-metaphyseal tissue from achondrogenesis shows epiphyseal cartilage above and abnormal metaphyseal bone below but the intervening region shows significant failure of development of physeal structure. **h** Matrix abnormalities at the light microscopic level can involve abnormally high deposition of (**i**) fibrinous or fibrotic (*F*) material or (**ii**) preferential proteoglycan staining in the immediate pericellular matrix. When present the fibrotic deposits can be generalized or, as seen in this case of diastrophic dysplasia cartilage, present in localized foci. (Reprinted with permission from Shapiro F, Light and electron microscopic abnormalities in diastrophic dysplasia growth cartilage. Calcif Tissue Int 1992;51:324–331. Copyright 1992 Springer Science + Business Media). **i** Ultrastructural abnormalities of chondrocytes are characteristic of many skeletal dysplasias. A common abnormality is a dilated rough endoplasmic reticulum, interpreted as a sign of imperfect protein synthesis and secretion. In spondyloepiphyseal dysplasia congenita the dilated RER often appears to fill the entire cell segment being sectioned. In this disorder it is filled with a slightly radiodense material with a grainy appearance but otherwise without distinguishing features. **j** Matrix abnormalities at the ultrastructural level almost always involve increased matrix fibrosis. This tends to occur initially in the immediate pericellular area **i** as shown in this example from a patient with diastrophic dysplasia. **ii** At higher power there is characteristic appearance of markedly widened and irregularly adherent fibrous bundles with characteristic cross banding of collagen

series of phenomena which if thrown off early in the sequence demonstrates little ability to rearrange itself into a normal pattern. The disorganization is characterized by a tendency which in the very mild disorders is an irregularity in columnar formation and with major involvement simply leads to the presence of cartilage with essentially no organization at all (Fig. 3.3g). When the finely organized hierarchical system of the endochondral sequence is disorganized, major alterations in the chain of events can follow. These generally lead to such associated findings as premature vascular invasion of the physeal cartilage with aberrant bone deposition, vascular invasion of the physis associated with fibrosis, fibrosis with very little vascular invasion, and a disorganized metaphyseal region.

3.8.2.7 Change in Cellularity of Epiphyseal and Physeal Cartilage

Some skeletal dysplasias are characterized by increased cellularity of the epiphyseal, including physeal regions and some are characterized by a hypocellular cartilage. Achondrogenesis is an example of hypercellular epiphyseal cartilage owing to the fact that matrix synthesis is scanty since the defect in the disorder is virtual complete non-expression of type II collagen synthesis. In most other dysplasias with a chondrocyte cell number abnormality, the hypocellular features predominate. These findings occur when chondrocyte cell proliferation and differentiation are diminished or where the cells die prematurely and are replaced by fibrous tissue.

3.8.2.8 Altered Vascularity (Cartilage Canals) of the Cartilaginous Epiphyses

The epiphyses contain vessels present in cartilage canals. In the human these are seen initially in the distal femur as early as the third month in utero. The vessels are widely considered to actively invade the epiphysis from the perichondrium. They provide nutrition to the chondrocytes and are present several months before formation of the secondary ossification center. Little information is available on cartilage canals in abnormal epiphyseal development. In achondrogenesis however the vascularity is increased in association with the high fibrous content of the epiphyses. It would be interesting to know if delayed appearance of the secondary ossification centers, which characterizes some skeletal dysplasias such as spondyloepiphyseal dysplasia congenita, is or is not accompanied by alterations in the cartilage canals.

3.8.2.9 Altered Appearance of the Secondary Ossification Center

The time of appearance of the secondary ossification center in the skeletal dysplasias can be normal, premature, or delayed. Premature appearance of secondary ossification centers is rare but is seen sometimes with osteogenesis imperfecta, presumably in relation to microtrauma and the increased vascularity of the epiphyseal/metaphyseal region which ensues due to intrauterine or early post-natal fractures and in the short-rib polydactyly syndrome. A more common occurrence is a delay in appearance of the secondary center, which is sometimes the earliest warning of some underlying skeletal dysplasia. The delayed appearance of the secondary ossification center in spondyloepiphyseal dysplasia congenita is particularly noteworthy in the proximal femurs and is often associated with a coxa vara deformity. In those instances in which it is delayed, the most common pattern seen, there is also a frequent occurrence of multiple discrete regions of calcification and bone formation when it does finally form rather than a uniform appearing centrally placed and gradually enlarged radiodensity as is normally the case. Fragmentation of the secondary center once it appears is also known to occur, and is often seen in the femoral head in multiple epiphyseal dysplasias. The fragmentation can lead to confusion with Legg–Perthes disease.

3.8.2.10 Stippling of the Epiphyses

Radiodense calcification can be seen throughout the epiphyseal region in a set of disorders referred to as stippled epiphyses (Fig. 3.3d). The calcification is not necessarily concentrated in what would normally be the position of appearance of the secondary ossification center but can occur throughout the epiphyseal and physeal cartilage. There are several causes of stippled epiphyses and considerable variations in prognosis, so accurate syndromal diagnosis is extremely important [128]. Some are present in the lethal chondrodysplasia punctata characterized by marked rhizomelic limb shortening. In the benign form, referred to as Conradi–Hünermann chondrodysplasia punctata, patients survive and these stippled regions are eventually incorporated into bone as it forms and do not lead to any negative long-term sequelae. In addition, stippled epiphyses can occur as an epiphenomenon with few or no negative sequelae in several skeletal disorders, including multiple epiphyseal dysplasias.

3.8.2.11 Abnormal Cell Appearance at the Light Microscopic Level

Abnormal chondrocyte appearance at the light microscopic level can involve such findings as increased inclusion materials, an increased number of cells which is generally reflective of a decreased amount of matrix synthesis, and a decreased number of cells which is generally reflective of the occurrence of premature cell death. In association with the latter is the tendency for the chondrocytes to be smaller and more densely staining with subsequent premature death and replacement by fibrosis. In chondrocyte areas where the cell has died and been resorbed, the persistent empty lacuna is frequently referred to as a ghost cell. On occasion, circumferential rings of fibrous tissue are deposited in the empty lacuna and pericellular matrix and the degenerated cell is

referred to as a target cell. A characteristic cell inclusion in epiphyseal chondrocytes is fat as demonstrated on tissue sections prepared by plastic embedding and stained by toluidine blue for light microscopy and on tissue examined by transmission electron microscopy. The fat is intracytoplasmic, always assumes a circular globular shape, and stains a green-blue or turquoise with the toluidine blue. Other intracytoplasmic structures stain a light blue and generally assume a less discrete shape. It is important not to interpret epiphyseal chondrocyte fat globules as pathologic although we have not seen them in physeal chondrocytes. Other intracytoplasmic inclusions in either epiphyseal or physeal chondrocytes may be pathologic indicators. Histochemical analyses were done previously by investigators in the field but reproducibility of results was difficult. Newer immunocytochemical techniques combined with greater knowledge of normal and abnormal molecular components of cartilage should improve light microscopic identification.

3.8.2.12 Matrix Abnormalities at the Light Microscopic Level

The uniform appearing and uniform staining hyaline cartilage matrix can show abnormalities which involve (i) replacement by fibrotic material or (ii) preferential proteoglycan staining in the immediate pericellular matrix (Fig. 3.3j). Pathologic fibrotic deposits can be present in abnormal localized foci or can be generalized throughout. Fibrotic collections stain a deeper red with hematoxylin and eosin, a deeper blue with toluidine blue and green, instead of a uniform red, with Safranin O–fast green. The presence of pericellular staining for proteoglycans with less prominent staining in inter-territorial areas reflects efforts at matrix synthesis which are continuing but are insufficient to maintain normal cartilage formation throughout the entire mass of articular, epiphyseal, and physeal cartilages.

3.8.2.13 Ultrastructural Cell Abnormalities of the Epiphysis and Physis

The disordered chondrocyte as shown by light microscopy will frequently manifest more specific structural abnormalities at the higher power ultrastructural level (Fig. 3.3i). These can be characterized by the abnormal appearance of organelles or inclusions in the chondrocyte cytoplasm or by premature cell necrosis. Many early reports on ultrastructural abnormalities in the chondrodysplasias commented on and demonstrated increased intracellular fat; it is now recognized, however, that intracytoplasmic fat is a normal finding in many epiphyseal chondrocytes which is important in interpretation of the findings. The most classic occurrence within the chondrocyte cytoplasm at the ultrastructural level in the skeletal dysplasias is the increase in dilated cisternae of rough endoplasmic reticulum. Indeed, in some cells, there is only a single dilated cisterna filled with moderately electron-dense material in a thin section profile. This is interpreted as an indication of the fact that the cell is synthesizing protein but presumably because of its abnormal structure, the normal secretion mechanism fails and the protein persists within the cell. Findings such as this are particularly characteristic of spondyloepiphyseal dysplasia congenita. They are, however, not pathognomonic for it and are seen in many other disorders. A laminated appearance of alternating electron-dense and electron lucent lines is seen within the dilated rough endoplasmic reticulum in pseudoachondroplasia and in some variants of multiple epiphyseal dysplasias. In spondyloepimetaphyseal dysplasia dilated rough endoplasmic reticulum of epiphyseal chondrocytes contained electron-dense wavy rod-like structures with a circular orientation parallel to the outer edges of the RER [142].

3.8.2.14 I. Endoplasmic Reticulum Storage Disorders

The structural abnormalities of the epiphyseal chondrocytes in this study of SEMD define an endoplasmic reticulum storage disorder (ERSD) [143]. The rough endoplasmic reticulum is the intracellular organelle where synthesis of extracellular matrix proteins occurs prior to their passage to the Golgi complex and eventual extrusion into the extracellular matrix. The molecular activities accompanying RER function are being increasingly defined [144]. Mildly dilated RER is an ultrastructural sign of a cell actively involved in protein synthesis. Massively dilated RER, however, is an ultrastructural indication of improper processing associated with a disorder where a mutation prevents proper folding and extrusion of protein products. Improperly folded proteins in the RER are normally transported back into the cytosol by a process referred to as retro-translocation where they undergo degradation by the ubiquitin–proteasome system [145]. In some cases, the abnormal protein accumulates in the RER and is there for a sufficiently long period of time that it begins to aggregate forming differing patterns of electron-dense inclusions, such as the one we have identified here. This further complicates cell function since it appears to overwhelm the normal synthesis–degradation mechanisms. The aggregates eventually fill the interior of the cell leading to cell degeneration and death. In this study those chondrocytes where the dilated RER is packed with electron-dense inclusions are often degenerated while those with definite but less extensive accumulations are still structurally intact.

Abnormalities of endoplasmic reticulum processing in other disorders have been defined. Kim and Arvan reviewed RER storage disorders in relation to endocrinopathies, but few ultrastructural examples were given for bone and cartilage and most of those showed only dilated RER with uniform, homogeneous content [143]. Since extracellular matrix protein mutations are prominent in the skeletal dysplasias, it is not surprising that ultrastructural findings can accompany

gene and molecular abnormalities. Bonnemann et al. demonstrated dilated RER inclusions in chondrocytes in a case of multiple epiphyseal dysplasias (MED 3) with a mutation in type IX collagen (alpha 3 chain) [78]. The RER contained alternating parallel bands of electron-dense and electron-lucent material. Epiphyseal chondrocytes also showed the phenomenon clearly while physeal chondocytes were characterized by dilated RER without aggregates. Previously, chondrocytes from patients with pseudoachondroplasia, now known to be due to COMP mutations, were shown to contain dilated RER with spirally oriented bands of electron-dense and electron-lucent material [146, 147]. This observation in pseudoachondroplasia has been made by several different groups which supports its specificity as a marker for this disorder. Menger et al. reported a similar electron microscopic finding of RER inclusions to our case in physeal hypertrophic chondrocytes in a case of SEMD with extreme short stature [148]. In other skeletal dysplasias, chondrocytes have been shown with massively dilated RER containing homogeneous material, for example spondyloepiphyseal dysplasia congenita and Kniest dysplasia both type II collagenopathies [149–151]. Osteoblasts in patients with osteogenesis imperfecta have moderately dilated RER with homogeneous material [151].

3.8.2.15 Matrix Abnormalities at the Ultrastructural Level

The ultrastructural appearance of the normal cartilage matrix is well known. In many skeletal dysplasias, in particular diastrophic dysplasia, there are increased foci of fibrous tissue within the normally cartilaginous matrix (Fig. 3.3J). These fibrils are characteristically cross-banded but are quite irregular and markedly thicker both in terms of diameter and in their appearance on longitudinal sectioning. They represent the aggregation of normally dispersed and much thinner type II collagen molecules owing to a deficiency to type IX collagen which normally coats the type II fibril and prevents its aggregation with adjacent fibrils. The initial foci of increased fibrosis are usually in the immediate pericellular area.

3.8.2.16 Abnormalities of the Epiphyseal–Metaphyseal Junction

In the normal endochondral sequence, the lowest regions of the cartilage of the epiphyseal growth plate in the hypertrophic zone become mineralized. Vascular invasion from the metaphysis then occurs with vessels accompanied by undifferentiated mesenchymal cells passing into the lowermost two or three hypertrophic cell lacunae and coincidentally laying down new bone on the calcified cores of cartilage. The metaphyseal region is thus characterized by the presence of these columns of tissue composed of the central mineralized cartilage cores and the surrounding deposits of the new bone. At the outermost reaches of the metaphysis immediately adjacent to the hypertrophic layer, the columns are composed almost exclusively of calcified cartilage but as one passes deeper into the metaphysis, there is relatively less cartilage and relatively more new bone. The region is also characterized by active resorption both of the calcified cartilage cores and of the recently deposited bone with replacement by trabeculae composed exclusively of bone. The resorption is mediated by the multinucleated osteoclasts. Since there is considerable disorganization of the endochondral sequence in many of the skeletal dysplasias, this disorganization is reflected not only in the growth plate itself, but particularly in the adjacent metaphysis since the new bone is normally deposited on the calcified core of cartilage. If the cartilage is either not deposited, not appropriately mineralized, or deposited in an irregular arrangement, then new bone synthesis in the metaphyseal region must of necessity be disordered itself since the organized linear scaffold effect of the mineralized cartilage is imperfect. The problem can also lie in a failure of appropriate resorption of bone and cartilage by osteoclasts. In some skeletal dysplasias the physeal–metaphyseal interface is irregular rather than being relatively smooth since mineralization, vascularization, and bone formation proceed at different times and levels in response to the disordered physeal tissues. In osteopetrosis the metaphyseal regions are both widened and radiographically dense owing to failure of normal resorption. The widening is due to persistence of physeal synthesized bone since the osteoclasts at the lower region of the groove of Ranvier are unable to function normally at the so-called “cutback” zone of remodeling.

3.8.3 Interpretation of the Pathogenesis of Skeletal Dysplasias in Relation to the Structural Approach

Understanding of the skeletal dysplasias was based initially on clinical appearances. The next era of definition was based on radiographic appearances with many disorders defined by the region of prominent radiographic abnormality such as multiple epiphyseal dysplasias or metaphyseal dysostosis. With the recognition of proteoglycan abnormalities underlying many variants of what radiographically are spondyloepiphyseal dysplasias, the focus of investigation shifted to biochemical and more recently to molecular and gene abnormalities.

Many reports on histologic and ultrastructural aspects of various skeletal dysplasias have appeared but the findings have rarely if ever been specific to a particular entity. Over the past several years investigation has been almost exclusively on molecular and gene abnormalities underlying these disorders. There is great value in assessing how gene,

molecular, and biochemical abnormalities translate via micro to macro epiphyseal, physeal, and metaphyseal structural changes into the gross alterations seen clinically and by radiographic projection. Rubin in his classic text attempted to relate the pathogenesis of the various dysplasias to the regions of the epiphyseal–metaphyseal ends of the bone as defined radiographically [9]. With the increasing sophistication of microstructural assessments the cell and matrix functioning in both normal and abnormal epiphyses is becoming better known. The array of structural techniques includes light microscopy; polarizing light microscopy to assess fiber orientation; histochemistry and immunocytochemistry to assess matrix composition; and transmission electron microscopy.

Development, be it normal or abnormal, is a series of events in which early developments define and direct those occurrences that follow them. The eventual structural defects will reflect not only the molecular abnormality causing them but also (i) the time of function of the molecule in the developmental cascade, (ii) the extensiveness of the molecular abnormality, and (iii) the presence or absence of other molecules which could partially or totally replace the functions of the disordered molecules. It appears meaningful to incorporate microstructural morphologic studies into assessment of skeletal dysplasia disorders. Morphogenesis is an ordered hierarchical series of events in which an abnormality can set up an altered cascade predisposing to even greater deviations from the norm. The regional hierarchical approach to assessing tissue structure in the skeletal dysplasias can bridge the gap between definition of gene–molecular–biochemical events and the ultimate clinical and radiographic deformities that define the phenotype.

3.9 Histopathologic Changes in Specific Chondrodysplasias

Histopathologic changes in the skeletal dysplasias have been reviewed in several articles as well as in individual case reports [149, 152–156].

3.9.1 Lethal Chondrodysplasias

Many of the abnormal findings have been reviewed by Gilbert et al. [152].

3.9.1.1 Achondrogenesis I (Parenti–Fraccaro)

All zones of the growth plate are densely hypercellular. The normal chondrocyte progression is lost. Calcification of cartilage and trabecular bone formation are disorderly with irregular capillary penetration and little column formation. The cartilage canals within epiphyseal cartilage are markedly increased. There is diminished width of the longitudinal septae between the hypertrophic chondrocytes. The physeal growth zone is extremely retarded developmentally and disorganized. Resting chondrocytes are slightly enlarged and frequently contain large PAS positive spherical to oval cytoplasmic inclusions. The vesicles correspond to markedly dilated cisterns of rough endoplasmic reticulum on electron microscopy [124].

3.9.1.2 Achondrogenesis II (Langer–Saldino)

There is a deficiency of cartilage matrix, markedly enlarged cell lacunae, and chondrocytes with abundant clear cytoplasm [68]. The entire cartilage region is hypercellular owing to a scanty matrix and the physeal growth zone is markedly retarded and disorganized. No growth plate columnation is seen. The epiphyseal cartilage is lobulated and mushroomed with increased vascularity. There is irregular vascular invasion of the hypercellular cartilage (Fig. 3.4a–d). The primary bone trabecular formation is very abnormal and decreased, and trabeculae are oriented horizontally. There is overgrowth of peripheral membranous bone leading to cupping of the epiphyseal cartilage. Long bones and ribs have grossly thinner physeal growth zones than normal and are fragile and brittle with the cartilage portion separating readily from the underlying metaphysis. Microscopy of the proximal humerus confirmed marked disorganization of the growth zone, with cupping of subchondral bone and lipping at the periphery. The normal parallel configuration of the hypertrophic and proliferative columns was absent. Short transitional columns were occasionally seen but were of haphazard orientation, often interspersed with primitive mineralizing cartilage. Primary osteoid seams were present in some places adjacent to poorly formed and shortened transitional columns. The resting cartilage in all sites was markedly abnormal, being abundantly cellular, and composed of large and ballooned chondrocytes with little intercellular matrix. It was arranged in large nodular masses interspersed with abnormally abundant blood vessels. Membrane bone and bone marrow appeared to be normal.

Electron microscopy of cartilage. In cross-sections of cartilaginous rib, two zones were apparent, an outer opaque and more fibrous zone and an inner translucent, gelatinous zone. Sections of humeral head cartilage showed similar cartilaginous whorls and interspersed fibrous septa. Electron microscopy of the chondrocytes in the gelatinous region showed abnormal accumulations of amorphous material in dilated lakes of rough endoplasmic reticulum while the extracellular matrix showed a random feltwork of well-spaced, uniformly thin (15–20 mm diameter) fibrils typical of young, growing hyaline cartilages. Perichondral regions, however, showed the parallel arrays of densely packed, much thicker fibrils that are more typical of tissues

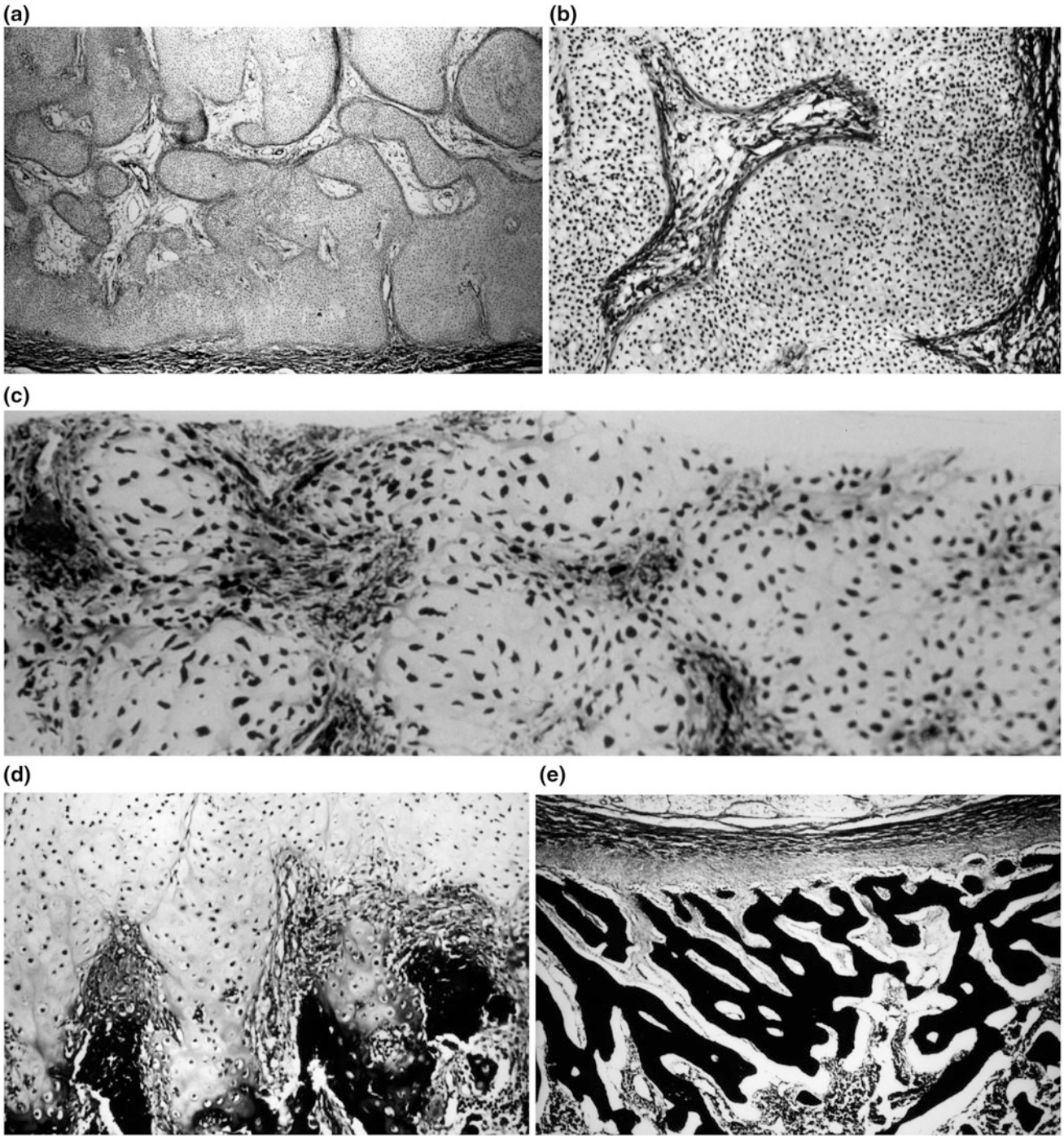


Fig. 3.4 Histopathologic findings in Langer-Saldino achondrogenesis are shown. **a** Photomicrograph shows hypercellular cartilage with fibro-vascular invasion. The cartilage canals are increased in achondrogenesis in association with a high fibrous content of the epiphyses. The absence of normal type 2 collagen and associated proteoglycan leads to a relative abundance of type 1 collagen which might encourage vascular invasion. **b** At higher power the cartilage canal centrally is evident. The numerous cells are surrounded by only a scanty matrix. **c** In many areas, regions of chondrocytes with matrix and fibrovascular tissues have a whorled conformation. **d**. The markedly abnormal and almost absent physis is illustrated here. The epiphyseal cartilage above appears to merge with the metaphyseal bone below with no intermediation of normal appearing physeal tissue. The metaphyseal bone is synthesized around regions of cartilage but appears to occur more in association with the fibrovascular invasion of the physeal region rather than due to any sequence of cartilage changes. **e** Since type I collagen is normal in this disorder cortical bone formation is normal

rich in type I collagen. Although the appearance of the collagen in the gelatinous central regions of cartilage gave the impression of young type II collagen, the biochemical results clearly showed that type II was absent and the bulk of the collagen was type I. At all sites, hyaline cartilage had a watery, gelatinous texture and translucent appearance in contrast to the stiff, opaque properties of control neonatal cartilages.

The resting cartilage had little extracellular matrix surrounding the large, dilated chondrocytes. The low collagen content was consistent with this observation and appeared to result from a failed expression of type II collagen by the chondrocytes. Type I collagen on biochemical assessment was the main type of collagen present in all cartilage samples including the gelatinous rib core and appears to have replaced type II collagen in the sparse matrix.

3.9.1.3 Hypochondrogenesis

Histopathologic changes are similar but somewhat milder to those in achondrogenesis II. Matrix deficiency and large ballooned chondrocytes are seen but there is a rudimentary growth plate formation with hypertrophy of cells and some sense of columnation but true endochondral bone formation rarely occurs [124].

3.9.1.4 Thanatophoric Dysplasia

Thanatophoric dysplasia is the commonest lethal skeletal dysplasia. There is relatively normal resting cartilage of the physis with subsequent generalized disruption of the physeal endochondral sequence with no orderly progression of cell change, no attempts at column formation, and an irregular hypertrophic zone. There are some areas of hypertrophic cellular alignment. Vascular invasion of the growth plate occurs at irregular intervals leading to an irregular array of short, blunt and broad spicules of calcified cartilage and bone and often with metaphyseal trabeculae aligned horizontally. Lateral overgrowth of metaphyseal bone around the physis is described [118].

3.9.1.5 Homozygous Achondroplasia

There is considerable similarity clinically, radiographically, and histopathologically between thanatophoric dysplasia and homozygous achondroplasia, since both represent abnormalities of the FGFR3 molecule. Stanescu et al. noted in histologic examination of a child who died at 2 months of age that the growth zone of the upper tibial cartilage was very narrow with the chondrocytes irregularly arranged and without column formation [157]. In most areas chondrocyte hypertrophy was not seen although occasional areas of clustered hypertrophic cells were noted. The primary cartilage/bone trabeculae were infrequent, short, and irregularly arranged with some of them actually being horizontal to the long axis. In some areas the growth cartilage was replaced by islands of fibrous or fibrocartilaginous tissue. The periphyseal groove of Ranvier, similar to what is seen in achondroplasia, was more prominent than normal and prolonged toward the center of the growth zone by a band of young fibrous tissue bordered by a narrow bone rim. In contrast to the abnormal and scanty physeal cartilage the epiphyseal cartilage had an apparently normal cell density and distribution with normal cartilage vascular canals. Electron microscopy showed that the chondrocytes both in the physis and epiphyseal cartilage were active with a well-developed rough endoplasmic reticulum, Golgi systems, and many mitochondria. Degenerating cells were rare. The matrix of the epiphyseal cartilage appeared relatively normal while that of the physis had many thickened collagen fibers irregularly arranged. The pericellular matrix of chondrocytes from the physis showed accumulation of dense, relatively thick and cross-banded collagen fibers with diminished proteoglycan granules, a finding similar to that seen in many skeletal dysplasias.

3.9.1.6 Short Rib-Polydactyly Syndromes

SRPD 1 (Saldino–Noonan). There is disorganized proliferative and hypertrophic cartilage of the physis with decreased numbers of chondrocytes. The zone of chondro-osseous transformation is irregular. Columnation is disorganized and the formation of trabecular bone abnormal with short, stumpy trabeculae. There are often central areas of fibrosis in the physis and premature ossification centers of proximal humerus and proximal femur. By electron microscopy, the physeal matrix is abnormal with fibril disorganization, abnormal fibrils with tapered ends, and abnormal amounts of mature collagen.

SRPD 2 (Majewski). The physeal growth zone is markedly retarded and disorganized. There is only minimal endochondral bone formation. There is no specific delineation between resting, proliferating, and hypertrophic zone regions, although there is some hypertrophy of cells which are arrayed irregularly immediately adjacent to the metaphysis. Premature epiphyseal ossification occurs.

3.9.1.7 Chondrodysplasia Punctata

This disorder, more commonly known as stippled epiphysis, encompasses several variants not all of which are lethal. The punctata appearance is an epiphenomenon rather than a primary defect. The lethal disease variant is rhizomelic chondroplasia punctata but usually non-lethal variants are Conradi–Hünermann chondrodysplasia punctata and sex-linked chondrodysplasia punctata. Stippled epiphyses are also seen with cases of multiple epiphyseal dysplasias and some of the mucopolysaccharidoses.

Rhizomelic chondrodysplasia punctata. Most of these patients die in infancy. There is increased vascularization of

the reserve zone of cartilage with associated fibrosis, dysplastic calcification, and microcystic degeneration. There are decreased numbers of proliferative chondrocytes and endochondral ossification is abnormal. There is decreased vascular invasion at the lower regions and tongues of cartilage extend into the metaphysis. Jeune et al. reviewed the histopathology from 11 autopsy descriptions with similar findings. The physeal proliferating and hypertrophic columns were short and irregular and sometimes were grouped only in randomly non-oriented masses. The line of ossification was fragmented and irregular with the endochondral ossification retarded and disorganized while periosteal ossification was normal. The physeal cartilage was characterized by fibrinous, mucoid necrosis with fibrovascular invasion. Calcifications were seen throughout the cartilage from articular to physeal regions. These were often present in relation to vessels but did not represent centers of bone formation. Studies from varying stages indicated initial calcification in cartilage alone followed by calcific deposits among reactive giant cells and eventually deposits in relation to fibrovascular tissue. The latter finding was considered to be compatible with eventual resorption of the calcific deposit if the patient survived.

3.9.1.8 Campomelic Dysplasia

i. **Long-limbed campomelic dysplasia**. Growth plate disorganization has been relatively mild with a normal progression of cells. Any resting chondrocytes appear vacuolated.
ii. **Short-limbed campomelic dysplasia (normocephalic type)**.
iii. **Short-limbed campometic dysplasia with craniosynostosis**. There have been histopathologic descriptions in the latter two types.

3.9.1.9 Fibrochondrogenesis

Histopathology of growth regions shows no columnar arrangement of either proliferating or hypertrophic cells. Metaphyseal bone is immediately adjacent to virtually undifferentiated cartilage. There is some calcified cartilage surrounded by bone in the metaphyseal region but certainly no orderly array. Resting cartilage is characterized by chondrocytes in a lacy woven fibrillar network. There are numerous fibrous connective tissue septa forming a lattice appearance with small chondrocytes within surrounded by very little matrix. The chondrocytes are often elongated and flattened. There is no regular growth plate, but some evidence of cell hypertrophy toward the metaphyseal areas. There is some provisional calcification of the matrix but irregular vascular invasion.

3.9.1.10 Asphyxiating Thoracic Dysplasia

In Type I the physis shows patchy distribution of endochondral ossification only with an irregular cartilage–bone junction. In Type 2, a physeal region can be identified but is shortened and irregular in particular showing little column formation. Histologic changes are variable. They include reduction in the number of proliferating hypertrophic chondrocytes, irregular vascular invasion, cartilage islands in the metaphysis, and transverse bony plates extending across the metaphysis. By ultrastructure extensive number of lipid inclusions in chondrocytes have been reported.

3.9.1.11 Hypophosphatasia

There is marked underformation of bone throughout the skeleton in this lethal condition. Physeal areas show normal resting cartilage, although the chondrocytes are somewhat disorganized. The underlying problem relates to failure of calcification and new bone formation.

3.9.2 Histopathologic Changes in Non-lethal Chondrodysplasias

Histologic studies of normal human iliac crest cartilage serve as an important baseline for study of pathologic tissue. A report by Ponseti et al. is very helpful in this regard [158].

3.9.2.1 Achondroplasia

Despite the marked short stature, the growth plate is structurally regular with a well-organized endochondral sequence. Column formation appears normal as does cellularity. Periosteal bone formation at the perichondral groove of Ranvier is more extensive than normal. Ultrastructurally, the cartilage contains relatively normal chondrocytes and matrix [159].

In a study by Rimoin et al., biopsies of rib and iliac crest from 10 individuals with typical achondroplasia ranging in age from 10 months to 35 years have shown that the endochondral sequence is quite regular and well organized with normal cell columnation and an unremarkable appearance of the matrix [160]. He stressed that the ribs were short even though the rib physeal cartilage was structurally unremarkable. One common finding, however, is the relatively more extensive periosteal ossification deep into the perichondrial groove of Ranvier. This led to a relatively cup-shaped appearance at the ends of some long bones and the comparatively short (endochondral effect), widened (normal intramembranous bone effect) appearance of the long or tubular bones. This was also noted by Keith as early as 1920 [161]. It is the endochondral growth sequence that is affected in achondroplasia whereas the intramembranous bone sequence is not affected. Ponseti also found the iliac

crest growth plate to be close to normal in histologic sections [162]. When he assessed fibular growth plates however some structural abnormalities of the physis were noted. Sections of the proximal fibular epiphyseal regions were present from seven patients. The plates were V shaped toward the metaphyseal region, a finding also noted radiographically in larger epiphyses especially the distal femur. The periosteal intramembranous bone overall was normal and Ponseti also noted that the periosteal bone of the periphyseal groove of Ranvier was abundant and wider and deeper than normal around the adjacent physis. There was more bone formation by the physis of the fibula at its periphery than centrally and the central regions of the physis had relatively little and markedly thinned cartilage. The physis was somewhat irregular with the proliferating cells tending to be in clusters rather than in columns and to be separated by wide septae of cartilage matrix which was more fibrous than normal. The hypertrophic zone was more narrow and irregular than normal and the normal maturation of the hypertrophic cell was disturbed. The vascular invasion of the growth plate at the hypertrophic zone was very uneven such that the vascular front "appeared to face an insurmountable barrier of fibrotic cartilage and bone". The central half of the fibular plate was thin and wavy, although that specimen was from a girl 13 years 4 months of age. The secondary ossification centers formed normally. Photomicrographs showed that the structure of the achondroplastic physis, while not perfectly normal, deviates relatively minimally from normal.

3.9.2.2 Hypochondroplasia

There is a normal growth plate with regular well-organized endochondral ossification sequences. Even by ultrastructural analysis, the growth plate matrix and cells are normal. Overgrowth of circumferential periosteal bone in the periphyseal groove of Ranvier is not a feature of this disorder.

3.9.2.3 Diastrophic Dysplasia

Light and electron microscopic studies of diastrophic dysplasia iliac crest growth cartilage reveal extensive cell and matrix abnormalities at each time period (Fig. 3.5a–d) [138, 163, 164]. Light microscopy shows atypical chondrocytes with extreme variation in size and shape, premature cytoplasmic degeneration, and formation of target ghost cells. Prominent, densely staining fibrotic foci are present throughout the cartilage. Ultrastructure reveals some structurally intact chondrocytes with a single large fat inclusion, slightly dilated rough endoplasmic reticulum, and abundant glycogen. As early as 1 year of age, cystic degeneration of chondrocyte cytoplasm is evident with indistinct organelles seen. The cartilage matrix demonstrates a general increase in fibrous tissue as well as the fibrotic foci. The collagen in these foci is remarkably abnormal. It is composed of short, extremely broad fibrils ranging from 150 to 950 nm in width which are separated at their terminal ends but fused to each other centrally in random fashion. On cross-section, there are very few round fibrils but rather a marked irregularity in shape giving the appearance of having fibrils randomly added to others to form enlarged nonuniform fibril aggregates. On longitudinal sectioning, regular cross-banding across the entire fibril width is seen but fibril splitting and aggregation are highly irregular. The disordered self-assembly process points to either a secondary modification on one of the collagen molecules probably type IX favoring the abnormal fibril aggregation or a defective noncollagenous matrix molecule which secondarily interferes with normal cartilage synthesis and allows for deposition of a broad, cross-banded collagen in what should be a strictly cartilage domain.

3.9.2.4 Metatropic Dysplasia

The resting cartilage matrix appears normal, but the resting chondrocytes are more vacuolated and contain metachromatic inclusions. Cell progression appears normal, but vascular invasion is very irregular and foci of ossified cartilage extend into the metaphysis. A thick band of calcified cartilage bridging the chondro-osseous junction has been described. Ultrastructural study shows cytoplasmic vacuolation, some of which are membrane bound and others non-membrane bound containing the appearance of glycogen-like material.

3.9.2.5 Spondyloepiphyseal Dysplasia

In SED congenita there is regular chondrocyte proliferation and maturation in most cases, although the physeal columns are short and the septa wide. On occasion, there is irregular vascular invasion from the metaphysis. By ultrastructure chondrocytes in all zones contain cytoplasmic inclusions of widely dilated rough endoplasmic reticulum containing a homogeneous mildly electron-dense finely granular material (Fig. 3.6) [165].

Spondyloepiphyseal dysplasia tarda. The epiphyses remain unossified until late in childhood. Cartilage tissue shows normal chondrocyte maturation although there is clustering of proliferative chondrocytes.

3.9.2.6 Kniest Dysplasia

Resting cartilage is markedly abnormal showing large chondrocytes in a loosely woven matrix with numerous empty spaces which led to the term "Swiss cheese cartilage syndrome [150]." In young children, the growth plate is hypercellular with large chondrocytes and little intervening matrix. Vascular penetration is irregular leading to the formation of broad, short, irregular spicules of calcified cartilage and bone. With increasing age, there is some attempt at column formation but the cartilage is still hypercellular. The

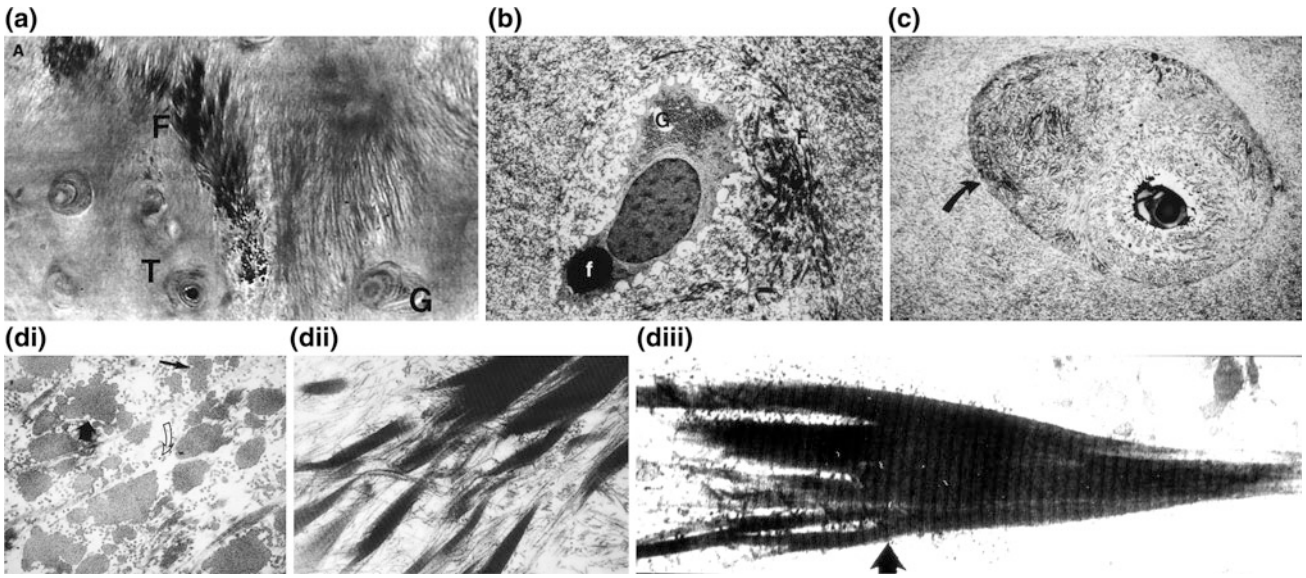


Fig. 3.5 Histopathology from cases of diastrophic dysplasia are shown. **a** Photomicrograph from iliac crest cartilage shows increased tissue fibrosis in association with premature chondrocyte degeneration. The dark staining regions of fibrosis (*F*) are totally abnormal for this part of the iliac crest growth plate physis. The tissue is relatively hypocellular. Chondrocytes have died and formed either ghost cells (*G*) or target cells (*T*). The ghost cells are pyknotic and the chondrocyte lacunae begin to fill with fibrous tissue. The presence of a target cell refers to the pericellular circumferential rings of increased fibrosis. (Reprinted with permission from Shapiro F, Light and electron microscopic abnormalities in diastrophic dysplasia growth cartilage. Calcif Tissue Int. 1992;51:324–331. Copyright 1992 Springer Science + Business Media). **b** Pericellular fibrosis is seen in this electron micrograph. The chondrocyte shows a normal intracellular fat (*f*) collection as well as slightly increased glycogen (*G*). **c** Electron micrograph shows a pyknotic cell with increased fibrosis within the chondrocyte lacunae. This would appear as a ghost cell at the light microscopic level. **d** Examples of the fibrotic tissue within cartilage matrix at increasingly higher levels of ultrastructural resolution. Random collagen deposits are seen in this figure **d i** Cross-sections of the large collagen fibril aggregates highlight the extremely wide diameters and irregular outlines (*closed arrows*). Some accumulations have distinctly abnormal flat borders. The size variability is extensive and several fibrils (*closed arrows*) give the appearance of having been formed by a random "tacking on" of fibrils at the periphery. The normal-appearing collagen components of cartilage matrix (*open arrow*), which are 20–30 nm wide, are in marked distinction to the large fibril accumulations (×47,250). **ii**, **iii** Collagen fibrils from one of the fibrotic foci. Note the continuity of the cross banding across the widest diameter of the accumulation (*arrow*). The fibril is 890 nm wide at this point. As the splitting begins, each individual segment retains its cross-banded appearance (×38,259).

physeal growth zone is disorganized with little evidence of proliferating and hypertrophic cell columnation. There is an abnormally short proliferative zone. The chondrocytes show cytoplasmic inclusions which by ultrastructural studies show dilated cisternae of rough reticulum. In the hypertrophic zone, irregular columns of several enlarged cells are seen and often there are cytoplasmic inclusions in the hypertrophic cells. Throughout the growth plates, scattered foci of fibrillated matrix with mucoid degeneration are found as well as larger acellular areas.

3.9.2.7 Metaphyseal Dysplasia

Histopathologic changes are similar in variants such as Jansen (the most severe), Schmid (the mildest), and McKusick (cartilage-hair disease variant) [166]. The cartilage stains unevenly, the matrix has a fibrillar appearance, and the chondrocytes are larger than normal. There are clusters of proliferating and hypertrophic cells surrounded by dense staining collagen rather than linear columns. The septae are wider than normal and composed of dense fibrous material. Metaphyseal vascular invasion is irregular and hypertrophic cartilage cells often persist in the metaphysis. The tongue-like extensions of cartilage into the metaphysis result in the radiolucent linear metaphyseal streaking often seen. Chondrocytes at all levels contain rough dilated endoplasmic reticulum as seen by electron microscopy, although this observation has not been made universally [167, 168].

3.9.2.8 Spondylometaphyseal Dysplasia

The growth cartilage contains short and irregular columns and often fibrous septae which are quite wide. There is a reduced proliferative zone and irregular formation of cartilage columns. The hypertrophic zone is present and vascular invasion regular in some areas but uneven in others. Electron microscopy shows large inclusion bodies bound by a smooth membrane within the chondrocytes.

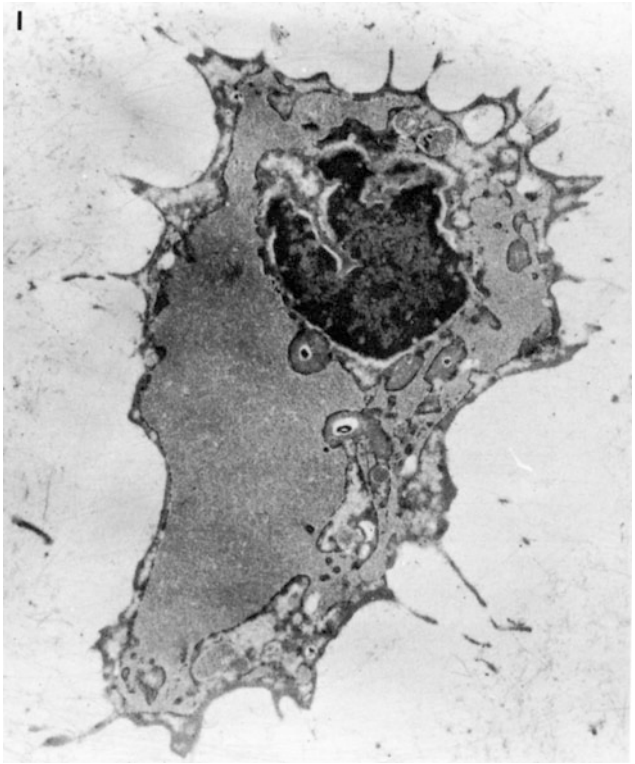


Fig. 3.6 Electron micrograph from iliac crest chondrocyte in a patient with SED congenita shows characteristic massively dilated rough endoplasmic reticulum

3.9.2.9 Multiple Epiphyseal Dysplasias

End-stage osteoarthritis characterizes many cases of multiple epiphyseal dysplasias. Gross and histologic findings of osteoarthritis have been demonstrated on specimens removed at the time of total joint arthroplasty, usually for hip and knee problems. There are few if any histopathologic samples of articular cartilage from the early stages of multiple epiphyseal dysplasias. Iliac crest biopsies and a tibial physeal biopsy report however show cartilage changes characterized by inclusions in chondrocytes and increased fibrosis in the septae of the hypertrophic zone. A recent case of MED showed rough endoplasmic reticulum of epiphyseal chondrocytes filled with linear lamellar arrays of alternating electron-dense and electron lucent material, presumably abnormally processed type IX collagen (Fig. 3.7) [78]. Many cases show normal histology at iliac crest and costochondral junction although this is not surprising since often some regions only are affected.

3.9.2.10 Chondrodysplasia Punctata: Conradi–Hünermann Variant

The proliferative cartilage of the growth plate can show areas of degeneration and cyst formation, often with excessive fibrous tissue and dysplastic calcification. Endochondral bone formation is normal in some growth plates and abnormal in others. Studies of the Conradi–Hünermann form of this disorder show normal resting cartilage but areas of calcification throughout the cartilage matrix in particular around individual lacunae. There are extensive areas of fibrous tissue replacement of cartilage within the growth plate and bony spicules arising directly from the fibrous connective tissue rather than from a classic endochondral sequence. Isolated areas of endochondral ossification are also seen however. In those who survive, the calcific punctate lesions begin to resorb toward the end of the first year of life and have usually disappeared by 4–5 years of age. Some appear to undergo actual resorption but others are incorporated into secondary center bone.

3.9.2.11 Mucopolysaccharidoses

MPSI (Hurler), MPSIII (SanFilippo), MPSIV (Morquio), and MPSVII (Sly) all show similar histopathologic changes [169, 170]. The disorder is associated with large chondrocytes that are filled with several independent lysosomal vacuoles as seen by electron microscopy [171]. Light microscopy reveals large areas of connective tissue that focally disrupt the growth plate although the rest of the growth plate undergoes a fairly normal endochondral ossification. Where fibrous tissue replaces growth cartilage, a fibrous ossification follows at the metaphyseal end of the lesion.

3.9.2.12 Mucolipidosis

In mucolipidosis II marked abnormalities of the growth plate with loss of normal cartilage architecture and the absence of endochondral ossification were noted [172]. In a child who died at 1 day of age there was histologic evidence of abnormally long columnar and hypertrophic cell layers of the growth plate with failure of the normal pattern of vascular invasion and no evidence of metaphyseal bone formation. The cartilaginous septae were not calcified and invasion of connective tissue with vascularization from the metaphysis into the cartilaginous was irregular.

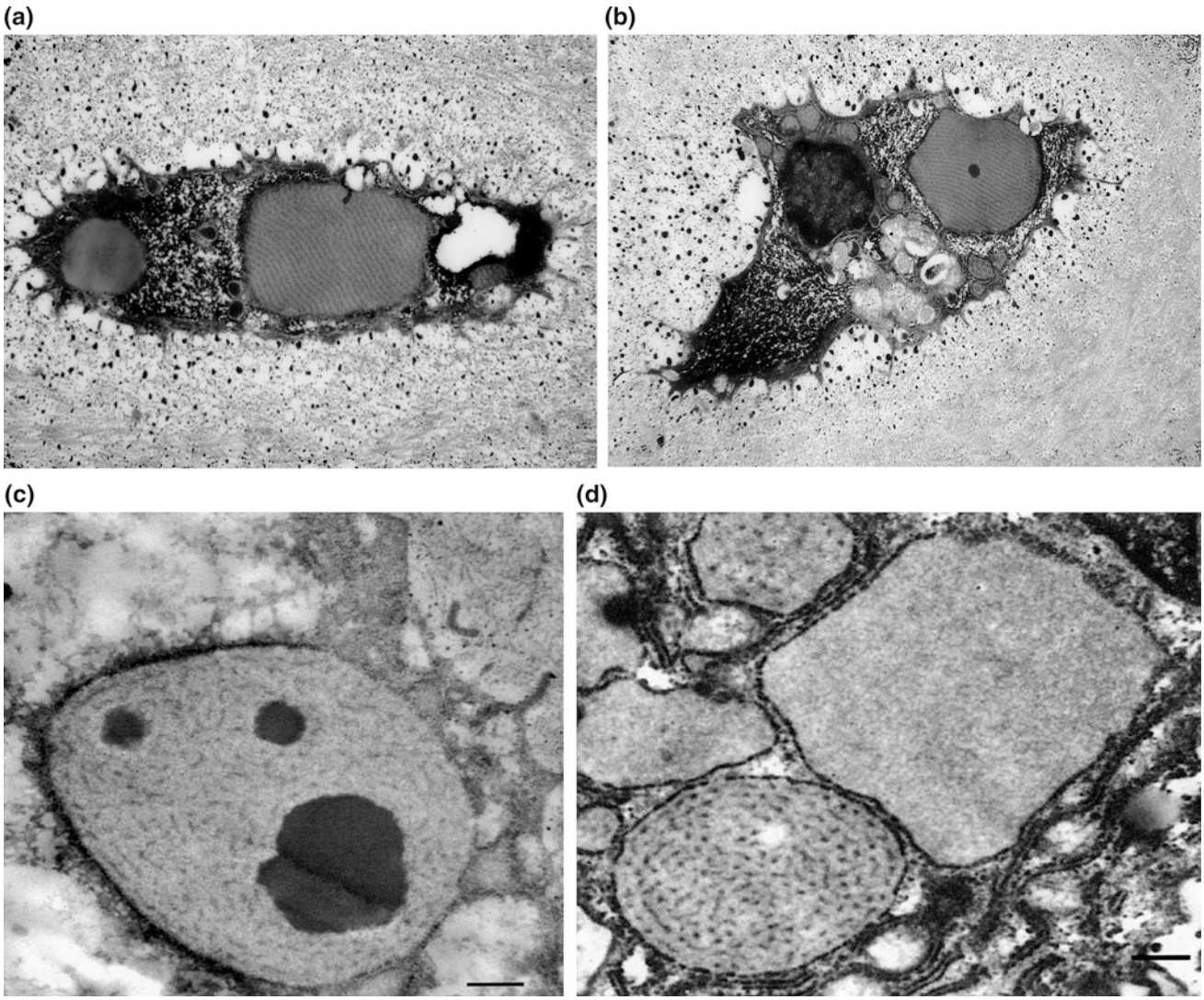


Fig. 3.7 **a**, **b** Electron micrographs show parallel linear lamellar collections of alternating electron dense and electron lucent material in dilated rough endoplasmic reticulum from a patient with multiple epiphyseal dysplasia due to a mutation in the alpha 3 chain of type IX collagen. (Reprinted with permission from Bonnemann et al. A mutation in the alpha-3 chain of type IX collagen causes autosomal dominant multiple epiphyseal dysplasia. PNAS. 2000;97:1212–1217. Copyright 2000 National Academy of Sciences, USA). **c**, **d** Electron micrographs show abnormal electron-dense structures in dilated segments of rough endoplasmic reticulum. These are discrete wavy short rod-like or circular structures. Three fat inclusions are also seen in **c**. Patient's short stature syndrome was spondyloepiphyseal dysplasia with scoliosis, joint laxity and finger deformities. (Reprinted with permission Shapiro et al. Rough endoplasmic reticulum abnormalities in a patient with spondyloepimetaphyseal dysplasia with scoliosis, joint laxity, and finger deformities. Ultrastruc Pathol. 2006;30:393–400. Copyright 2006 Informa Helathcare)

3.9.2.13 Pseudoachondroplasia

This disorder shows a highly characteristic ultrastructural finding. Chondrocytes from all layers of iliac crest and proximal fibular physeal cartilage show curvilamellar bodies within the dilated rough endoplasmic reticulum consisting of alternating layers of electron-dense and electron lucent layers arranged in a curvilinear or whorled array. This finding has been noted in several patients in several reports [146, 149, 164, 173].

3.9.2.14 Spondyloepimetaphyseal Dysplasia (SEMD)

This disorder refers to a group of skeletal dysplasias where vertebrae and long bone epiphyses and metaphyses are radiographically abnormal. The term encompasses considerable clinical, radiographic, and molecular heterogeneity. There are several subgroups with variable features such as joint laxity, multiple dislocations, scoliosis, and finger abnormalities [142, 174–177].

Table 3.8 Abnormalities of the lower extremities—approaches to their treatment[a]

Hip	Congenital hip dislocation	Closed treatment is often ineffective; may need open reduction, with or without pelvic and femoral osteotomy
	Acetabular dysplasia	Pelvic osteotomy
	Congenital coxa vera	Valgus osteotomy of proximal femur
	Flexion contracture	Soft tissue release; proximal femoral extension osteotomy
	Abduction or adduction contracture	Soft tissue release
	Lack of sphericity of femoral head	No current therapy
Thigh	Anterolateral bowing	Improvement is usually spontaneous; may require femoral osteotomy
Knee	Bowleg (genu varum) or knock knee (genu valgum)	Osteotomy of proximal tibia-fibula or asymmetric stapling of proximal tibial growth plate
	Flexion contracture	Soft tissue release at posterior knee; distal femoral extension osteotomy
	Patellar dislocation (lateral)	Soft tissue realignment repair
	Misshapen epiphyses; lax ligaments	Bracing; surgery produces uncertain results
	Exostosis	Surgical excision if symptomatic
Leg	Anterior or anterolateral bowing of tibia	Improvement is usually spontaneous; may require osteotomy
Ankle	Valga tilt of ankle with pronated (flat) foot due to relative shortness of distal fibula; varus tilt of ankle with inverted foot due to relative overgrowth of distal fibula	Distal tibial fibular osteotomy near skeletal maturity; asymmetric distal tibial and /or fibular growth plate stapling
Foot	Clubfoot	Serial casting beginning at birth; frequently requires soft tissue posteromedial release; calcaneal and tarsal osteotomies or arthrodesis
	Toe deformities (hallux valgus, hammer toes)	Serial casting; sometimes requires metatarsal osteotomies, surgical correction if symptomatic

[a]*Derived from* Shapiro F (1987) Epiphyseal disorders N Engl J Med 317:1702–1710

3.10 Orthopedic Deformities in Skeletal Dysplasias: Regional Abnormalities and Their Relation to Clinically Significant Deformity

3.10.1 Overview

The skeletal dysplasias are characterized by structural abnormalities of developing bones. These are important in a clinical sense in two broad areas. One concerns diagnosis since the large majority of dysplasias are currently defined by the radiographic appearance of the skeleton. The other concerns bone deformities, some of which are incompatible with life, some of which are amenable to improvement with surgical intervention, and some of which have no clinical significance.

There are three general approaches a practitioner can take in assessing a child with a skeletal dysplasia. One is to review the spectrum of the child's clinical and radiographic findings in relation to described syndromes as outlined in several large texts, make a diagnosis as to the name of the disorder, and then assess the patient searching for the skeletal abnormalities described in the literature for that particular disorder. A second approach is to focus on specific structural abnormalities such as hypoplastic clavicles, short neck, coxa vara, etc., and refer to lists available, which give differential diagnoses of disorders based on specific anomalies. A valuable book for this approach is "Gamuts in Bone, Joint and Spine Radiology" by Reeder [178]. The third is simply to use a patterned approach to each patient assessing each region of the body in a generalized-to-specific fashion, defining structural abnormalities, and deciding on therapeutic approaches with syndromal diagnosis then following. The regional abnormalities characteristic of skeletal dysplasias are summarized in Table 3.2 and the lower extremity problems in Table 3.8. Although the majority of dysplasias are encompassed within a relatively few diagnostic entities, many patients fit no described criteria. For these reasons, assessment region by region in relation to management concerns for any particular case has much to recommend it.

The orthopedic concerns in a skeletal dysplasia patient can be divided into four major categories: spinal deformity, neurologic complications of spinal deformity, upper and lower extremity deformities, and limb shortening. The orthopedic consequences of the skeletal dysplasia diagnosis are reviewed in Table 3.2 and in more detail below. Reviews of diagnostic

Table 3.9 Upper cervical anomalies in the skeletal dysplasias

	# of patients	Age range (years)	# with odontoid hypoplasia	# with absence	# with other defects base of skull to C3	# with known neurological complications	Total # (%) with bony defect
Morquio's disease	15	1–15	7	8	0	5	All 15 (100)
Other mucopolysaccharide disease							
Hurler's	6	1–13	4	0	4	0	
Hunter's	5	3–14	3	0	0	0	
Scheie's	3	6–14	1	0	1	0	15 of 20 (75)
Sanfilipo	3	1–11	3	0	0	0	
Maroteaux Lamy's	3	3–6	3	0	0	0	
Spondyloepiphyseal dysplasia							
Congenita	24	Neonate-54	15	1	4	1	20 of 24 (83)
tarda	18	3–62	3	0	1	1	4 of 18
Pseudoachondroplasia	23	Neonate-53	8	0	5	0	13 of 23 (27)
Achondroplasia and hypochondroplasia	23	2 month-65	1	0	1	0	2 of 23
Multiple epiphyseal dysplasia	18	4-adult	6	0	0	0	6 of 18
Chondrodysplasia punctata	14	Neonate-11	2	0	9	0	11 of 14
Metatropic dysplasia and Kniest disease	7	Neonate-15	1	1	2	0	4 of 7
Distrophic dysplasia	6	Neonate-48	1	0	3	1	4 of 6
Spondylometaphyseal dysplasia	3	7–16	1	0	0	0	1 of 3
Total	171		59	10	30	8	80(47)

Note # = *number*
[a]*Derived from* Arch Dis Child 64:283–288, 1989

and orthopedic management of skeletal dysplasias have been published with varying degrees of details [179]. Spinal deformities have been reviewed well by Tolo [180].

A significant number of the spinal deformities in the skeletal dysplasias have neurologic complications, most of which develop slowly over a few years. These involve spinal cord compression leading to myelopathy, paraparesis, and even quadriparesis. They occur secondary to atlanto-axial instability, due to C1–C2 abnormalities with ligamentous laxity, cervical kyphosis, thoracolumbar kyphosis abnormalities, and cauda equina or nerve root compression syndromes due to lumbar spinal stenosis. If cervical abnormalities are ruled out, spinal cord compression tends to be associated with a severe angular kyphosis usually at the thoracolumbar junction or lumbar spinal stenosis.

3.10.2 Cervical Spine Abnormalities

Developmental abnormalities of the cervical vertebrae occur in many skeletal dysplasias and, if unrecognized, can lead to compression of the spinal cord with gradual paraparesis or quadriparesis or even to acute quadriparesis and sudden death with minimal trauma [181]. The skeletal dysplasias with cervical spine problems include about 35 of the 150 well-described disorders [52]. A developing cervical myelopathy is suspected in a child with easy fatigability, hyperreflexia, or weakness. Pain is not a prominent symptom in the childhood skeletal dysplasia patient with cervical instability; in one series of 6 patients all of whom came to cervical fusion surgery, no patient complained of cervical pain and in another study, none of 11 patients with odontoid dysplasia and atlanto-axial instability in Morquio's disease had significant neck pain [182, 183]. All patients with a skeletal dysplasia should have cervical radiographs, especially prior to any anesthesia where intubation is to occur. Even when vertebral stabilization surgery is done in the first decade, subsequent recovery of any cervical myelopathy can be limited so that early diagnosis and pre-symptomatic fusion is desirable. An assessment of upper cervical abnormalities in 171 patients with skeletal dysplasia has been presented (Table 3.9) [184]. Lachman has briefly reviewed

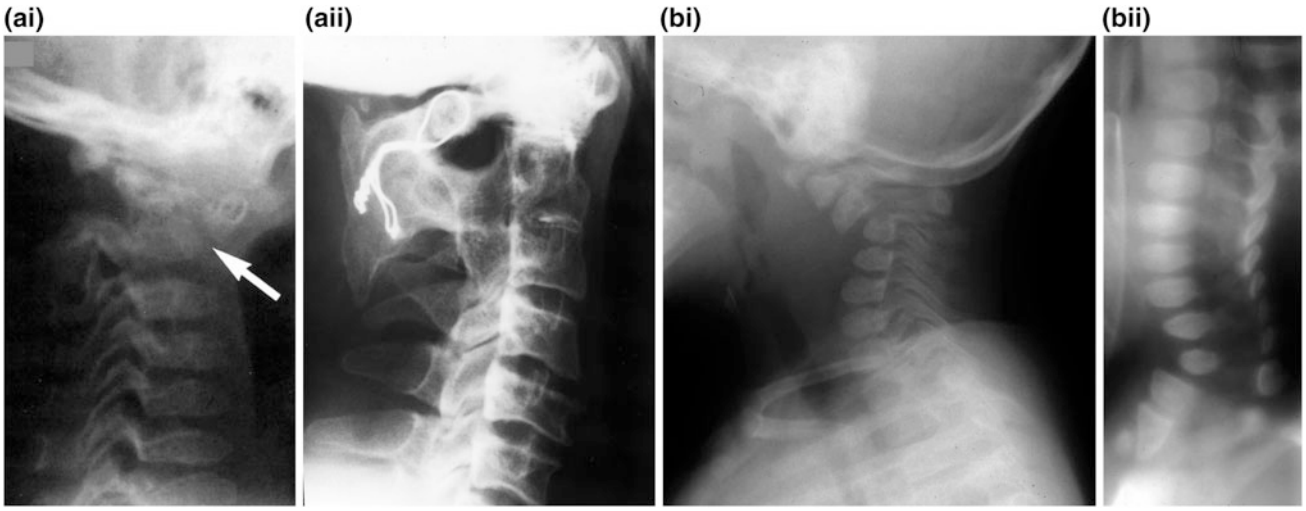


Fig. 3.8 Characteristic cervical spine abnormalities in the skeletal dysplasias are shown. **a** Lateral radiograph shows C1–C2 anterior subluxation in a 7-year-old female with SED who presented with quadriparesis. **i** Lateral cervical view in forward flexion shows C1 anterior subluxation on C2 (*arrow*), **ii** lateral view shows stabilized alignment following C1 to C2 fusion. **b** Mid cervical kyphosis is shown **i** lateral and **ii** lateral tomogram radiographs of a patient with diastrophic dysplasia at 18 months of age. Note the underdevelopment of the anterior parts of the vertebral bodies of C3, C4, and C5. This is a characteristic deformity at this age in diastrophic dysplasia and most will correct spontaneously with growth

the primary cervical spine abnormality seen in each of 35 syndromes [181]. The specific cervical spine abnormalities in the skeletal dysplasias follow.

3.10.2.1 Maldevelopment of the Odontoid Process with Atlanto-Axial Instability

Maldevelopment of the odontoid process (the dens) of C2 and laxity of the ligaments result in subluxations of cervical vertebra 1 on cervical vertebra 2 (C1 on C2) in many dysplasias (Fig. 3.8a) (155). The odontoid process may be absent, markedly hypoplastic, or not united to the main body of C2. It is important to assess cervical stability since vertebral anomalies alone are not always associated with instability if adjacent ligamentous structures compensate. Diagnosis is confirmed by some or all of lateral cervical radiographs in flexion and extension, open-mouth views to show the atlanto–axial–occipital complex, C1–C2 tomograms, CT scans with myelography or magnetic resonance imaging (MRI) studies. The lateral radiographs show odontoid abnormality but any instability is best shown with the active flexion–extension views with forward shifting of the axis (C1) on C2 with flexion. The atlanto-odontoid interval should not exceed 4–5 mm in the child and 2–5 mm in the adult. All patients with Morquio's disease (MPS IV) have dysplasia of the odontoid process with atlanto-axial instability; 11 of 11 and 15 of 15 in 2 series studied. There is also a very high incidence of upper cervical bony anomalies in the other mucopolysaccharidoses [75 % (15 of 20) of patients with Hurler, Hunter, Scheie, Sanfilipo and Maroteaux-Lamy disorders]. A patient (15 years of age) with quadriparesis in MPS VII has been reported. The condition is also extremely common in spondyloepiphyseal dysplasia congenita occurring in one series in 20 of 24 patients (83 %) and pseudoachondroplasia (13 of 23 or 57 %). It is also seen in Kniest dysplasia, chondrodysplasia punctata (C–H type), metatropic dysplasia, spondyloepiphyseal dysplasia tarda, Larsen's syndrome, Dyggve–Melchior–Claussen dysplasia and spondylometaphyseal dysplasia. All cases of odontoid hypoplasia or absence have a higher than normal risk for cervical spinal cord compression. Neurologic symptoms of cervical compression (myelopathy) include decreased physical endurance, progressive weakness, and pyramidal tract signs including spasticity, clonus, hyper-reflexia, and extensor plantar reflexes. Sensation tends to be maintained for a considerable period. Neurologic findings are often greater on one side than the other since the cervical cord is often displaced to one side. In those children with the triad of odontoid hypoplasia, instability of C1 on C2, and spinal cord compression, the onset of symptoms often becomes apparent between 5 and 10 years of age. Gait problems are often attributed to the hip and knee deformities of the dysplasia and the cervical component is often delayed in diagnosis. Diagnosis is best performed with plain radiographs including antero-posterior, open-mouth, and lateral flexion, neutral, and extension views, MR imaging for soft tissue and spinal cord visualization and CT scanning for bony anatomy. Treatment involves an occiput-to-C2 posterior fusion or a

C1-to-C2 fusion if the posterior arch of C1 is intact (Fig. 3.8a(iii)). Early diagnosis and fusion represent the ideal treatment since recovery of lost function post-surgery is often incomplete if it had reached moderate to severe levels.

The skeletal dysplasias with common and significant C1–C2 instability requiring careful early observation are the type II collagenopathies SED congenita, Kniest dysplasia, and spondyloepimetaphyseal dysplasia (Strudwick), pseudoachondroplasia, metatropic dysplasia, chondrodysplasia punctata (Conradi–Hünermann), diastrophic dysplasia, and Dyggve–Melchior–Clausen dysplasia.

3.10.2.2 Mid-cervical Kyphosis

Mid-cervical kyphosis due to underdevelopment of the vertebral bodies of C3, C4, or C5 occurs frequently in diastrophic dysplasia (Fig. 3.8b). Treatment is by posterior cervical fusion if there is worsening deformity and cord compression although in the absence of neurologic symptoms expectant observation can be used in the first few years of life as spontaneous correction of the kyphosis with associated stabilization in many has been described up to 5 years of age. If the angulation is worsening however posterior fusion regardless of age is warranted since cases of progressive kyphosis, quadriparesis, and death have been described. Cervical kyphosis is also seen in type II collagenopathies of the SED and SEMD types and can be severe in lethal campomelia, in those few campomelic patients who survive, and in de la Chapelle, atelosteogenesis III, chondrodysplasia punctata (rhizomelic), and hypochondrogenesis disorders.

3.10.2.3 Cervical Spina Bifida Occulta

Cervical spina bifida occulta is an almost invariable occurrence in diastrophic dysplasia. It was noted in each of 16 patients in 2 published series. The spina bifida is usually narrow in the 2–4 mm range but defects as wide as 10 mm have been described. It is generally present in the mid- and lower cervical vertebrae but can extend to the upper thoracic area. It appears not to cause deformity by itself but must be carefully assessed at the time of posterior surgical procedures.

3.10.2.4 Cervical Spinal Stenosis

Cervical spinal stenosis of variable degree usually accompanies foramen magnum stenosis in achondroplasia but rarely is severe enough to require surgical decompression.

3.10.2.5 Cord/Root Compression by Exostoses

Intraspinal protrusions of exostoses in hereditary multiple exostoses can produce cord and root compression at each of cervical, thoracic, and lumbar levels [185].

3.10.3 Thoracolumbar Spine Abnormalities: Scoliosis, Kyphosis, and Kyphoscoliosis

There is a high incidence of thoracolumbar scoliosis, kyphosis, or kyphoscoliosis in many dysplasias including in particular spondyloepiphyseal dysplasia congenita, spondylometaphyseal dysplasia, spondyloepimetaphyseal dysplasia, diastrophic dysplasia, Kniest syndrome, Morquio's disease, metatropic dwarfism, and pseudoachondroplasia (Fig. 3.9) [186]. These deformities in the skeletal dysplasias have a marked tendency to occur much earlier, progress more quickly, and be more rigid than those in idiopathic conditions. Compression of the spinal cord and spastic paraparesis can occur, primarily with kyphosis or kyphoscoliosis, whereas such neurologic sequelae are extremely rare in patients with even advanced idiopathic scoliosis or scoliosis as the main deformity in a skeletal dysplasia.

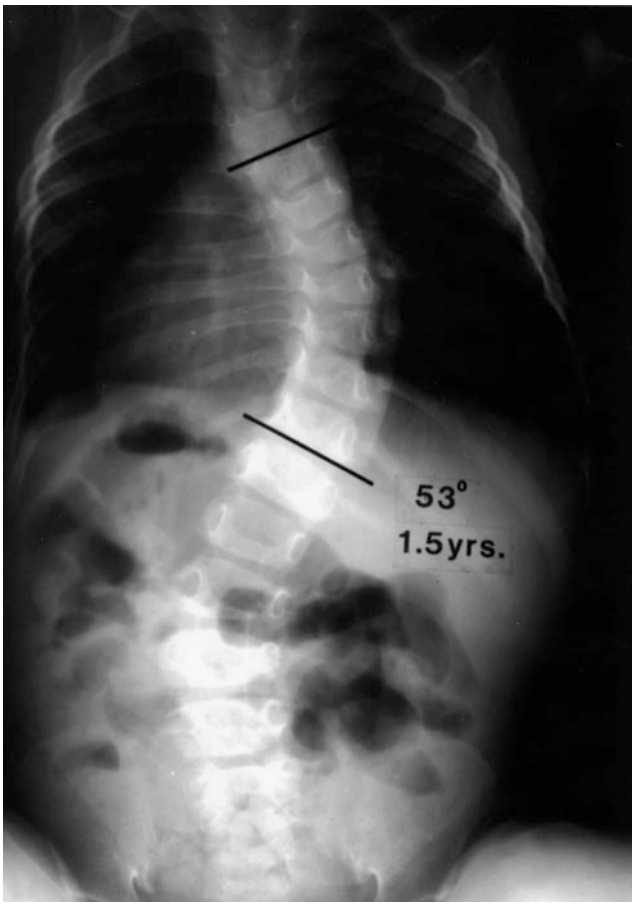


Fig. 3.9 A severe scoliosis can occur in the skeletal dysplasias. They tend to occur earlier, progress more rapidly, develop rigidity, and cause spinal cord compression to a greater extent than in idiopathic varieties. Spine in diastrophic dysplasia with 53° curve at 1½ years of age

Kyphosis of a moderate to severe form can occur as an exclusive deformity in achondroplasia or as the major component of a kyphoscoliosis with spondyloepiphyseal dysplasia congenita, MPS IV (Morquio's disease), diastrophic dysplasia, pseudoachondroplasia, and metatropic dysplasia.

An isolated thoracolumbar kyphosis is particularly common in achondroplasia. Essentially all newborns with achondroplasia have a mild thoracolumbar kyphosis, and this may be associated with anterior wedging of the apical vertebra. The kyphosis usually resolves to a normal configuration on its own as the patient becomes ambulatory but in about 30 % of patients the kyphosis persists and in one-third of these it can progress to a major fixed thoracolumbar kyphosis. Two types are seen: one a long moderate kyphosis extended over several segments and the other sharply angulated localized kyphosis centered at one or two wedged vertebrae and referred to as a gibbus deformity. The latter group is particularly likely to develop neurologic symptoms but even a relatively gentle kyphosis can lead to symptoms in the achondroplastic individual because of the associated spinal stenosis with the narrowed inter-pedicular distance. The neurologic complications in achondroplasia are more likely to occur and are far more serious in those with thoracolumbar kyphosis, in particular the short gibbus-type deformity. Scoliosis can also occur in achondroplasia but rarely reaches a degree of deformity requiring full-time brace use or spinal fusion procedures. Symptoms referable to the kyphosis with increased discomfort and neurologic dysfunction are generally not seen until the third or fourth decade. Although those with scoliosis in achondroplasia rarely proceed to a significant deformity, kyphosis is different and the progressive nature of the deformity in those where it is present is such that aggressive early treatment even in the immature age group is recommended. Bracing is used to hyperextend the deformed region. It remains important in the child with achondroplasia and indeed with any skeletal dysplasia to associate any increase in symptoms not just with the deformity itself but also with the possibility of a herniated disk since the narrowed canal leads to cord and root pressure much earlier than is the case where a normal spacious canal is present. Anterior release and posterior spinal fusion or posterior fusion alone are needed depending on the nature of the symptoms and deformity.

Hensinger points out that kyphosis may occur in nearly every type of dwarfism and that even though all vertebrae are dysplastic the deformity tends to be concentrated at the thoracolumbar junction [187]. Kyphosis is also seen fairly frequently in spondyloepiphyseal dysplasia, a disorder characterized by a shortened trunk due to decreased height of the vertebral bodies. SED congenita has the more severe thoracic kyphosis and exaggerated lumbar lordosis. Progressive kyphosis can also occur in pseudoachondroplasia. Individuals with this disorder have the same basic body appearance as those with achondroplasia, except that the skull and facial features are normal and the hand findings are different. Radiologically the spine abnormalities are similar to a spondyloepiphyseal dysplasia and there is no decrease in the interpedicular distance of the lumbar spine. It can show exaggerated dorsal kyphosis and lumbar lordosis, and neurogenic degeneration distal to the kyphosis site has been shown.

In the mucopolysaccharidoses spinal deformity, which on occasion is an isolated kyphosis, can be seen with Morquio's (MPS IV), Hurler's (MPS1H), and Maroteaux–Lamy (MPSVI). One of the earlier features of Hurler's is a prominent gibbus at the dorso-lumbar junction with the vertebral body on the lateral radiograph at the apex of the kyphosis wedged with an anterior beak. In Morquio's disease there is universal flattening of the vertebrae (platyspondyly) and kyphosis with anterior beaking and wedging of the vertebra, most marked at the dorsal–lumbar junction. In the MPS VI syndrome deformities are mild with flattening of the vertebrae not as severe and only a mild gibbus at the thoracolumbar junction. In Hurler's syndrome the child's overall condition generally deteriorates over the first decade and treatment would be symptomatic or at most with bracing. In MPS IV and VI however survival is prolonged with good mental status, and aggressive brace treatment at the onset of deformity is used. Operative stabilization is occasionally required with posterior fusion predominating.

A thoracolumbar kyphoscoliosis is particularly common in diastrophic dysplasia. It is invariably progressive and often rapidly so even in the first decade. Deformity also occurs with metatropic dysplasia.

In those patients with campomelic dysplasia who survive, severe spinal problems are invariably seen. These can involve severe cervical kyphosis and cervical instability but all patients will develop a severe progressive thoracic kyphoscoliosis. Late ossification of the mid-thoracic pedicles is a clear and early diagnostic finding and vertebral body hypoplasia is the cause of the deformity. In one review of eight patients (collected from several centers) all of them had scoliosis averaging 63° at 6 years, and 6 of the 8 had severe kyphosis averaging 126°. The cervical kyphosis in three was 16°, 32°, and 150°. Congenital vertebral anomalies were present in all. The hypoplastic vertebral bodies appeared to be the major deforming regions. Late ossifying thoracic pedicles appear unique to this disorder. Scoliosis requiring treatment occurred in a high percentage of patients with

diastrophic dysplasia, spondyloepiphyseal dysplasia, metatrophic dysplasia, and chondrodysplasia punctata in one review.

Bracing is attempted for both kyphotic and scoliotic deformity but is often ineffective in the skeletal dysplasias owing to the small trunk size, the rigidity of the curves and the marked amount of trunk deformation. Increasing improvements in orthotic design and fabrication however allow for more accurate and comfortable fitting and should soon indicate somewhat improved results. Spinal fusion is resorted to relatively early if the deformity worsens with bracing. In patients between 3 and 10 years of age, worsening scoliosis not amenable to bracing can be treated surgically. Two growing rods, inserted without a spinal fusion, allow growth to continue for several years, stabilizing and minimizing the scoliosis until spinal fusion is performed close to skeletal maturity. Instrumentation systems designed for smaller younger patients combined with use of somatosensory-evoked potentials for intraoperative spinal cord monitoring further increase the value and safety of surgical intervention. Imaging improvements by CT scanning, MR imaging, and 3-dimensional reconstructions provide for more specific understanding of deformity.

3.10.4 Lumbar Spinal Stenosis and Lumbar Lordosis

In achondroplasia and some other dysplasias, the interpedicular distance of the lumbar vertebrae progressively narrows from L1 to S1, as seen on anteroposterior radiographs (Fig. 3.10a) [33, 188, 189]. The distance in the lower three vertebrae in particular becomes markedly narrowed. This finding is present even in the newborn period and allows for diagnosis of some skeletal dysplasias at that time. Thoracolumbar kyphosis that worsens instead of resolving and that is associated with spinal stenosis can lead to compression of the spinal cord in the first 10 years of life. The pedicles are also shortened as seen on lateral radiographic projections further narrowing the spinal canal (Fig. 3.10b). If

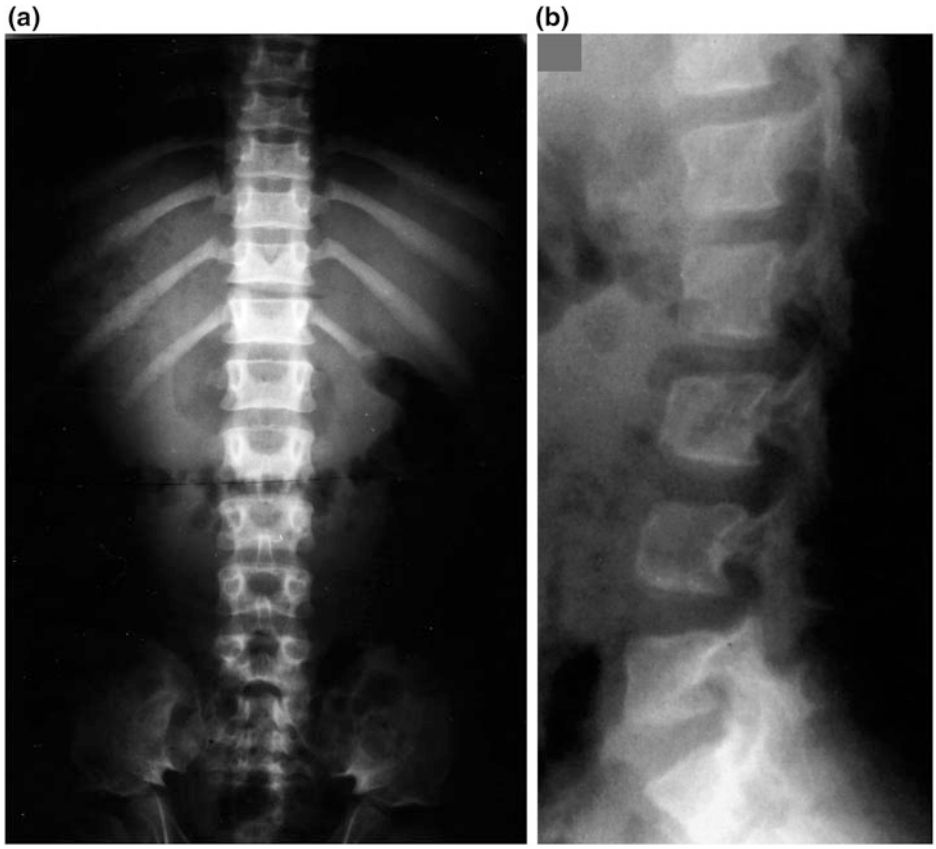


Fig. 3.10 Abnormalities of the lumbar vertebrae are characteristic of achondroplasia and some other skeletal dysplasias such as thanatophoric and diastrophic dysplasia. **a** Narrowing of the interpedicular distance of the lumbar vertebrae is characteristic of achondroplasia. This is evident radiographically even in newborn. In the normal there is progressive widening of the distance from L1 to S1. In achondroplasia there is narrowing at each successive level in particular from L3 down to S1. This results in a spinal stenosis. **b** Lateral radiograph in achondroplasia also shows the shortened pedicles contributing to the spinal stenosis. Concavities in the posterior margins of the vertebral bodies are characteristic. A prominent lumbar lordosis is seen. Shortening of the pedicles limits growth posteriorly while anteriorly the vertebral body growth is relatively less affected

herniation of an intervertebral disk occurs in the lower lumbar region, the spinal stenosis limits space in the canal and puts pressure on the cauda equina and the nerve roots, resulting in claudication and flaccid paralysis. These neurologic sequelae are far more extensive than those in patients with disk herniation into an otherwise normally sized spinal canal. Progressive neurologic symptoms at any age can necessitate anterior or posterior spinal decompression and spinal fusion.

A prominent lumbar lordosis is seen in achondroplasia (Fig. 3.10b) and in many other skeletal dysplasias including pseudoachondroplasia and diastrophic dysplasia. Although anti-lordotic bracing has been used there is no published indication of its effectiveness. The lordosis is not of sufficient concern to warrant primary surgery. In some disorders such as diastrophic dysplasia much of the lumbar lordosis is secondary or compensatory to marked hip flexion contractures and will improve upon surgical correction of the hip position.

Bethem et al. reviewed 80 patients from their institution with disproportionate short stature with virtually all showing some aspect of a spinal disorder [190]. Their study continues to serve as an indicator of the relative frequency of specific deformities in the skeletal dysplasias. Kyphosis was the most common clinically significant axial deformity in the skeletal dysplasias being present in 57 patients (71 %). Scoliosis considerably greater than 30° was present in 21 patients (26 %). Atlanto-axial instability was documented in 10 patients (13 %) with a total absence of the odontoid process in 5 patients (6 %). Neural symptoms occurred in 13 patients (16 %) with 10 having paraparesis and 3 quadriparesis.

A summary of the spinal disorders in the more common skeletal dysplasia syndromes is shown in Table 3.10.

3.10.5 Abnormalities of the Skull

The skull is often relatively large (macrocephaly) in the skeletal dysplasias since it is pre-formed in intramembranous bone which is unaffected in the chondrodystrophies. On occasion as in achondroplasia, this enlargement is associated with hydrocephalus, although this is usually of the benign, communicating variety without negative sequelae. The nasal region of the face, which is pre-formed in cartilage, is smaller than normal leading to the depressed nasal bridge appearance and the base of the skull surrounding the foramen magnum is also of cartilage origin and smaller than normal. Marked delay in closure of the anterior fontanelle occurs in cleido-cranial dysplasia, osteogenesis imperfecta, and some other disorders (Fig. 3.11a). Wormian bone formation characterizes type II and III osteogenesis imperfecta but is also seen in cleido-cranial dysostosis, hypophosphatasia, and pycnodysostosis (Fig. 3.11b). The softened osteopenic bone in OI leads to a flattened posterior skull region and there is also prominent frontal bossing. In the infantile-malignant form of osteopetrosis, the skull bone is also thickened and dense but the major negative sequelae result from the narrowed optic and auditory canals which fail to enlarge (remodel) with growth and whose stenosis contributes to pressure on the optic and auditory nerves with progressive blindness and deafness. There is a group of disorders characterized by craniosynostosis and peripheral limb malformations including Apert syndrome with symmetric syndactyly of hands and feet, Pfeiffer syndrome with broad thumbs and great toes, Jackson–Weiss syndrome with tarsal–metatarsal coalitions, and Crouzon syndrome with midface deficiency [17, 59]. [The broader range of

Table 3.10 Spinal disorders associated with different types of dwarfism

	Scoliosis	Kyphosis	Atlanto-axial instability	Decreased interpedicular disease	Cervical kyphosis	Spina bifida
Achondroplasia	No	Yes	No	Yes	No	No
Spondyloepiphyseal dysplasia	Yes	Yes	Yes	No	No	No
Mucopolysaccharidosis	No	Yes	Yes	No	No	No
Diastrophic dwarfism	Yes	Yes	No	Yes	Yes	Yes
Metatropic dwarfism	Yes	Yes	Yes	No	No	No
Kniest syndrome	No	Yes	No	No	No	No
Metaphyseal dyostosis	No	Yes	Yes	No	No	No
Chondrodystrophia calcificans congenita	Yes	No	No[a]	No	No	No

[a]Although atlanto-axial instability was not evaluated in our patients with chondrodystrophia calcificans congenita, it has been reported in patients in other series

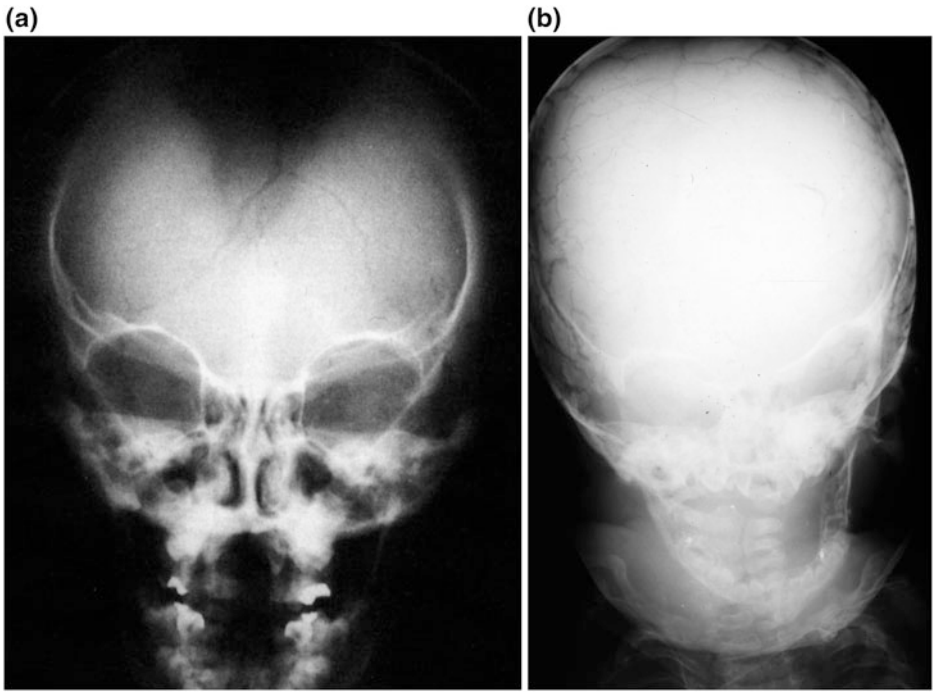


Fig. 3.11 Developmental abnormalities of the skull are common in many of the skeletal dysplasias. **a** Marked delay in closure of the anterior fontanelle occurs in cleidocranial dysplasia, osteogenesis imperfecta, and some other disorders. Anteroposterior skull radiograph in a patient with cleidocranial dysplasia is shown. **b** Radiograph shows wormian bone formation, a disorder of intramembranous skull bone seen in osteogenesis imperfecta of the more severe congenita or Sillence type 2. It has no particular clinical significance but is helpful diagnostically

craniofacial dysostoses is beyond the scope of our discussions of the osteochondrodysplasias.]

3.10.6 Abnormalities of the Clavicles

One specific dysplasia, cleido-cranial dysplasia, is characterized either by absent or markedly shortened clavicles such that the patient can touch the shoulders to each other in front of the chest (Fig. 3.12).

3.10.7 Abnormalities of the Extremities

3.10.7.1 Micromelic, Rhizomelic, Mesomelic, and Acromelic Shortening

Shortening of specific segments of limbs is characteristic of many disproportionate skeletal dysplasias with short stature, often to the point of being the feature defining the disorder. Micromelic refers to shortening of all parts of a limb; rhizomelic to proportionally greater proximal shortening (humerus and femur); mesomelic to mid-limb shortening most involved in the forearm (radius, ulna) and leg (tibia, fibula); and acromelic to most significant distal segment shortening of the hands and feet. In most skeletal dysplasias the shortening is symmetric.

3.10.7.2 Lower Extremity Length Discrepancies

In some of the skeletal dysplasias limb shortening is asymmetric. Discrepancy itself is rarely if ever significant in the upper extremities but differences in lower extremity lengths can reach clinical significance. The most significant lower extremity length discrepancy in a skeletal dysplasia occurs in Ollier's enchondromatosis and in the related Maffucci syndrome. Since involvement in these disorders is predominantly unilateral by definition, length discrepancies can be considerable. Lesser but still clinically significant length discrepancies also occur in hereditary multiple exostosis where many of the differences require epiphyseal arrest on the longer side for appropriate clinical management. Significant discrepancies in other dysplasias are infrequent but can occur usually in association with asymmetric angular deformities in which shortening can be a component not only of the original malformation but also of the treatment used to correct the deformity.

3.10.7.3 Angular Bone Deformity Due to Asymmetric Physeal Involvement

Asymmetric physeal involvement can lead not only to shortening but also to angular deformation owing to unequal growth across the entire physis. The angulation which is centered in the upper metaphysis can involve any of varus, valgus, flexion, extension, or rotational malpositions.

3.10.7.4 Limb Deformity Due to Unequal Growth Rates of Paired Long Bones in Forearm and Leg

In many skeletal dysplasias there is unequal involvement of radius and ulna in the forearm and tibia and fibula in the leg.

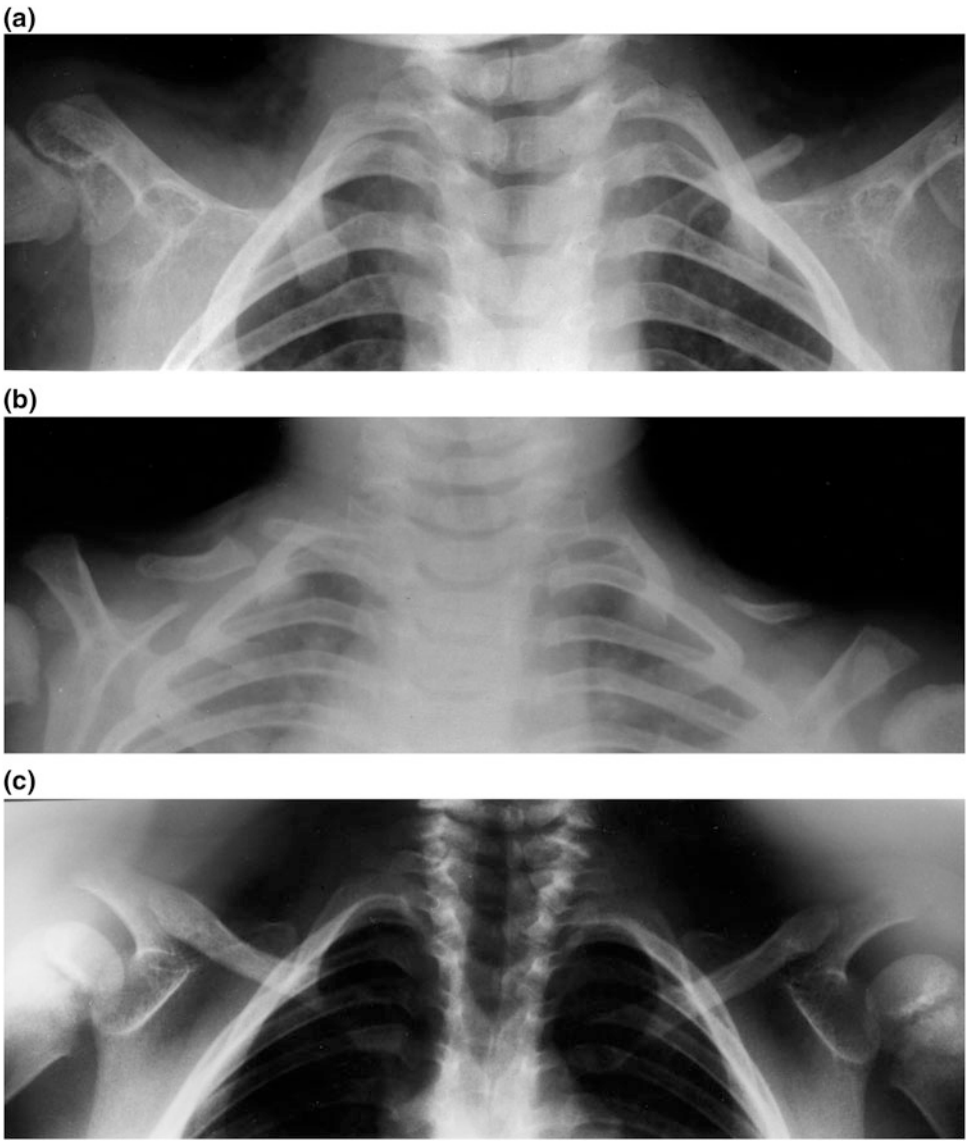


Fig. 3.12 Abnormalities of the clavicle characterize some skeletal dysplasia disorders, the commonest being cleidocranial dysplasia. The abnormalities include shortened clavicles (in particular laterally), aplastic clavicles with isolated remnants, and areas of discontinuity like with a pseudarthrosis. In **a** the *right* clavicle is absent and the *left* is deficient laterally in **b** there is a *right* pseudarthrosis (*arrow*) while on the *left* there is only a small central fragment, and in **c** the clavicles are shorter than normal especially laterally

Disparate growth rates can lead to deformation with resultant angular deformation and joint displacement (Fig. 3.13a–c). As a general rule the ulna is more seriously affected in skeletal dysplasias than the radius. The longer radius compensates for its relative overgrowth by one or all of several mechanisms including increased metaphyseal–diaphyseal curvature with the concavity toward the shortened ulna (Fig. 3.13a), gradually developing subluxation, and even complete dislocation of the radial head proximally at the elbow, and ulnar deformation and angulation at the distal radial physeal–metaphyseal region owing to medial physeal tethering by the shortened ulna and its associated ligamentous structures (Fig. 3.13a). In the leg the fibula can be either more affected or less affected than the adjacent tibia. In those situations where the fibula is relatively longer, it tends to ride higher at its relationship to the proximal tibia, sometimes coming to lie at the level of the knee joint whereas relative overgrowth distally leads to a tendency to varus deformation at the ankle (Fig. 3.13b). If the fibula is relatively shorter than the tibia, which most commonly occurs in hereditary multiple exostosis, there are few problems proximally but distally the ankle tends to have a valgus deformation and tethering by the shortened fibula and adjacent ligaments on the distal lateral tibial epiphysis further augments both the valgus deformation of the ankle and obliquity of the distal tibial physis and adjacent articular surface (Fig. 3.13c).

3.10.7.5 Joint Contractures and Instability

On occasion, angular deformation is centered at the joints themselves rather than in the adjacent physeal, metaphyseal, or even diaphyseal regions of the developing bones. The contractures are almost always to the flexed position and are a particular characteristic of diastrophic dysplasia (Fig. 3.14a). Joint instability characterizes many of the more

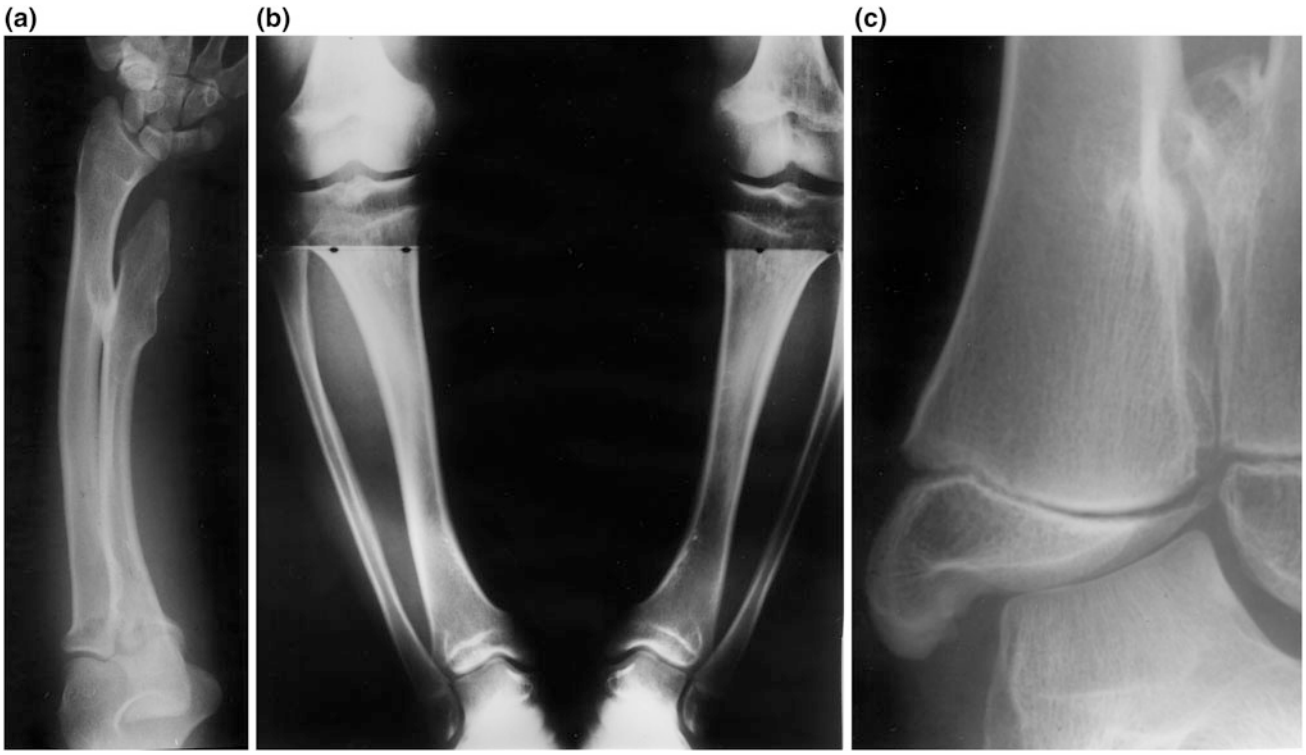


Fig. 3.13 Disparate growth rates between radius and ulna in the forearm and tibia and fibula in the leg are characteristic of many of the skeletal dysplasias and usually lead to limb deformation. **a** Radiograph of a forearm in hereditary multiple exostosis shows a markedly shortened ulna. The radius is curved owing primarily to tethering of its distal medial physis. **b** Relative overgrowth of the distal fibula (*arrows*) compared to the distal tibia can lead to varus malformation at the ankle. This radiograph is from a patient with achondroplasia. **c** Anteroposterior radiograph of the ankle in a patient with severe hereditary multiple exostosis shows the shortened fibula in relation to the relatively longer tibia. At the ankle this causes the lateral malleolus to be positioned more proximal than normal leading to valgus deformation. The lateral physeal region of the distal tibia suffers some limitation of growth owing to tethering associated with the shortened fibula

severe dysplasias. This results from a combination of ligamentous laxity and relative underdevelopment of parts of the entire epiphyses allowing for the more spacious joint cavity and predisposing to malalignment (Fig. 3.14b).

Surgery is performed on the lower extremities far more frequently than on the upper, since problems in the lower extremities result in considerable short-term and long-term morbidity and are also more amenable to correction. The operative procedures for the various deformities in the skeletal dysplasias are not specific for the various diseases but simply utilize operative approaches designed for the deformity which occurred regardless of their cause.

A large number of deformities of the upper and lower extremities occur in the various skeletal dysplasias. The presence of a deformity alone does not necessitate surgery. Rather, the decision to intervene should be based on the current degree of discomfort or limitation of function. Correction of deformity because of concern about problems which might develop in the future is not necessarily warranted in the skeletal dysplasia patient. The tendency to operate on deformities based on similar disorders that occur post-trauma in otherwise normal patients has not infrequently led to unimpressive results. The importance of intermediate and long-term study of the natural history of skeletal dysplasia deformity and of post-surgical results is leading to some data accumulation but much remains to be done.

3.10.8 Abnormalities of the Hip Region

3.10.8.1 General Considerations

A large number of patients with skeletal dysplasias, especially the multiple epiphyseal and spondyloepiphyseal types, develop premature osteoarthritis which necessitates total-joint arthroplasty in early to middle adult life. Surgery is performed increasingly in an attempt to forestall expected problems owing to deformity, especially in the hip region. Preoperative study of hip geometry has been improved by the use of arthrography, CT scans, MR imaging, and 3-dimensional computerized reconstructions. Many types of pelvic and proximal femoral osteotomies have been devised, as have bone-fixation devices specifically for children.

It is important to distinguish a skeletal dysplasia from bilateral Legg–Perthes disease since both can present with

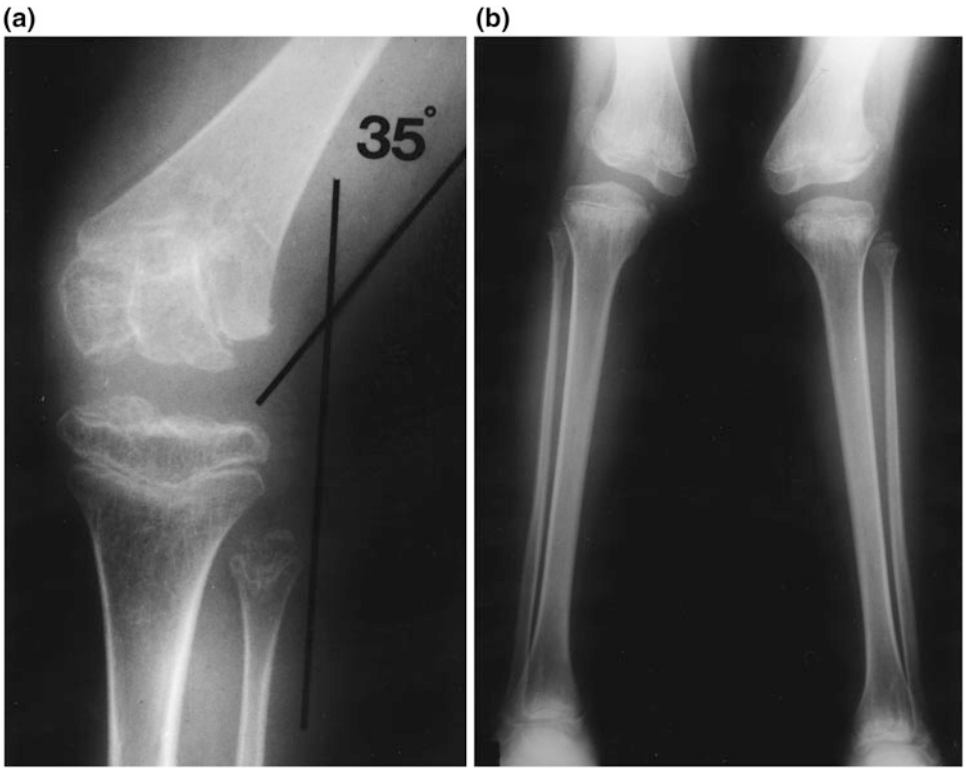


Fig. 3.14 Joint contractures and joint instability can be seen in certain types of skeletal dysplasia. Contractures are particularly common in diastrophic dysplasia and they are almost always of a flexion type. Instability tends to occur with underdevelopment of epiphyseal regions of an asymmetric fashion with persistence of relatively normal capsular and ligamentous tissues. **a** Flexion contracture of the knee characteristic of diastrophic dysplasia is shown here on a lateral radiographic projection. The film was taken with the knee in maximum extension. **b** Joint instability can represent a combination of bone malformation from asymmetric physeal growth and underdevelopment of parts of epiphyses with either normal joint contours persisting or in association with ligamentous laxity. Note lateral patellar dislocations. This patient had spondyoepiphyseal dysplasia with scoliosis, joint laxity and finger deformities

clinical and radiographic abnormalities of the proximal femoral capital epiphyses. The main disorders to be differentiated from Legg–Perthes disease are multiple epiphyseal dysplasias, pseudoachondroplasia, and spondyloepiphyseal dysplasia congenita and tarda [191]. Of these it is the multiple epiphyseal dysplasia diagnosis which can be the most difficult to make. The most relevant features in the differential diagnosis are: the size, shape, texture, and density of the capital femoral epiphyses; the appearance of the metaphyses; and the shape and texture of the acetabulum. In bilateral Legg–Perthes disease, present in about 15 % of patients, a most striking distinguishing feature of the capital femoral secondary ossification centers is the asymmetrical involvement. The hips in Legg–Perthes disease never appear to be equally affected by the disease process simultaneously; the fragmentation is characterized by irregular areas of variable density; there are often cystic changes in the metaphyses; and the acetabulum is almost always normal in particular in the early phases. The diagnosis always becomes evident with time since Legg–Perthes disease improves with healing of the secondary ossification center to a uniform appearance while in the skeletal dysplasias the irregular radiographic appearance persists longer. In multiple epiphyseal dysplasias on the other hand the capital femoral epiphyses are initially almost always of homogeneous texture and symmetrically affected. In more than one-half of the patients they are late in appearing. They are initially of the normal round shape but subsequently most become flat and appear to arise from multiple centers although the fragmentation tends to be characterized by uniformly dense bone. There are no cystic changes in the metaphysis and the acetabulum is often shallow but sometimes normal. At a later stage there is also delayed formation of the secondary centers of the greater trochanter in MED.

In SED tarda the appearance is almost indistinguishable from MED although the femoral capital epiphysis has a greater tendency to a low, flattened crescent-like shape. These patients tend to present clinically for diagnosis around 10 years of age so earlier findings are often not defined. In SED congenita the disorganization of the hip is usually marked with gross irregularity of the bony pelvis, poorly formed acetabulae, delayed appearance of the secondary

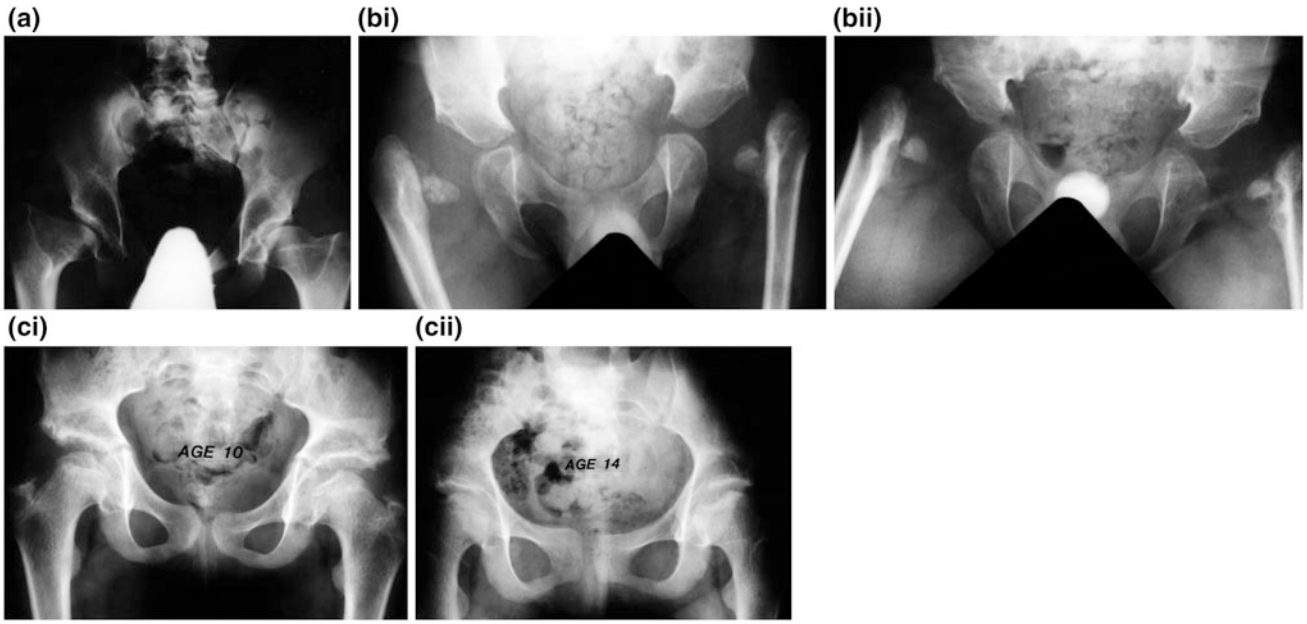


Fig. 3.15 Abnormalities of the hip are common in many of the skeletal dysplasias. **a** Acetabular dysplasia develops in many of the skeletal dysplasias, usually in relation to underdevelopment or subluxation of the femoral head. This patient had a spondyloepiphyseal dysplasia. Note the severe acetabular dysplasia with the coxa vara deformity on the *right*. **b** Coxa vara is commonly associated with many of the skeletal dysplasias. It is present in virtually all instances of SED congenita. Bilateral involvement is seen in anteroposterior (**i**) and limited abduction frog-lateral (**ii**) views. The femoral necks are short and the femoral heads are oval and located in the acetabula but there is markedly delayed formation of the femoral head secondary ossification centers. **c** Development of a misshapened femoral head is common in skeletal dysplasias such as multiple epiphyseal dysplasia. The femoral heads are spherical in the neonatal period. **i**, **ii** Hip radiographs show improvement of the acetabular dysplasia following bilateral innominate osteotomies but continuing femoral head deformation from age 10 years to age 14 years

ossification center, and delayed closure of the triradiate cartilage. Coxa vara is frequently seen. In general there should be no difficulty in the differentiation of SED congenita from other disorders. Pseudoachondroplasia also presents generally with severe abnormalities in pelvis and hip; the triradiate cartilage is strikingly wider than normal and the acetabulum poorly formed. The capital femoral epiphysis appears late and is small and irregular with marked delay in maturation. The metaphyses usually show medial beaking. The major differential diagnosis for Legg–Perthes disease is with MED, with each of the other deformities showing characteristics which should not be confused. In summary, the characteristic of bilateral Legg–Perthes disease is its asymmetry of involvement and its changing nature over a 1- to 3-year period whereas with the inherited dysplasias there is no evidence of a relatively rapid worsening phase with subsequent improvement. In the generalized skeletal dysplasias the capital femoral epiphyses invariably show symmetrical homogeneous involvement while maturation may be severely retarded and structurally abnormal. The following specific hip abnormalities should be assessed.

3.10.8.2 Congenital Hip Dysplasia

Congenital hip dysplasia does occur in the skeletal dysplasias although there has been no specific increased incidence defined in any of the various syndromes. In some instances the dislocation is of teratologic appearance but in others the hips are dislocatable and thus relocatable at birth and treatment is the same as that used in idiopathic developmental dysplasia of the hip. Closed or conservative treatment, however, is sometimes ineffective and there is an increased need for open reduction with or without pelvic and femoral osteotomies.

3.10.8.3 Acetabular Dysplasia

Acetabular dysplasia is quite common in many of the skeletal dysplasias (Fig. 3.15a). In MED, virtually all patients have hip involvement, even in those mild forms where all other joints are normal or close to normal and skeletal stature is also in the low normal range. There is an understandable tendency to consider treating the acetabular dysplasia surgically usually in the middle of the first decade with an innominate or Dega osteotomy. No data is available to assess the overall effectiveness of this intervention. There is often lack of femoral head sphericity in association with the acetabular dysplasia owing to a primary modeling defect of the epiphyseal region such that premature osteoarthritis would be expected even in the presence of a normal shape to the acetabulum. An acetabular redirection procedure can be recommended in the sense it would at least minimize hip deformity.

3.10.8.4 Coxa Vara

Congenital or developmental coxa vara characterizes many of the skeletal dysplasias (Fig. 3.15b). It is particularly common in spondyloepiphyseal dysplasia congenita. Two types of coxa vara are seen. In some, there is the characteristic non-united segment of bone at the inferior medial surface of the neck and in others the growth plate between the head and neck region is present but only minimally to non-functional such that trochanteric overgrowth soon occurs. In the former type there is frequently a delay in the appearance of the proximal femoral ossification center and indeed this may not be present within the first decade of life. The shape and position of the femoral head must be assessed by means of other than plain radiographs such as arthrography or magnetic resonance imaging. Treatment involves a proximal femoral valgus osteotomy. Delayed appearance of proximal femoral capital ossification centers is marked in spondyloepiphyseal dysplasia and Kniest dysplasia. The shape of the femoral head and its relation to the acetabulum can be defined by arthrography but MR imaging is now more commonly used.

3.10.8.5 Hip Contractures

Hip contractures can characterize some patients with underlying bone and cartilage hip joint abnormalities in the skeletal dysplasias. Flexion contractures, which are particularly common in diastrophic dysplasia, can be treated with soft tissue releases although a proximal femoral extension osteotomy may be needed. Abduction or adduction contractures are also seen and are best treated with soft tissue releases.

3.10.8.6 Lack of Sphericity of Femoral Head

This is a common associated finding in the skeletal dysplasias as the epiphyseal model is misshapen leading to lack of congruity of adjacent articular surfaces and early osteoarthritic symptoms (Fig. 3.15c). In some disorders such as diastrophic dysplasia stiffness and joint pain can render walking difficult to impossible as early as the start of the second decade of life. Joint stiffness also characterizes Kniest dysplasias. There is no current therapy for the misshapen epiphysis other than perhaps a varus or valgus osteotomy if there is one segment of the head which appears to relate well to the acetabulum as determined by arthrography and X-rays with the femoral head in varying positions. Misshapen epiphyses develop as early as the second decade in multiple epiphyseal dysplasias and pseudoachondroplasia.

Stelling has summarized hip disorders in the skeletal dysplasias (Table 3.11) [192].

3.10.9 Knee Abnormalities

3.10.9.1 Bowing or Knock-Knee Deformities (Genu Varum/Genu Valgum)

Multiplanar deformities. Either bowing (genu varum) or knock-knee (genu valgum) deformities can be seen in the skeletal dysplasias (Fig. 3.16a). Bowing is more common and is often seen in achondroplasia, metaphyseal dysplasia (Schmid type), spondylometaphyseal dysplasia, and dyschondrosteosis. Genu valgum is common in Morquio's disease and hereditary multiple exostoses. Surgical treatment for bowing has involved excision of the head of the fibula although there are no definitive results published for this procedure. The more common approach is a proximal tibial and fibular osteotomy to correct the deformity. On occasion, asymmetric stapling of a proximal tibial growth plate can be performed. Multiplanar and often asymmetric deformity characterizes some skeletal dysplasias such as pseudoachondroplasia (Fig. 3.16b). Osteotomy might thus be required to correct, for example, a varus–flexion–internal rotation deformity centered at the proximal tibial metaphysis.

3.10.9.2 Patellar Dislocation (Lateral)

Lateral patellar dislocation is relatively frequent in the skeletal dysplasias primarily because of shaping abnormalities of the distal femoral condyles (Fig. 3.16c). It is fairly common in diastrophic dysplasia, multiple epiphyseal dysplasias, and spondyloepiphyseal dysplasia. Treatment is conservative or surgical as dictated by circumstances.

3.10.9.3 Exostoses

Exostoses are extremely common in the knee region in hereditary multiple exostoses owing to the fact that most of the growth in the lower extremity occurs in this area. Management is by excision as warranted.

3.10.9.4 Instability

Instability of the knee joint is seen, usually in the more severely deforming dysplasias involving the epiphyses such as diastrophic dysplasia and multiple epiphyseal dysplasias. It is not primarily ligamentous laxity that is causative, although that is one aspect, but rather asymmetric malformation of the epiphyses affecting one condyle which can be smaller, more angled, or flatter than normal leading to an imperfect articulation. Great care is required in the skeletal dysplasias in determining the site of angular deformity. Figure 3.16e indicates the possible sites of deformation.

Table 3.11 Hip disorders in skeletal dysplasia

	Proximal femoral capital epiphyseal abnormalities	Acetabular abnormalities	Coxa vara	Coxa valga	Dislocation	Contractures	Early	Late	Head acetabular incongruity	Genetics
Spondyloepiphyseal dysplasia	Moderate to severe	Protrusion large and irregular	Frequent	+ −	+ −	+ −	No	Yes	Severe	X-linked tarda A D cong
Multiple epiphyseal dysplasia	Mild to severe	Mild irregular	+ −	+ −	+ −	Yes	No	Yes	Yes	A D
Chondrodystrophia calcificans congenita	Stippling early irregular late	Mild irregular	+ −	+ −	+ −	Yes	No	Yes	Yes	A R, also A D type
Dysplasia epiphysealis Hemimelica (of hip)	epiphyseal osteochondroma	No	No	No	No	+ −	No	+ −	Yes	
Diastrophic dysplasia	Severe	Dysplastic	+ −	No	Frequent	Severe	No	Yes	Severe	A R
Achondroplasia	No	No	No, short neck	No	No	No	No	No	No	A D most mutation
Hypochondroplasia	No	No	No	No	No	No	No	No	No	A D
Hurlers	Mild to moderate	Mild, usually good shelf	Rare	Yes	Rare	Yes	No	Yes	Yes	A R
Hunters	Mild to moderate	Mild, usually good shelf	Rare	Yes	Rare	Yes	No	Yes	Yes	X-linked recess
Polydystrophy dwarf (Lamy-Marateaux)	Mild to moderate	Mild, usually good shelf	Rare	Yes	Rare	Yes	No	Yes	Yes	A R
Morquio	Enlarged–irregular severe	Gross enlargement severe	No	+ −	Yes	Yes	No	Yes	Yes	A R
Ellis Van Creveld	Early ossification	No	No	No	No	No	Yes	No	No	A R
Thoracic pelvic phalangeal dystrophy	Early ossification	Oblique superior margin in infant	No	No	No	No	Yes	No	No	A R
Mesomelic dwarf Langer	No	No	No, short neck	No	No	No	No	No	No	A R
Mesomelic dwarf Lamy-Marateaux	No	No	No	No	No	No	No	No	No	A D
Cartilage hair hypoplasia	No	No	No	No	No	No	No	No	No	A R
Metaphyseal chondrodysplasia (metaphyseal dysostosis) (Jansen type) (Schmid type)	No No	No No	+ − Yes	No No	+ − No	Yes No	No No	No No	No No	A D A D
Osteodysplasty (Melnick-Needles)	No	Rare	No	Yes	No	No	No	No	Rare	Uncertain

(continued)

Table 3.11 (continued)

	Proximal femoral capital epiphyseal abnormalities	Acetabular abnormalities	Coxa vara	Coxa valga	Dislocation	Contractures	Early	Late	Head acetabular incongruity	Genetics
Enchondromatosis	No	No	+ −	No	No	No	No	No	No	No genetic basis
Dyschondrosteosis	No	No	No	No	No	No	No	No	No	A D
Hypophostasia	No	No	+ −	No	No	No	No	No	No	A R A R sev
Osteopetrosis	No	No	+ −	No	No	No	No	No	No	A D
Craniometaphyseal Dysplasia (Pyles)	No	No	No	No	No	No	No	No	No	A R
Multiple exostoses	No	No	No	No	No	No	No	No	No	A D
Osteogenesis imperfecta	No	Protrusion	+ −	No	+ −	No	No	No	+ −	A D
Pyknodysostosis	No	No	+ −	No	No	No	No	No	No	A R
Cleidocranial dysplasia (cleidocranial dysostosis)	No	No	50 %	Rare	No	+ −	No	No	No	A D

Modified from Stelling (Ref. [192])

3.10.9.5 Contractures

Flexion contractures are common in particular in diastrophic dysplasia and respond best to distal femoral extension osteotomies rather than to posterior soft tissue releases.

3.10.10 Ankle Abnormalities

The commonest deformity of the ankle in the skeletal dysplasias is a valgus tilt with a pronated flat foot deformity owing to relative shortness of the distal fibula. Treatment is generally by a distal tibial–fibular osteotomy near skeletal maturity. On occasion, hemiepiphyseal stapling of the distal medial tibia plays a role. Varus tilt of the ankle occurs less frequently, usually with relative overgrowth of the distal fibula. Distal prolongation of the fibula is an important diagnostic feature in hypochondroplasia and is also seen in some metaphyseal dysplasias.

3.10.11 Foot Abnormalities

Foot deformities are common in many skeletal dysplasia syndromes, in particular with diastrophic dysplasia and spondyloepiphyseal dysplasia. The deformities are usually quite rigid being connected with cartilage/bone model defects rather than ligamentous or perinatal positioning irregularities. Metatarsus adductus is frequently seen with management varying from observation, to serial casting if rigid and sometimes progressing to multiple metatarsal osteotomies. Clubfeet are treated in the usual fashion beginning with serial casting but frequently, as in diastrophic dysplasia, requiring soft tissue posteromedial releases and often additional calcaneal and mid-tarsal osteotomies or triple arthrodesis toward skeletal maturity.

Toe deformities such as hallux valgus and hammer toes are also seen in these disorders. Management is by surgical correction if symptomatic. Many of the dysmorphic syndromes are accompanied by structural tarsal, metatarsal, and phalangeal anomalies, relatively few of which need surgical correction. Abnormalities include various tarsal coalitions, metatarsal widening with or without fusions, and syndactyly.

Abnormalities of the lower extremities are summarized in Tables 3.2, 3.8 and 3.11.

3.10.12 Abnormalities of the Upper Extremities

Patients with a skeletal dysplasia often lack full extension of the elbow by 10° or 15°—a limitation that is generally non-progressive and of no clinical importance but is helpful as a clinical diagnostic sign. The humerus is the site of significant shortening, called rhizomelic shortening, in many skeletal dysplasias including achondroplasia. Significant angular deformities of the humerus are rare however. The radial head can be subluxed or dislocated and limit pronation and supination in some skeletal dysplasias where ulnar growth is more limited than radial growth. The radius compensates by developing a curvature of the shaft but if this is insufficient the head will displace. The commonest disorder where this occurs is hereditary multiple exostosis. Closed or open reduction during the growing years is usually not indicated. Excision of the radial head in adulthood is occasionally required to alleviate discomfort. At the wrist, a shortened, malformed, and dorsally dislocated distal ulna associated with dorsilateral bowing of the radius (Madelung's deformity) can decrease the range of motion and cause ulnar deviation. These deformities are common in hereditary multiple exostosis and dyschondrosteosis and their management is discussed in the next section. Short metacarpals and phalanges and contractures of the interphalangeal joints rarely warrant intervention; the former lead to relatively little disability, and the latter cannot currently be repaired effectively.

3.11 Limb Lengthening

Limb lengthening is a potentially valuable intervention for short stature dysplasia patients but has not gained universal patient and surgeon acceptance. With technical improvements however better results are achieved. Both the circular Ilizarov and monolateral Wagner–Orthofix type lengthenings have been reported [80, 193]. Those disorders most amenable to lengthening have normal articular cartilage and normal joints, such as achondroplasia and the metaphyseal dysplasias. While lengthenings can be done in those with articular surface irregularity, contractures, and instability the amount of lengthening achievable is usually less and the complication rate high, especially in relation to joint problems such as stiffness and subluxation. In addition, bilateral procedures are required. In the lower extremities this means bilateral femoral and tibial lengthenings. In those patients and surgeons desiring relatively massive increases in length, two and even three separate lengthenings have been done. Some of the best functional results occur with humeral lengthenings since upper extremity length increases of relatively shorter amounts provide great help in personal care and independent living capabilities. The procedures used are outlined in the chapter on lower extremity length discrepancies.

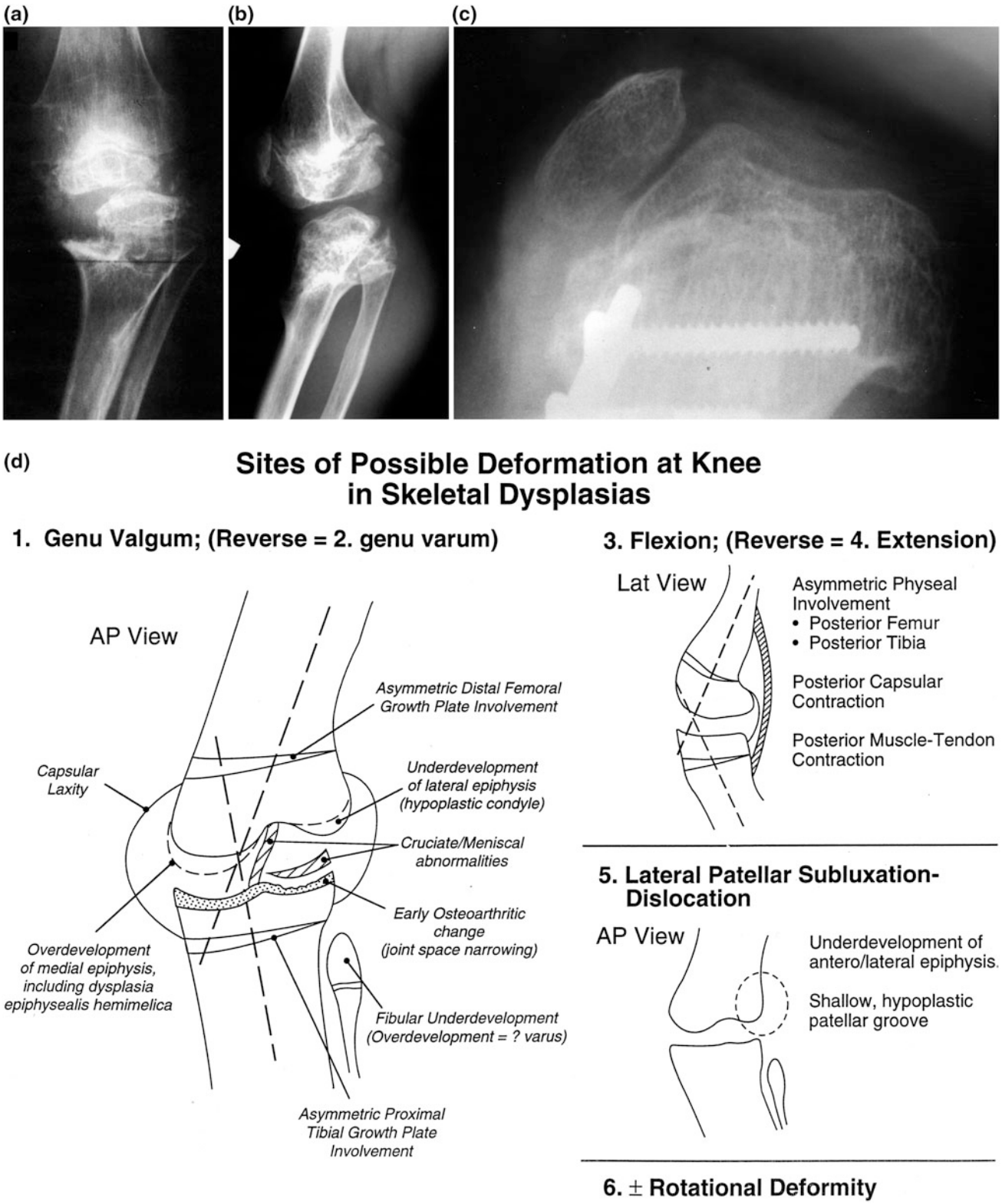


Fig. 3.16 Knee deformities are common in the skeletal dysplasias. These can involve varus, valgus, flexion, extension, and rotational deformities. **a** Anteroposterior knee radiograph demonstrates bowing. It is important to determine whether the bowing has its origin from ligamentous laxity, from contours of the joint, from the proximal medial tibial physeal region, or more rarely from the distal femur. **b** Lateral knee radiograph of patient with pseudoachondroplasia shows a multiplanar deformity. **c** Lateral subluxation or complete dislocation of the patella is seen in many skeletal dysplasias. This can be due to ligamentous laxity but is more commonly associated with asymmetric underdevelopment of the lateral condylar region of the epiphysis leading to a poorly formed patellar groove. **d** Possible sites of knee deformation in skeletal dysplasia syndromes are illustrated

3.12 Review of Specific Skeletal Dysplasias: Pathobiology, Clinical and Radiographic Characteristics, Orthopedic Management

Average heights reached in adulthood are summarized in Table 3.12 [39].

3.12.1 Achondroplasia

3.12.1.1 Overview

Achondroplasia is the commonest of the skeletal dysplasias. It has been recognized as a specific disorder since Parrot introduced the term in 1878, described living patients with the disorder, and theorized that the disorder was a "dystrophie du cartilage primordial," a fundamental or developmental dystrophy of cartilage [1]. It is autosomal dominant with about 85 % of cases representing a new mutation. It shows full penetrance and full expressivity. Short stature is an invariable occurrence. The mean adult height in males was 130 cm (range 118–142 cm) and in 214 females was 125 cm (range 112–138 cm). The mean weight is 50 kg. Achondroplasia is a clear example of a short-limbed disproportionate dwarfism. The outstretched upper extremities, more affected than the trunk or axial skeleton, reach only to the hip region. The disorder is diagnosable at birth based on clinical and plain radiographic findings. Achondroplasia was the first genetic disorder noted in which an increased incidence of mutation was associated with advanced paternal age [194, 195]. The sporadic mutations were studied in 40 cases and in all 40 the achondroplasia mutation (G 1138 FGFR3) occurred on the

Table 3.12 Adult heights in a selected listing of skeletal dysplasias

Disorder	Inheritance	Adult height	Mean
Short-limb dwarfism			
Achondroplasia	AD	F: 112–138 cm	125 cm
		M 118–142 cm (42–56″)	130 cm
Hypochondroplasia	AD	132–147 cm (52–59″)	
Diastrophic Dwarfism	AR	86–122 cm (34–48″)	118
Pseudoachondroplasia	AD, AR	80–130 cm (32–51″)	118
Metaphyseal Chondrodysplasias			
McKusick type	AR	105–145 cm (41–57″)	
Schmid type	AD	130–160 cm (51–63″)	
Chondrodysplasia Punctata			
Condradi-Hünermann type	AD	130–160 cm (51–63″)	
Chondroectodermal Dysplasia	AR	106–153 cm (42–60″)	
Grebe Chondrodysplasia	AR	99–104 cm (39–41″)	
Acromesomelic Dysplasia	AR	97–123 cm (38–48″)	
Multiple Epiphyseal Dysplasia			
Fairbanks type	AD, AR	137–155 cm (54–61″)	
Pycnodysotosis	AR	130–150 cm (51–59″)	
Short-trunk dwarfism			
Spondyloepiphyseal Dysplasia Tarda	XLR, AD, AR	132–156 cm (52–61″)	
Spondyloepiphyseal Dysplasia Congenita	AD, AR	84–132 cm (33–52″)	115
Dyggve-Melchior-Clausen Dysplasia	AR	130–135 cm (51–53″)	
Kniest Dysplasia	AD	104–145 cm (41–57″)	
Storage disorders			
Mucopolysaccharidoses			
Hunter's syndrome (MPS II)	XLR	120–150 cm (47–59″)	
Morquio's syndrome (MPS IV)	AR	80–120 cm (32–47″)	

AD autosomal dominant; *AR* autosomal recessive; *XLR* X-linked recessive; *XLD* X-linked dominant

[a]*Derived from* Scott CI Jr (1988) Clinical Symposia, Ciba-Geigy 40:1–32 (Ref. [39]); Horton WA et al. (1982) Am J Dis Child 136:316–319 (Ref. [37]); and Horton WA et al. (1978) J Pediatr 9:435–438 (Ref. [38])

paternal chromosome [196]. This observation suggests that the mutations occur preferentially during spermatogenesis by DNA replication copy errors in the male germ line and not during oogenesis. The risk of recurrence in sporadic cases is less than 1 %. The mean paternal age was 35.9 years (n = 40) in this study and 34.4 ± 7.2 years (n = 348) in another.

3.12.1.2 Clinical and Radiographic Characteristics

Marie described the clinical features of the fully developed adolescent and adult achondroplastic individual in 1900 [197]. These characteristics include: dwarfism, relative increased head volume, marked shortening of the upper and lower extremities with conservation of normal length of the trunk (first form of disproportion), and proximal portions of the extremity more shortened than the distal portions leading to a rhizomelia with the humerus more involved than the radius and ulna and the femur more involved than the tibia and fibula (second form of disproportion). The craniofacial appearance was characterized by macrocephaly which in some instances was relative only since the head remained the same size as that of a normal person while in others the enlargement was so great that it raised the question of a hydrocephalus, the skull with frontal and parietal bossing and a face which was relatively normal with the exception of the nose which was shortened and flattened at its base. There was marked lumbar lordosis, small hands with virtually equal length of the second through fourth digits, the "trident" appearance with separation between the third and fourth fingers with the proximal phalanges in normal position but deviation of the middle and distal phalanges beginning at the proximal interphalangeal joint, bowing of the lower extremities centered at the knees, no major angular deformity of the upper extremities, relatively large epiphyseal regions with short straight diaphyses, and no specific deformations of the sternum, ribs, or clavicle [188, 189, 198–200]. Subsequent studies have confirmed the observations of Marie who was the first to describe the "trident" appearance of the hand and fingers (Fig. 3.17a).

The trunk height is normal at all ages, as determined by sitting height measurements. This was clearly documented by Nehme et al. in a study of 18 achondroplasia patients [201]. The sitting height in both males and females was within normal limits with the average just below the normal average at all ages. The extremity shortening is rhizomelic with arms (humeri) shorter than forearms and thighs (femurs) shorter than legs. The hands have a characteristic "trident" appearance with widened spaces between fingers, equal length of 2nd, 3rd, and 4th fingers and thickened digits. Many are hypotonic in the early months and this combined with a relatively large head and shortened extremities leads to mild motor delay.

There are many typical radiographic skeletal abnormalities. The long bones have shortened diaphyses, broad and flared metaphyses, and relatively enlarged and slightly irregular shaped epiphyses often (e.g., distal femur) with more sharply curved physes (Fig. 3.17b). The distal femoral physis has an inverted "V" shape into the metaphysis. Its secondary center tends to form close to the physis within the V-shaped notch. The femoral necks are short but in valgus position and the trochanters are prominent. The fibula and clavicle are less affected than the other long bones. The fibulae tend to be longer than normal both proximally at the knee and distally at the ankle. The 3rd ray of the hand is more shortened than the others with the 2nd, 3rd, and 4th rays being almost the same length. Hip and pelvic radiographs from the newborn period on are characterized by a horizontal acetabulum and small sciatic notch but hip malposition is extremely rare (Fig. 3.17c). The acetabular index approaches 0°. The major clinical deformity of the lower extremities involves a genu varum which is seen in most patients. In relatively few however is it sufficiently severe to warrant operative intervention. Since the children have developed with the varus deformity from the early weeks of life, the tendency for the knees to be symptomatic in terms of discomfort and later osteoarthritis is relatively small. If intervention is warranted for the bowing, three operative approaches have been used. The commonest is a proximal tibial and fibular valgus osteotomy. Once done the tendency to recurrence is extremely low. Hemiepiphyseodesis can be used to correct deformity. On occasion, the fibular head has been removed using the rationale that relative overgrowth of the fibula proximally predisposes to the varus deformity by limiting growth in the proximal tibia. No published series are available to show results of this intervention and it is not recommended [198]. Shirley and Ain refer to studies which conclude that fibular overgrowth does not correlate with genu varum [198]. The general approach is to favor the proximal tibial and fibular valgus osteotomy although relatively few interventions have been needed. Tibial torsion should also be addressed at the time of tibial osteotomy. External tibial torsion in achondroplasia is slightly less than normal but the limb is still externally rotated [198]. The mild deformities of the upper extremities rarely warrant intervention in the vast majority of patients. The lack of full elbow extension is rarely of clinical concern.

3.12.1.3 Morbidity and Mortality in Achondroplasia

The high incidence of achondroplasia has allowed for detailed studies from several centers concerning associated medical and neurologic problems. There is a considerable morbidity and occasional mortality with this disorder such that these patients must be followed closely from birth [202]. Possible problems include: stenosis of the foramen magnum and cervical spinal canal causing cervicomedullary

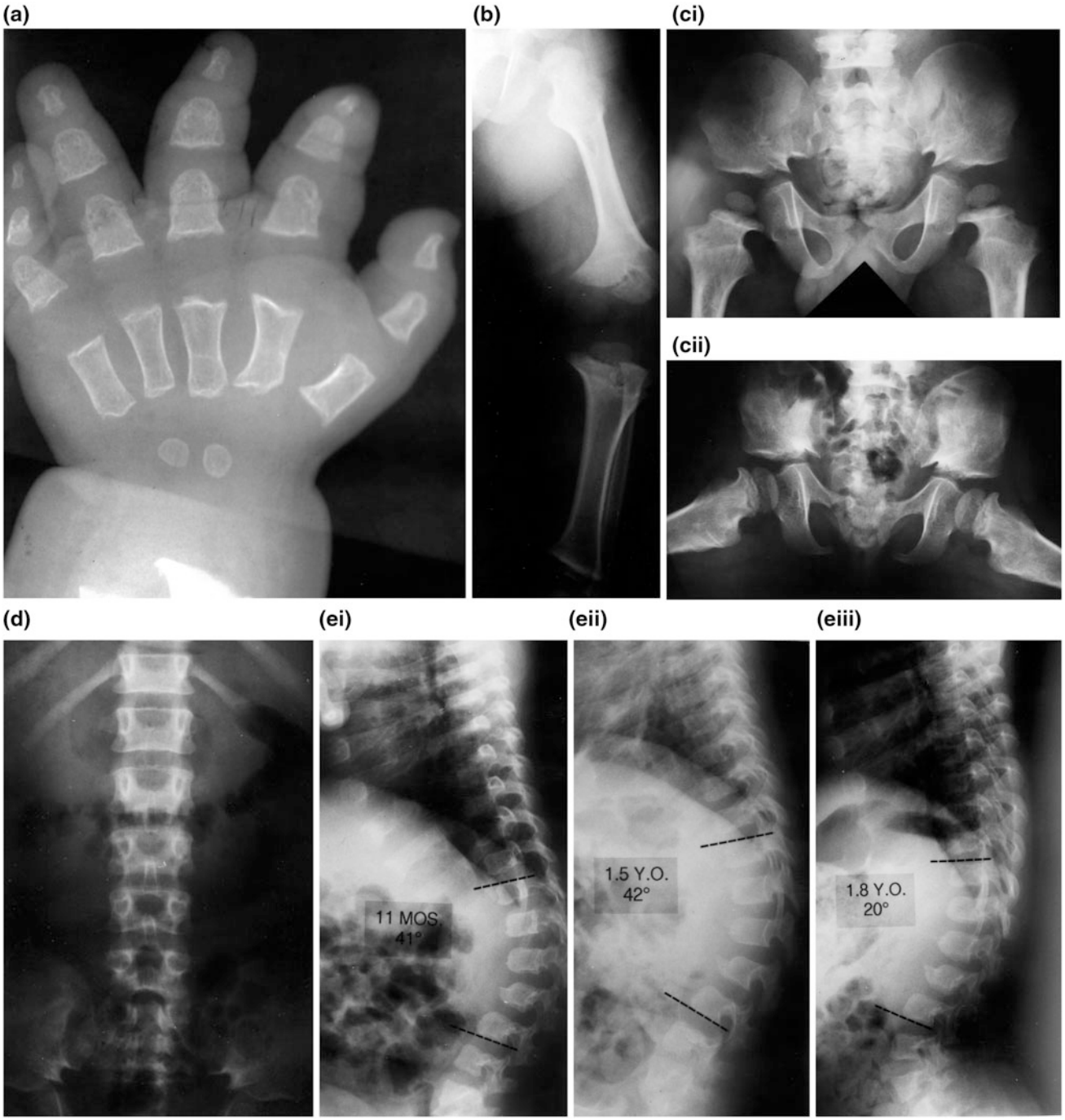


Fig. 3.17 Radiographic abnormalities in achondroplasia are shown. **a** Trident appearance of the hand in achondroplasia. There is a relatively shortened hand with equal length of the second through fourth digits and a characteristic separation between the third and fourth fingers with the proximal phalanges in normal position but separation of the middle and distal phalanges beginning at the proximal interphalangeal joint. **b** The long bones are characterized by shortened diaphyses, broad and flared metaphyses, and relatively enlarged and slightly irregular epiphyses with the distal femur showing a more sharply curved and inverted "V" physis. **c**(**i**, **ii**) Hip and pelvic radiographs of a patient with achondroplasia shows the horizontal acetabulae, flared metaphyses of the femoral neck, and the short sharp sciatic notch. **d** Anteroposterior lumbosacral radiograph shows the narrowed interpedicular distance of the *lower* lumbar and sacral vertebrae. **e**(**i–iii**) Thoraco-lumbar kyphosis is quite common in achondroplasia, in the first and second years of life. Lateral radiographs show the spontaneous correction of the kyphosis over a 4-year period. No treatment was used

compression with risk of death, central apnea, and neurological dysfunction including paraparesis; respiratory difficulty as a result of central apnea, a small ribcage, and upper airway obstruction; gross motor delay associated with macrocephaly, hypotonia, and joint laxity; frequent otitis media which may be accompanied by hearing loss and delay of speech; genu varum; hydrocephalus; and later onset neurological complaints owing to lumbar spinal stenosis.

A detailed review of 701 persons with achondroplasia by Hecht et al. showed an increased mortality ratio with the rate more than double that of the general population [203]. The increase in mortality was particularly apparent in early childhood. Sudden death accounted for excess deaths in those less than 4 years of age with brainstem compression identified as the cause in half of these. The central nervous system and respiratory causes accounted for half of the deaths in those from 5 to 24 years of age. In the older age groups severe disability resulting from marked spinal canal stenosis was noted. The problematic axial bony abnormalities associated with achondroplasia are stenosis of the foramen magnum and thoraco-lumbar spinal canal stenosis. The greatest threat to life occurred in the first 5 years of age and in particular during the first year with the problem being sudden death. Most of these were felt to be due to compression of the brainstem and/or upper cervical spinal cord owing to stenosis of the foramen magnum.

A detailed study by Hunter et al. of 193 patients from several centers reviewed complications of the disorder [204]. Otitis media had been reported in 90 % of all children by the age of 2 years with 80 % having undergone insertion of ear tubes by 10 years of age. Middle ear infection had contributed to speech delay in 20 % of children and to conductive hearing loss in 38 % of adults. Dental malocclusion owing to mid-face hypoplasia led to associated orthodontic problems. More serious respiratory problems can contribute to major illness in some achondroplastic patients. Tasker et al. separated infants presenting to the respiratory unit with achondroplasia into three problem groups [205]. The mildest were in group 1 with obstructive sleep apnea which responded well to nasal steroid therapy supplemented when necessary by removal of the adenoids and tonsils. Those in group 2 had sleep apnea plus hydrocephalus resulting from jugular foramen stenosis while the most severe group 3 children actually developed cor pulmonale in which three of five died. The final group of problems is neurologic ranging from sudden death or progressive paraparesis to milder lower extremity problems relating to weakness and fatigability [203, 206, 207]. Smallness of the foramen magnum as well as cervical canal spinal stenosis can lead to central apnea, hydrocephalus, and cervical spinal cord pressure.

3.12.1.4 Macrocephaly/Hydrocephalus in Achondroplasia

Although the head appears large in achondroplasia, most often this macrocephaly or megalencephaly is not indicative of a serious underlying problem. Hydrocephalus involving head enlargement with mild dilatation of the ventricles (ventriculomegaly) is a consistent finding in achondroplasia but is rarely symptomatic. It appears to be secondary to raised intracranial venous pressure due to back pressure which is hemodynamically significant from stenosis of the jugular foramen. The head growth curves are usually above the 97th percentile but parallel the normal slope for age. Synostosis of the skull seen in achondroplasia narrows and distorts the foramen magnum, which causes the hydrocephalus-like condition. Most patients with achondroplasia studied will show this phenomenon. There is however a great difference in neurosurgical centers as to whether or not this requires treatment by shunting. Although there are many reports of surgery the issue appears not to have been settled definitively. Many clinics seeing these patients observe only thus clearly feeling that hydrocephalus does not occur to a degree that requires shunting in most cases. Shunting is done only in symptomatic cases where increased intracranial pressure, increasing head size, and neurologic changes have been documented.

3.12.1.5 Cranio-Cervical Junction Abnormalities in Achondroplasia

Stenosis of the foramen magnum is an invariable finding in achondroplasia. CT studies of large numbers of patients from birth to skeletal maturity and beyond have established means and standard deviations in achondroplasia as well as comparisons with the normal population. Hecht et al. documented 157 normal individuals in relation to the size and shape of the foramen magnum including both transverse and sagittal measurements and compared them with measurements from 154 achondroplastic individuals [206]. The achondroplastic foramen magnum is small at birth and during the first year it has a severely impaired rate of growth especially in the transverse dimension. This diminished growth results not only from abnormal endochondral bone growth but also because of premature fusion of the synchondroses. The mean size of the adult achondroplastic foramen magnum is that of a nonachondroplastic individual at birth in the transverse dimension and in a 24-month-old child in the sagittal dimension. There was no detectable difference of statistical significance in achondroplastic patients who were clinically normal from those who were experiencing cervicomedullary compression syndromes although there was a tendency for those with narrower dimensions to have greater clinical problems. It would

appear that many if not all cases of achondroplasia suffering from sudden death usually in the first few years of life represent examples of cervicomedullary compression owing to tightness of the foramen magnum and adjacent upper cervical canal. Symptomatic patients have been helped by surgical decompression of the skull base although these procedures themselves have a considerable morbidity and there are no definitive standards indicating which patients should undergo surgery. The surgery involves posterior fossa decompression and laminectomy of the posterior body of C1. In a study of six patients by Ryken and Menezes symptoms warranting operative intervention included occipitocervical pain, ataxia, incontinence, apnea, and respiratory arrest [208]. Detailed studies involved plain radiographs with flexion and extension views, CT scanning, and MR imaging. Typical findings included marked foramen magnum stenosis, ventrolateral cervicomedullary junction compression secondary to central and paramesial basilar invagination, and dorsal cervicomedullary junction compression secondary to ligamentous hypertrophy and invagination of the posterior arch of the atlas. Surgical decompression is not warranted based on the presence of foramen magnum stenosis alone since essentially all patients with achondroplasia have that finding and only 5–10 % develop symptoms. Careful examinationis essential for symptoms which include quadriparesis, paraparesis, dysphasia, poor head control which fails to improve with time, hypotonia, and delayed motor developmental milestones. Respiratory difficulties can include apnea spells and cyanosis. Other problems include occipitocervical pain, myelopathy with ataxia, incontinence, spasticity, and hyperreflexia.

Since the craniocervical junctional stenosis is a potentially lethal problem in a subset of young infants with achondroplasia, prospective studies have been helpful. Pauli et al. evaluated and followed an unselected consecutive series of infants with achondroplasia to assess the development of problems [209]. Of 53 prospectively studied infants 5 were judged to have sufficient craniocervical junction compression to require cervical decompression, a rate of 9 %. All children showed subsequent marked improvement of neurological function. Findings of high cervicomyelopathy, the most frequently seen clinical abnormalities, included lower limb hyperreflexia or clonus on clinical exam, central hypopnea demonstrated by polysomnography, and foramen magnum measurements below the achondroplastic mean. Hecht et al. showed that the excess risk of death in infants with achondroplasia may approach 7.5 % largely because of cervical cord compression [203]. In a larger group studied there were 10 (13.3 %) infants judged to be in need of suboccipital decompressive surgery including 5 (9.4 %) of those studied prospectively. Surgery in the prospective group was at a mean age of 10.7 months (8.3–12.8 months) while in the overall group the age was 24 months (range 7.6–52 months). In every instance at surgery marked abnormalities of the upper cervical cord were demonstrated involving indentation, deformation, marked compression, and ribboning of the cord. In two instances fibrous constriction bands were also identified. Pauli et al. also stressed the importance of finding multiple clinical and radiographic irregularities prior to surgery rather than intervening based on radiographic abnormalities alone. Infants who underwent decompressive surgery had multiple features of cervical myelopathy including hypotonia, weakness, asymmetric motor signs, and hyperreflexia. The most important three variables were considered to be hyperreflexia or clonus, foramen magnum measurements below the mean for achondroplastic patients, and central hypopnea.

The mortality rate in achondroplasia is becoming known although there is considerable variability in separate studies. Rimoin indicated that mortality was less in his group than in those of other centers, even though his center was less aggressive in performing occipital–cervical compression [207]. Mortality rate estimates in achondroplasia have ranged from 2.7 to 7.5 % with almost all deaths in the first few years of life and considered to be due to the cranial–cervical stenosis. Rimoin states however that even young patients with neurologic abnormalities such as hypotonia, clonus, and hyperreflexia will eventually attain normal motor development and become normal neurologically if left alone. Since the average age of the five patients operated on by Pauli was 10.7 months the implication is clear that some of these might have gone on to normal development if left unoperated. Rimoin felt that the two MRI features most indicative of the need for surgery are “a lack of CSF flow both anteriorly and posteriorly and intracord lesions as indicated by abnormal cord signal on T-2 weighted imaging.” He felt that those patients with decreased space around the cord at the cervicomedullary junction, occipital bone impingement on the posterior cord, and even lack of CSF flow posteriorly developed normally with no neurologic sequelae if left alone. Although the posterior decompressive surgery can be done safely Rimoin indicated that there were a considerable number of postoperative problems in historical series which could not be overlooked. While surgery was on occasion needed his feeling was that only progressive worsening of neurological symptoms to a “severe” stage warranted the intervention especially those who were very floppy with significant truncal and limb hypotonia, significant apnea, or evidence on MRI of a total lack of CSF flow anteriorly and posteriorly and/or intracord lesions on T-2 wave imaging.

3.12.1.6 Developmental Milestones in Achondroplasia

The achondroplastic patient must be followed carefully in terms of medical and neurologic development in the early

months and years of life. The Committee on Genetics of the American Academy of Pediatrics has published supervision guidelines for children with achondroplasia [210]. Unexpected infant death occurs in less than 3 % of those affected and usually only in the most severe cases. Although motor development is somewhat slow it should progressively improve. Many achondroplastic infants do not sit without support until 9–12 months of age nor ambulate until a period of time between 1 and ½ and 2 years of age. Rimoin indicates that almost all achondroplastic children will gain normal strength and muscle tone and catch up on motor skills by 2–3 years of age.

3.12.1.7 Spinal Abnormalities in Achondroplasia

Cervico-thoracic spinal stenosis. Although stenosis of the foramen magnum and lower lumbar spinal canal is recognized to occur in all achondroplastic patients, there is considerable evidence that cervical and thoracic stenosis is also present. Clinical compression sequelae are infrequent at these levels compared to the others but they do occur. There are reports of surgical decompression in achondroplasia at multiple levels for neurologic cord/root compression. Uematsu et al. reported on complete craniospinal posterior bony decompression (brainstem to cauda equina) in seven patients [211]. Adult age group lumbosacral decompression-laminectomies are well known. An extensive thoracolumbar decompression has been reported based on the clinical areas of symptoms and signs in a patient as young as 7 months. In that case, cord compression was directly due to a thickened layer of fibrous tissue such that laminectomy with resection of the constricting soft tissue was needed.

Narrowed interpedicular distance, L1 to S1. Interpedicular narrowing in achondroplasia from L1 to S1 represents a spinal stenosis which can predispose to relatively rapidly developing neurologic symptoms in adult life should the patient have a herniated or bulging disk or an arthritic spine. The progressively narrowed interpedicular distance can be seen on the anteroposterior spine film even in the newborn. In the normal the interpedicular distance widens with each progressively lower vertebra from L1 to S1 while in achondroplasia the distance becomes progressively narrower in particular from L3 to S1 (Fig. 3.10a). On the lateral lumbar film in achondroplasia the posterior border of the vertebral bodies is concave and the pedicles are short (Fig. 3.10b). Caffey has estimated that the achondroplastic pedicles can be as short as one-half the normal length [188]. This lumbar spinal stenosis is infrequently a problem in the childhood or adolescent age group but tends to lead to symptoms when the individuals are in their early to mid-adult years. The sacrum articulates with the fifth lumbar vertebrae lower than in the normal in relation to the adjacent iliac bones.

Lumbar lordosis. Associated with the spinal stenosis is a lumbar lordosis present also from the early years of life. The lordosis is structural to a great extent. The lumbosacral angle is increased in the newborn and the plane of the sacrum becomes nearly horizontal after walking. This is not progressive. Lumbar lordosis is almost an invariable occurrence, associated with the lumbar spinal stenosis. Treatment either primary or secondary has not been effective or particularly necessary. Efforts have been made to treat this with an anti-lordotic spinal orthosis. Although the brace has been used in many centers, no report of its effectiveness has appeared. The brace would have to be worn several hours per day for several years to have any chance for a definitive effect on bone development.

Spinal Stenosis. Lutter and Langer studied neurologic symptoms in achondroplastic dwarfs severe enough to require surgical treatment [212]. Problems were due to distal neurological deficits with 27 cases of the cauda equina syndrome, impending paraplegia or actual paraplegia. The average age of onset of symptoms in 14 patients was 38 years. All were adults ranging from 23 to 68 years of age. The space for the neural elements already limited by the spinal stenosis with shortened pedicles and a narrowed interpedicular distance was further reduced by a combination of herniation of the intervertebral disk, degenerative arthritis with the development of osteophytes, and anterior wedging of 1 or more vertebral bodies concentrated from T11 to L2. The small size of the spinal canal however was the principal cause of the neurologic problems. In general there was a progressive slow onset of the disorder beginning with discomfort and later altered sensations and motor and sensory deficits. Intermittent claudication with pain in the back and limbs was noted frequently. Only rarely was a formal nerve compression syndrome or acute paraparesis seen. Kyphosis was commonly associated with spinal cord and nerve root damage owing to increased mechanical compression.

Approximately one-fourth of all patients with achondroplasia will require surgery for spinal stenosis. Laminectomy alone is usually not sufficient for decompression with lateral nerve root releases also needed. Post-laminectomy kyphosis appears not to occur in the adult but is almost invariably seen in the immature patient, such that posterior spinal fusion at time of initial surgery is recommended for laminectomy of five levels or more [213].

Lutter et al. have documented the diminution in the size of the spinal canal [189]. Postmortem studies documented a 39 % decrease in the transverse area of the first lumbar level and a 27 % decrease at the fifth compared to normal controls.

Thoraco-lumbar kyphosis. Another concern in the developing spine relates to the thoraco-lumbar kyphosis which is seen frequently in individuals in the first and second year of life (Fig. 3.17d). There is a marked tendency for this kyphosis to improve spontaneously as the individuals begin

standing on their own and walking at age 12–18 months. Kopits reported the frequency of kyphosis in achondroplasia as 87 % from age 1 to 2 years, 39 % from age 2 to 5 years, and 11 % from age 5 to 10 years [214]. Radiographs may show a slight decrease in the height of the anterior vertebral bodies at the kyphotic site on lateral views but this also tends to self-correct. In those relatively few patients in whom the thoracolumbar kyphosis persists, neurologic complications tend to occur earlier and be more marked owing to the associated spinal stenosis. An effective management plan is to use a spinal orthosis if the kyphosis develops a fixed component >30° on prone lateral radiographs or evidence of substantial anterior vertebral body wedging [198]. Lutter et al. studied 25 patients with achondroplasia who had reached a minimum of 5 years of age and in 22 of these standing lateral radiographs showed 15 having a thoracolumbar kyphosis associated with one or more hypoplastic or wedged vertebral bodies [189]. The kyphosis came first with subsequent maldevelopment of the bodies secondary. On occasion, the kyphosis was marked with five patients showing deformity from 100° to 132°. Surgical treatment has become better defined. Surgery for kyphosis is done at the onset of neurologic compromise, or for kyphosis >50° because of risk of progression. Pedicle screw placement has minimized the need for anterior approaches. Ain and Browne reported on 12 patients (4–21 years of age, mean of 12 years). Pedicle screws at every level with posterior fusion are favored with corpectomy for cord impingement if needed and anterior release/fusion less necessary with relatively early intervention [198].

Scoliotic deformity. Spinal alignment was studied in 94 achondroplastic patients 15 years of age or older with 53 from a series of Langer and 41 from a series of Bailey [215]. Scoliosis was centered at the thoracolumbar junction and into the lumbar region. It was defined as mild, less than 20°, in 25 patients and moderate 20°–45° in 7. There were no severe curves. Kyphoscoliosis was not as common with four mild deformities, one moderate deformity, and six with moderate and localized scoliosis in whom however the kyphosis was either moderate to severe degree. There were 22 patients with kyphosis 8 of which were mild, 8 moderate, and 6 severe. The greatest amount of wedging was at the T12 or L1 vertebra with some adjacent vertebrae also slightly wedged anteriorly. On occasion, the kyphosis was quite localized with a severe gibbus involving 1–3 vertebrae.

3.12.1.8 Other Orthopaedic Aspects in Achondroplasia

One of the most detailed studies of the orthopaedic aspects of achondroplasia was done by Bailey who reviewed 63 patients studied clinically and 87 studied radiographically [215]. There were a large number of achondroplastic patients in whom lower extremity pain and weakness were due to an excessive number of discogenic problems in relation to the lumbar spinal stenosis. Bailey felt that serious neurological difficulties would be seen in slightly more than 10 % of patients owing almost exclusively to the spinal canal stenosis. Bilateral hip flexion contractures of mild to moderate extent were noted in most patients; the extent documented in children from 0 to 12 years of age was an average of 12.5°, 13–21 years of age, 23.5°, and adults over 21 years of age, 33°. Patellar subluxation or dislocation was not a problem but the majority of patients had a genu varum deformity. Surgery was rarely required for these deviations from the norm.

There were no instances of coxa vara while coxa valga was quite constant being present in almost all patients with an average measurement of 162°. The femoral head was well located in the acetabulum however as the neck was short. There was no tendency to arthritic changes in the joints in adulthood although arthrosis was present in cervical and lumbar vertebra. Although hip contractures were documented they rarely appeared to be of clinical significance to the patient and surgical intervention was not reported. The skeletal features of the spine predisposing to premature neurologic problems related to the occurrence of a herniated nucleus pulposus, exaggerated lumbar lordosis, narrowed spinal canal, articular process arthritis with osteophyte formation, a recessed vertebral body, slight malalignment of the vertebral column, and possibly constriction of the formen magnum. The commonest reason for orthopedic treatment in achondroplasia related to the bow leg or genu varum deformity. Braces are of no benefit and even if attempted are poorly tolerated. The failure to observe adult onset arthritis even with the bow leg deformity mandates caution in treating the varus in childhood unless it is symptomatic.

Kopits reviewed 158 patients with achondroplasia and found no cases of odontoid hypoplasia or congenital hip dysplasia and only one case of scoliosis of 40° [179]. Osteoarthritis of the hip or knee was seen only occasionally in spite of the considerable bowleg deformity in several patients.

3.12.2 Hypochondroplasia

Hypochondroplasia is a distinct clinical disorder with similarities to achondroplasia although it is much milder and more variable. It is autosomal dominant with a mild rhizomelic pattern. At a molecular level it is part of the FGFR3 gene abnormality family which includes thanatophoric dysplasia and achondroplasia [103, 216]. It is differentiated from achondroplasia by a lack of craniofacial involvement with a normal appearing nose, relatively greater height, and milder features in the pelvis and spine [150, 217, 218]. Radiographs of skull, hands, and feet are normal. The hands

may be short but there is no trident configuration. There is a lower than normal articulation of the sacrum on the iliac bones. Hydrocephalus and spinal stenosis syndromes in childhood or adult years have not been features. In the spine, changes are limited to the lumbar vertebrae. The interpedicular distance does not widen from L1 to S1 tending to remain the same without the distal narrowing seen in achondroplasia. The vertebral canal is also narrowed in the lateral view with a concave shape to the posterior borders of the lumbar vertebrae since the pedicles are somewhat shorter than normal. Mild lumbar lordosis is present. The fibula is relatively long leading to altered relations at both knee and ankle. The distal fibula tends to be longer than normal with some varus tilt to the ankle and the proximal fibula is also longer reaching in some to the mid-tibial epiphyseal region. Bowing at the knee is infrequent. The elbows lack full extension and the fingertips do not reach the mid-thigh region. The ulna tends to be somewhat shortened distally although the styloid process is longer than normal. The femoral neck is shortened but there is no coxa vara. The pelvis is virtually normal, the acetabulae are not horizontal, and there is only slight reduction in size of the sciatic notch. Bowing of the radius and short broad long bones especially in the metaphyseal regions are seen. Muscle insertion regions of the deltoid at the proximal humerus are prominent. Deformities requiring orthopedic management and neurologic sequelae of the mild structural spine abnormalities are virtually never seen. Adult height ranges from 127 to 152 cm.

3.12.3 Multiple Epiphyseal Dysplasias

In multiple epiphyseal dysplasias the changes in the long bones are limited to the epiphyses and any spinal involvement is absent or sufficiently mild that it does not clinically affect structure or height of the vertebral bodies. The main determinants of an MED diagnosis involve epiphyseal irregularities on plain radiographs (Fig. 3.18a). Suggestive factors for early diagnosis include stippled epiphyses in the newborn (although this is infrequent) and abnormalities of development of the secondary ossification centers include delayed appearance, fragmented structure, eccentric positioning, subchondral flattening, and smaller size than expected for age. Early clinical presentation, often in the first decade and preceding plain radiographic changes, involves transient episodes of joint discomfort especially in hips and knees, swelling and decreased ranges of motion, fatigability, and awkward gait. In some variants a mild proximal myopathy co-exists. Family studies indicate that, in retrospect, symptoms can begin as young as 2 years of age. Hips, knees, and ankle are the most common clinical sites of problems with elbow, hand, and shoulder occasionally involved. Five gene mutations are now identified as causing dominant MED [78, 79, 219, 220]. The commonest involve COMP (cartilage oligomeric matrix protein) along with the three genes composing type IX collagen COL9A1, COL9A2, and COL9A3 and MATN3, which encodes matrilin-3, a cartilage matrix protein. In about one-quarter of samples no mutation is identified, likely implying additional as yet undiscovered causative mutations [219].

There are many phenotypic variants of this disorder and variability can occur even between different members of the same family. Most are autosomal dominant with an incidence in the range of 1 in 10,000 [219]. On occasion, joint degeneration is great while stature is minimally affected with patient height normal or low normal. Many of these are now found to represent abnormalities of type IX collagen [78, 79, 221]. Early descriptions of MED defined the Ribbing or Fairbank types. In Ribbing MED abnormality is almost entirely confined to the proximal femoral epiphyses with short stature and early onset of hip osteoarthritis [222]. In Fairbank MED involvement is more widespread involving hips, knees, ankles, hands, and other areas [11, 223, 224]. In earlier reports the Ribbing variant was described as mild and Fairbank as severe but more detailed information now shows a continuum of clinical severity [220]. Owing to the extreme variability of involvement many other patterns of epiphyseal affection are seen. Bailey divided multiple epiphyseal dysplasia into congenita and tarda types with six MEDC variants and eight MEDT variants (with many subtypes) [8]. Van Mourik et al. have described a family with the absence of hip or shoulder involvement, despite widespread involvement at knees, elbows, ankles, and hands [221]. Other patterns include only lower extremity involvement or only hip involvement.

Radiographic features in the childhood hip are bilateral, symmetrical, and similar to the fragmentation stage of Perthes disease [191]. A major point in differentiation from Perthes is the fact that Perthes (i) shows either unilateral involvement (80 %) or if bilateral has asymmetrical temporal involvement with the two sides not equally affected at any one time, with second side involvement usually appearing one to two years or more after the first, (ii) has metaphyseal cystic involvement, and (iii) normal acetabulae in the early stages. The proximal femoral head secondary centers in MED are always symmetrically affected without cystic changes in the metaphyses and with dysplastic acetabulae seen often early in the first decade. The changes in Perthes rapidly worsen and then improve while in MED the changes progress slowly. A skeletal survey can remove many concerns about diagnosis since other major joints will usually show some subtle abnormalities in MED but are normal in Perthes. Pain and decreased range of motion are rarely seen in multiple epiphyseal dysplasias at this age while they usually represent the presenting phenomena in Perthes disease.

Fig. 3.18 Multiple epiphyseal dysplasia is characterized by epiphyseal flattening in the subchondral region leading to premature osteoarthritis. **a**–**d** are from an affected 13 year old male with multiple epiphyseal dysplasia due to a mutation in the alpha 3 chain of type IX collagen. Structural abnormalities of the join and epiphyseal regions are already evident radiographically in knees (**a**) and an ankle (**b**). **e**–**g** Examples are shown of progressive involvement of the knee in adult members of the family. **h** shows severe valgus deformity in a 7-year-old girl with a variant of spondyloepiphyseal dysplasia with scoliosis and joint laxity (see also figures **c**, **d**, and 3.14b). Distal femoral varus osteotomy **i** improved alignment and allowed the lateral femoral epiphysis to improve growth by decreasing pressure on it. (Reprinted with permission from Bonnemann et al. A mutation in the alpha-3 chain of type IX collagen causes autosomal dominant multiple epiphyseal dysplasia. PNAS. 2000;97:1212–1217. Copyright 2000 National Academy of Sciences, USA)

Knee changes are characterized by less distinct shaping of the secondary ossification centers with relative flattening of the distal femoral condylar contours, a shallow patellar groove on the anterior epiphyseal surface, and a tendency to lateral patellar subluxation or dislocation. It is likely that many patients diagnosed with primary osteoarthritis of the hip or knee represent unrecognized cases of multiple epiphyseal dysplasias. Involvement can also include shoulder, elbow and wrist joints; irregularly shaped tarsal and carpal bones; and shortening of the fingers due to metacarpal and phalangeal involvement. Short stature is variable from severe to mild to absent; the height of many is within the normal range. The skull and face are normal. Spinal changes are absent or extremely mild and radiographic changes should be limited to the epiphyses. The hands are often somewhat short with broad fingers.

The major orthopedic problem in multiple epiphyseal dysplasia, other than the short stature, is the high degree of localization at the hip and knee leading to premature osteoarthritis and the need for total joint arthroplasty in mid-adult life. The disorder leads to abnormalities in shape of the femoral head, distal femur, and proximal tibia leading to imperfect joint contours, collapse of the subchondral bone, and associated irregularities of the articular cartilage surface. The abnormal shape of the femoral head tends to become apparent late in the first or early in the second decade (Fig. 3.18b). The radiographic appearance of the hips in the first decade can be almost indistinguishable at first glance from a Perthes disorder as noted above with fragmentation of the developing secondary ossification center of the femoral head. Ingram has indicated that early diagnosis for MED can be enhanced by analyzing wrist radiographs for carpal and metacarpal measurements and antero-posterior films of the distal femur [225]. These films allow for the measurement of various indices such that 80 % of those with MED can be distinguished from normal with good confidence between approximately 5 and 13 years of age.

Symptomatic hip deformity may benefit from osteotomy. Degenerative cartilage change with varus deformation can also be seen at the knee and valgus osteotomy is generally the recommended approach. On occasion, ankle deformities also warrant distal tibial and fibular supramalleolar corrective osteotomies. There are no specific spine abnormalities with multiple epiphyseal dysplasias and lumbar lordosis is not usually seen. Many symptomatic patients with MED require total hip and total knee joint arthroplasties beginning in mid-adult life.

3.12.4 Dysplasia Epiphysealis Hemimelica

This disorder is characterized by a localized overgrowth of an epiphysis of a long bone or of a carpal or tarsal bone, which subsequently leads to joint malalignment (Fig. 3.3b). The initial report was put forth by Mouchet and Belot on tarsal bone (tarsomegalie) in 1926 [226]. The term tarsoepiphyseal aclasis was used by Trevor [227] who described eight cases. Fairbank further defined the entity describing 14 cases and further described it as dysplasia epiphysealis hemimelica [228]. It is not hereditary. The knee and ankle are most commonly affected. The disorder is more common in boys than girls by a 2-to-1 margin, and lower extremity bones are much more frequently involved than upper extremity bones. It is usually recognized in the first decade of life. In most instances one-half or less of an epiphyseal region is involved (hemimelica) and the medial aspect of the bone is more often involved than the lateral. The commonest areas of involvement are the distal tibial and the distal femoral epiphyses and the talus. Other sites include the proximal femoral capital epiphysis, acetabulum, patella, proximal tibial epiphysis, calcaneus, tarsal navicular, and first cuneiform and carpal bones and, very rarely, distal ulna, proximal and distal radius, proximal and distal humerus, glenoid of the scapula, or metacarpal and phalangeal bones [229–232]. In two-thirds of cases there are multiple lesions present in an involved limb. Not infrequently adjacent areas at a joint are both affected, for example the mediol malleolus and the medial talus. Talar lesions can be at the superior surface but usually extend anteriorly and posteriorly or both. When two bones in the same limb are affected the same side of the epiphysis in both (medial or lateral) is invariably involved. A rare instance of involvement of almost all the epiphyses of the left side of the body was reported by Cruz-Conde et al. representing the most marked manifestation of the disorder [233]. Skaggs et al. reported two cases with acetabular involvement presenting at 5 and 7 years of age with discomfort and hip subluxation. Good results occurred after removal of the lesions at open operation with dislocation of the hip and care taken to not damage the tri-radiate cartilage [234].

In a review of 57 cases from their service and the literature (many with two or more lesions) the distribution of involvement was: talus and calcaneus 22 %, distal tibia and fibula 22 %, distal femur 21 %, proximal tibia 11 %, tarsal navicular, cuboid, or cuneiform bones 10 %, tibial tuberosity 3 %, proximal femur 5 %, acetabulum 3 %, carpal bones 2 %, and scapula 1 %. This study confirms the commonly reported observations of predominant knee and ankle involvement with only rare upper extremity involvement. Expressed another way, ankle (distal tibia and fibula and talus [+calcaneus]) 44 % and knee (distal femur, proximal tibia) 32 % account for 76 % or three-quarters of regions affected [235].

The overgrowth initially affects part of the peripheral cartilage mass of the epiphysis although diagnosis is generally brought to light by associated angular deformity and

radiographic appearance of accessory and eccentric centers of ossification within the cartilage mass. The disorder has been likened to an osteochondroma affecting the epiphysis rather than the metaphysis. Histologic sections show a relatively normal appearing cartilage tissue which undergoes endochondral ossification in association with mineralization of the cartilage matrix, invasion of vascularity, deposition of bone on cartilage cores, and formation of a marrow. The junction of the cartilage tissue of the lesion can be indistinguishable from that of the adjacent epiphysis at gross inspection but usually a groove of varying depths demarcates it from normal tissue on histologic or MR imaging studies. The clinical problems with the disorder relate to the asymmetric cartilage surface of the joints and angular deformity.

With time, the bone from the overgrowth regions merges with that synthesized by the normal ossification processes of the secondary center of the rest of the epiphysis. Surgical treatment is indicated when the lesion causes discomfort, altered function, or deformity. Excision of the excess cartilage mass and surgical re-shaping of articular contours lead to good results. Bahk et al. recently confirmed this impression in six patients with complete excision of the lesional mass as well as in two with incomplete excision [236]. The masses did not recur or enlarge again with growth. Osteotomy of the adjacent bone might be needed. Asymptomatic lesions are observed since there is no known risk of malignant transformation. MR imaging outlines the extent of the cartilage mass, more accurately notes the developing secondary ossification regions, and defines the region of differentiation of normal epiphyseal cartilage and the affected hemimelic overgrowth. Keret et al. defined a definite cleavage plane between the epiphysis and the abnormal cartilage by MR imaging [237]. MR imaging defines the articular cartilage shape of the affected joint and assesses the physis which if contiguous with the hemimelica lesion might provide a reason for any continuing abnormal growth following surgical management.

3.12.5 Metatropic Dysplasia

Metatropic dysplasia is a rare disorder with a specific developmental pattern—newborn appearance similar to achondroplasia (short-limb dwarfism) with subsequent reversal to a Morquio-like (short-trunk dwarfism) appearance in the first few years of life. The vertebrae show platyspondyly at birth but no deformity. There is delay in ossification of the vertebral bodies. With time, a severe kyphoscoliosis develops. Atlanto-axial instability is common. The limbs are short and have a characteristic widened metaphyseal appearance (dumbbell shape) with oval cortical outlining. "Knobby"—knees reflect this. The acetabulae are initially horizontal with a lateral supra-acetabular notch. A prominent coccygeal skin fold is often seen. More severe variants are lethal. These have been divided into various types including lethal metatropic dysplasia-hyperplastic and lethal metatropic dysplasia-hyperchondrogenesis. [These are discussed with the lethal skeletal dysplasia earlier in the chapter.]

3.12.6 Kniest Dysplasia

Kniest dysplasia is evident at birth with disproportionate short stature, short limbs, and a prominent short barrel-shaped chest [58, 238]. A depressed nasal bridge and cleft palate are common. The joints tend to be enlarged with limited mobility and the limbs are short and bowed. Hips are often malformed with short necks, coxa vara, malformed heads, and acetabular dysplasia. There is a high incidence of hearing loss. Eye problems are common and severe with myopia, retinal detachment, glaucoma, and eventual blindness in many patients. Lumbar kyphoscoliosis tends to develop in the mid-first decade and will usually progress rapidly to a rigid deformity. The kyphotic element is usually more prominent than the scoliosis. It can be high or mid-thoracic and tends to be localized to a few vertebrae. Osteoarthritis as early as the second decade is fairly common with this disorder and thus more marked than in most skeletal dysplasias with the exception of diastrophic dysplasia. It is present virtually in all joints including the hands.

3.12.7 Chondrodysplasia Punctata

The benign Conradi–Hünermann type of chondrodysplasia punctata is autosomal dominant in comparison to the more severe and usually lethal recessive rhizomelic variant (RCP). The appearance of the stippled lesions in the various subtypes is the same radiographically in the first few months of life, so prognosis is guarded depending on the general condition. Even early resorption of some of the punctate areas is not definitive evidence that systemic recovery will occur. The benign autosomal dominant variant refers to those patients with stippled epiphyses but without rhizomelia who survive with only mild to moderate growth deficiency, which is usually unilateral in the limbs but may affect vertebral growth in an asymmetric fashion. The regions of calcification are gradually incorporated into the bone or resorbed in the first few years of life and the radiographic appearance becomes less evident and disappears with development. Orthopedic problems are fairly frequent involving kyphoscoliosis with structural irregularities of the vertebral bodies and asymmetric limb shortening with coxa vara or angular deformity. The patients should be examined for cataracts which can

occur in up to 20 % of cases and for ichthyosiform skin patterns. These two findings however are much more common in the lethal rhizomelic form. An X-linked dominant form described by Happle affects females and is accompanied by widespread atrophic and pigmented skin lesions.

Distinction must be made between the three specific forms of chondrodysplasia punctata and stippling as an epiphenomenon in such disorders as multiple epiphyseal dysplasia, spondyloepiphyseal dysplasia, hypoparathyroidism, trisomy 18 and 21, fetal warfarin syndrome, and maternal alcohol (first trimester) ingestion [128, 239]. The more severe the cartilage abnormality, the earlier in fetal life the occurrence of the stippling calcification and the more severe the eventual outcome. Jeune et al. felt that involvement concentrated in the distal femurs and proximal humeri were relatively poor prognostic signs while those patients with primarily hand and foot involvement would do better [131]. These findings also correlate with poorer prognosis with rhizomelic (humeral/femoral) shortening.

3.12.8 Spondolyoepimetaphyseal Dysplasia

This disorder has gradually come to be defined as a separate entity. It is characterized by marked shortness of stature, gross joint laxity, and a progressive kyphoscoliosis. The pelvis is characterized by large iliac wings with small hypoplastic iliac bodies, poorly formed acetabula, and smaller to absent capital femoral secondary bone centers of the epiphyses. The hips often proceed to dislocation and the secondary ossification centers remains small, irregular, and flattened. The femoral necks are short with the coxa valga deformity and skeletal age is delayed. Beighton and Kozlowski, among the early definers of this disorder, indicate that "epi-metaphyseal changes are obvious, but slight [240]. The metaphyses are widened with an abnormal trabecular pattern." The kyphoscoliosis is generally absent or minimal in the newborn but deformity increases rapidly during the first decade of childhood. The spinal deformity has led in severe cases to paraplegia, progressive respiratory failure, cor pulmonale and even death in the first two decades [241]. Early attention to the spinal deformity including surgical stabilization appears essential.

3.12.8.1 Spondyloepimetaphyseal Dysplasia with Scoliosis, Joint Laxity, and Finger Deformities

Major clinical problems from the early years of life can be marked bilateral genu valgum, patellar dislocations, knee instability, severe subluxation of the radial heads, dorsal subluxation of the distal ulnae, mid-face hypoplasia, and tracheobronchomalacia [142]. Moderate thoracic scoliosis develops but there is no interpedicular narrowing in the lumbar spine. Characteristic metaphyseal striations are seen most extensively on radiographs of distal femur and proximal tibia. Asymmetric and premature physeal fusion is common. Bracketing is prominent in the epiphyses of metacarpals 1–5 and of the proximal and middle phalanges of each hand during growth (Fig. 3.1b). Many of the long bone epiphyses demonstrate irregular shapes of the secondary centers and misshapen (primarily flattened) articular surfaces. Height at skeletal maturity is in the range of 50 in. (127 cm).

3.12.9 Diastrophic Dysplasia

Diastrophic dysplasia is diagnosable at birth [23]. It is an autosomal recessive disorder which was recognized as a separate, distinct skeletal dysplasia and called diastrophic (Greek = tortuous, twisted) in 1960 by Lamy and Maroteaux in a study of 3 of their own patients and 11 previously described in the literature [242]. The clinical picture includes hip, knee, and elbow flexion contractures, rigid equinovarus or metatarsus adductus foot deformities, "cauliflower" ear lobes swollen by fluid due to perichondritis of the external ear cartilage, stiff fingers, and a short, abducted "hitch-hikers" thumb [243–247]. The first metacarpal is short and more proximally positioned than normal and the thumbs are hypermobile. The ears are normal at birth but develop the swelling from 1 to 6 weeks of age. If not drained, the fluid eventually resorbs but the pinnae remain thickened and deformed and may develop calcification. The joints are rigid but hypermobility is seen in some. The limbs are shortened in a mesomelic fashion causing a disproportionate short stature. Kyphoscoliosis in the first decade is common and cleft palate can occur.

Diastrophic dysplasia is one of the most difficult of the dysplasias to manage from an orthopedic viewpoint for several reasons. The shortness of stature is extensive with most patients not destined to reach even the 4-foot level. This is due to the severity of epiphyseal involvement, worsening of the shortness by contractures of hip, knee, and ankle, premature cessation of physeal function around the age of 10 or 11 years, and an often progressive kyphoscoliosis. Contractures are present at virtually every joint in the upper and lower extremities. These tend to worsen with time and to be relatively rigid such that soft tissue surgery is often ineffective necessitating osteotomy for correction. A characteristic finding in many, in particular at knee and elbow, is associated subluxation due to cartilaginous epiphyseal deformity. Even when corrected, the tendency is for the contractures to recur in relentless fashion. Angular deformity of the long bones is not common with most limb deformity due to contractures and subluxations.

Early and relatively extensive surgery is needed to obtain correction. Attention to post-surgery detail is needed to minimize recurrence but if growth remains some recurrence is common. The characteristic contractures involve flexion deformities of the hip, knee flexion contractures, and a rigid talipes equinovarus (clubfoot) or metatarsus adductus deformity. Contractures of the upper extremity involve elbow flexion contractures and stiffness and rigidity of the interphalangeal and metatarsal–phalangeal joints in extension in digits 2–5.

The hip tends to be located at birth but stance and gait are worsened by progressive flexion contractures and the development of secondary acetabular dysplasia in some. Hip position is amenable to some improvement with anterior soft tissue release but full correction is generally achieved only with proximal femoral extension osteotomy. Recovery of hip range of motion is often slow and can be incomplete following hip osteotomy, so intervention must be done with caution. The knee flexion contractures rarely respond completely to soft tissue releases alone and can be dealt with by extension osteotomies of the distal femur (Fig. 3.19a). It remains essential to not further damage the physeal regions with these procedures. Extension osteotomy is not totally ideal because the remodeling potential of the distal femoral physis is limited owing to its severe involvement in the dysplastic process although the anterior surface concavity post-osteotomy is readily remodeled since this represents a periosteal intramembranous bone function. There is little capability however for the distal femoral growth plate to aid in any subsequent remodeling by differential growth of the dorsal in relation to the volar parts. Clubfoot treatment can begin with serial splinting and casting but surgery is almost always needed. Extensive postero-medial release has been effective in obtaining and maintaining correction. Many of these patients also have a metatarsus adductus. This tends not to be of great clinical significance but is difficult to correct because of the shortness of the metatarsals. If necessary however multiple metatarsal osteotomies can be performed.

Spinal Abnormalities. Spinal abnormalities are seen in the large majority of patients. The spectrum of abnormalities includes a cervical spina bifida, mid-cervical kyphosis (Figs. 3.18 and 3.9b), and a relatively high incidence of progressive thoraco-lumbar scoliosis (Fig. 3.9), thoraco-lumbar kyphosis, and increased lumbar lordosis [248]. The scoliosis is not seen at birth but often develops early, in the first 2 years of life, with a tendency to rapid increase and severe rigidity. Most patients have a decreasing interpedicular distance in the lumbar spine from L1 to L5, similar to that seen in achondroplasia. Quadriparesis and paraparesis can occur with rapidly worsening kyphoses [249]. Variable extent of scoliosis is seen with those destined to fall into the severe group having deformity beginning from 2 to 4 years of age.

Long-term studies of large numbers of patients from Finland have clarified the extent and nature of deformity in diastrophic dysplasia. There is a very high incidence in that country where diastrophic dysplasia is the most common skeletal dysplasia.

Spinal abnormality was assessed in 101 patients, 63 of whom were greater than 21 years of age [250]. Cervical Spine. One-third (33 %) of the patients had a cervical kyphosis usually associated with hypoplasia of the vertebral bodies of C3, C4, and C5. In most cases the kyphosis was progressive but in three cases it resolved before 5 years of age. Spontaneous correction if it was to occur did so before 5 years of age. Spina bifida occulta from C3–C4 to the upper thoracic spine was seen in two-thirds of patients with a greater incidence in females than in males (73–59 %). The dens was slightly abnormal in most, sometimes being very large.

A more detailed study of the cervical spine from Finland outlined the natural history in 122 patients following most with radiographs into the adult years [251]. The average lordosis in the last radiograph was 17°. Cervical kyphosis is usually present in DD in childhood but virtually all cases resolve spontaneously. Only five patients (4 %) had a persisting cervical kyphosis although it averaged 92°. Vertebral body hypoplasia and displacement were most common in the mid-cervical region and resolved with age (correcting the cervical kyphosis). Vertebral body C2 was never hypoplastic. The most severely affected bodies were C3 and C4, with C5 only moderately affected. Correction had generally occurred or was well underway by 5 years of age. Spina bifida occulta involving several of the mid-cervical vertebrae was present in 79 % (females 83 %, males 72 %). Instability between the vertebrae also disappeared with growth but degeneration of the cervical disks increased and the range of motion of the cervical spine decreased in adulthood.

Scoliosis. Natural History. Assessment of 98 patients older than 16 years and/or having had spinal surgery showed that 88 % had scoliosis (90 % among females and 84 % amongmales). Three subtypes were found: early progressive (11 patients) with an average deformity of 134° (range 83–188), idiopathic-like (41 patients) with an average deformity of 49° (range 20–104), and mild nonprogressive (33 patients) with an average deformity of 19° (range 11–40). The earlier the curve began the more severe its progression with early progressive deformity generally seen in the first 5 years of life [252]. An earlier study [250] of 101 patients showed scoliosis in 37 % with 13 patients showing curves greater than 50°.

MR Imaging of the thoracic and lumbar spine. MRI was done on 88 DD patients ranging in age from 3.4 to 56 years with an average 31 years [253]. Patients were grouped into ages by decades for study of changes with time. The spinal cord was normal. The spinal canal was narrowed but severe

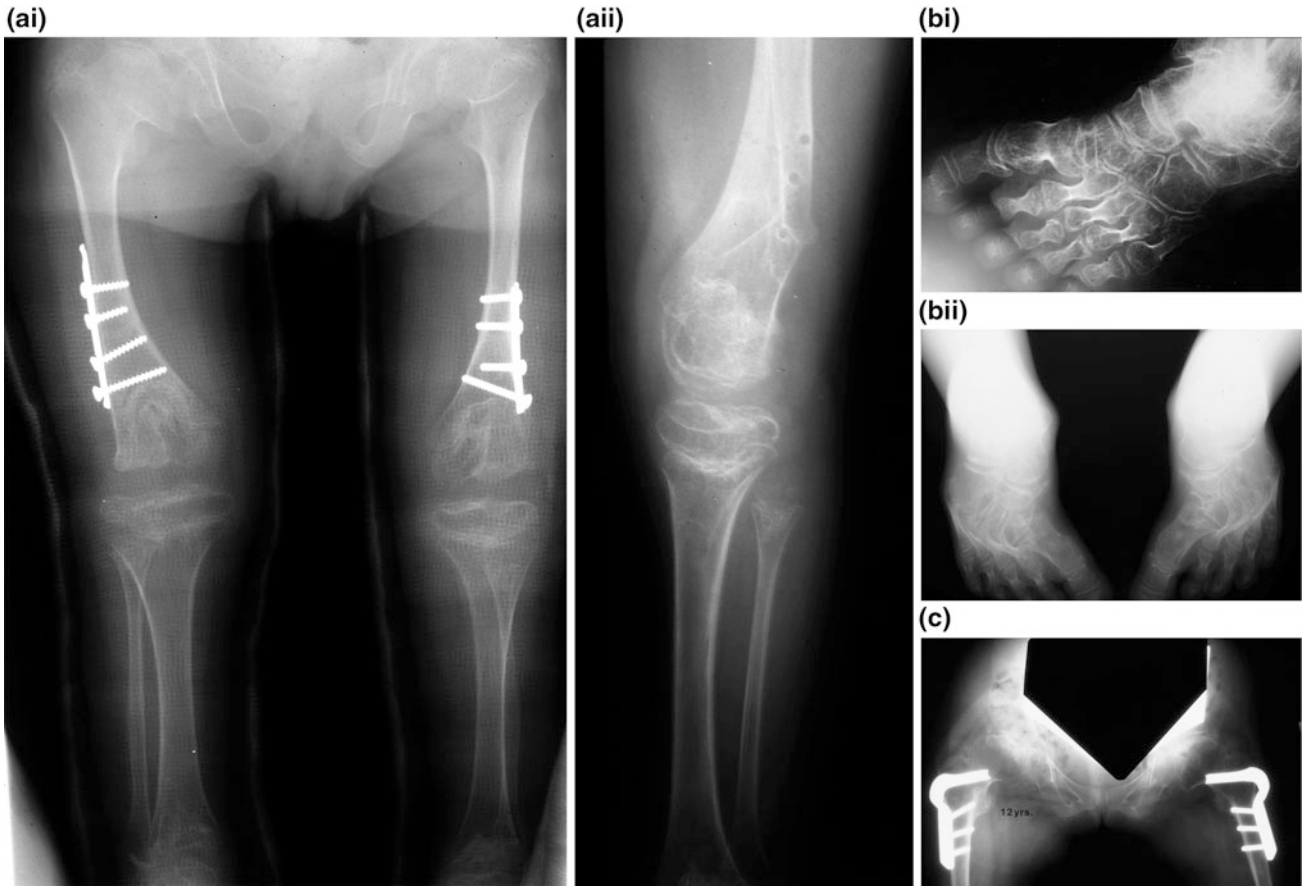


Fig. 3.19 Orthopedic management is frequently needed in diastrophic dysplasia but is difficult owing to the inexorable tendency to worsening of deformity with growth. **a** Extension osteotomy of the distal femurs is often needed to correct knee flexion deformities. Soft tissue releases can be attempted but are rarely fully effective. Preoperative film showing maximum knee extension is illustrated in Fig. 3.14a. Postoperative correction is shown in **a**(**i**, **ii**). Anteroposterior radiograph shows good alignment but marked distal femoral articular surface flattening. Note periosteal remodeling along anterior surface of femur on lateral view. **b** (**i**, **ii**) Radiographs show examples of clubfoot deformity. **c** Anteroposterior hip radiograph following bilateral proximal femoral extension osteotomies needed to correct severe flexion contractures of hips

spinal stenosis was uncommon. The most markedly narrowed levels were from L3 to S1. The intervertebral disks were abnormal in all patients. The disk spaces were narrower than in the normal. Disk prolapse was not common. Scoliosis was seen in 80 % with an average curve of 42°. Vertebral bodies showed expected secondary deformity but no developmental abnormalities. The location of the conus was normal. The study showed paraspinal muscle atrophy. The prevalence and distribution of Schmorl's nodes were normal.

Treatment. Treatment has followed the path of non-intervention with observation only [250] to bracing (which has been for the most part ineffective) to surgical intervention [249, 254, 255]. It soon became recognized that the severe early onset curves were best treated by both anterior and posterior approaches. The most common deformities are generally thoraco-lumbar kyphoscolioses with considerable rotational deformity. Brace treatment was found not to prevent progression of deformity and antero-posterior surgery was indicated for the severe spinal deformities. Today, some patients would be considered for growing rod instrumentation in the first decade and posterior pedicle screw techniques for definitive fusion but no large series results have been reported yet.

Foot–ankle abnormalities. In a large group of 102 patients, the feet were almost always deformed but not all were classical clubfoot deformities (Fig. 3.19b) [256]. Five gradations of deformity were found. The commonest pattern was a tarsal valgus with metatarsus adductus (43 %), followed by equino-varus (29 %), equinus (8 %), metatarsus adductus (13 %), and normal (7 %). Only 37 % could be described as having clubfeet and two-thirds of the feet were plantigrade. Soft tissue surgery alone for the clubfoot deformity was followed by recurrence in 80 % tenotomy (tenotomy, heel cord lengthening, or posteromedial release). Much of the deformity in tarsal valgus with metatarsus adductus was attributed to ligamentous laxity.

Hip abnormalities. Hip development was assessed in 50 patients [20]. Abnormality worsened with age in all, some

showing moderate and some severe changes (Fig. 3.19c). The hips were normal at birth with two fetal autopsy dissections and one newborn MRI showing joint congruity and no apparent deformities. Serial studies showed joint deformity to develop in a progressive fashion in all with changes seen by 1–2 years of age. The major deformity was hip flexion contracture seen in 93 % with a mean value of 23°. Rotation and abduction decreased with time. Acetabular dysplasia, a flattened enlarged femoral head often with medial inferior growth prominence, a shortened femoral neck with trochanteric overgrowth and variable joint incongruity developed. There was delay in ossification of the femoral capital epiphysis in almost all patients and the secondary center was not seen until 12 years of age in a quarter of the patients. Osteoarthritis in early adult life was common (Fig. 3.19c(iii–iv)). In three-fourth of the patients the femoral head remained spherical but in the others some flattening developed in adolescence. Magnetic resonance imaging was done in 35 patients 1–39 years of age [257]. Hip joint congruity was good although the joint surfaces were deformed. A misshapen femoral, short neck with varus positioning and a shallow deformed acetabulum were seen in virtually all patients. The thickness of the joint cartilage was diminished. The secondary ossification center of the femoral head was delayed in time of appearance and when present often appeared to lack sphericity and avascular necrosis.

The marked deformity of the typical hip and knee can be further delineated by 3-dimensional computer model reconstruction [258].

Knee. The knee is equally severely affected as the hip. Severe flexion contractures and misshapen epiphyses contribute to significant joint malformation and cartilage degeneration within the first decade of life. The MRI further highlights the destructive effect of this dysplasia [259]. In a study of 23 patients bilaterally by MRI, degenerative changes in the articular cartilage progressed from 6 years of age. The subchondral bone of femur and tibia was fragmented, menisci developed abnormally, the anterior cruciate ligament was absent on thin/rudimentary in 96 %, the posterior cruciate abnormal in 89 %, and the patellar tendon was thick and short placing the patella in an inferior position further predisposing it to wear.

3.12.10 Spondyloepiphyseal Dysplasia

3.12.10.1 SED Congenita

There is a high incidence of orthopedic deformity with SED congenita including C1–C2 abnormalities, thoraco-lumbar kyphosis, thoraco-lumbar scoliosis, and coxa vara [43, 260–262]. Clinical appearance is characterized by short stature, a short neck, barrel chest, kyphoscoliotic deformity, lumbar lordosis, either varus or valgus knee deformities, and a tendency to walk with slight hip and knee flexion. The autosomal dominant disorder is a disproportionate short-trunk dysplasia with spine and proximal epiphyseal abnormalities evident at birth. Characteristically the spine and epiphyses of the proximal joints are involved with the peripheral bones less involved or uninvolved. The hands and feet are normal in length and shape. The odontoid hypoplasia is often accompanied by a cervical myelopathy. Stabilization by occipital-C2 fusion is warranted (Fig. 3.8a(iii)). In spondyloepiphyseal dysplasia 7 of 12 patients had increased thoracic kyphosis ranging from 30° to 130° usually accompanied by increased lumbar lordosis. Scoliosis was present in 9 of the 12 patients and required treatment in 5 patients whose curves were larger than 35°. There is marked delay of secondary center ossification formation in particular at the proximal femoral capital epiphysis. There is retarded ossification of the vertebral bodies particularly in the lower thoracic region with oval, pear-shaped vertebral bodies on lateral projections. Coxa vara is almost invariable; the medial ossific non-union of the neck is seen early (Fig. 3.20). The distal femoral and proximal tibial secondary centers tend not to be ossified at birth and the primary centers of the calcaneus and talus are also not ossified. Many other secondary centers show variable amounts of delay in onset of ossification. Ophthalmological problems develop in many patients including myopia and retinal detachment. The disorder is distinguished from Morquio's mucopolysaccharidosis by the fact that it is diagnosable radiographically at birth and there is no increased excretion of urine mucopolysaccharides including keratosulfates. Morquio's mucopolysaccharidosis is not usually evident radiographically until 1 year of age.

In adulthood there is short stature, odontoid hypoplasia and non-union, thoracic kyphosis, lumbar lordosis, occasional severe scoliosis, flattened vertebral bodies, and narrowed disc spaces. Dysplastic acetabulae and coxa vara are seen. The long tubular bones are relatively short.

3.12.10.2 SED Tarda

Spondyloepiphyseal dysplasia tarda is similar to the congenita form but tends to be non-recognizable at birth with clinical onset at 5–10 years of age. It is less severe. There are examples of both autosomal dominant and recessive transmission [263]. The disorder clinically is a disproportionate short-trunk dwarfism. There are no currently detectable biochemical abnormalities of blood or urine. There tends to be flattening of the vertebrae (platyspondyly) with a mid-thoracic kyphosis due to anterior wedging, and a shortened trunk and neck. Scoliosis is mild. The secondary ossification centers of the hip and knee region are present but tend to develop with irregular shaping. The major problems involve premature osteoarthritis especially of hips and knees and cervical arthritis in early to mid-adult life [264].

Fig. 3.20 **i** Coxa vara deformity in SED congenita is seen. **ii** Anthrogram shows femoral head to be well positioned in acetabulum. Proximal femoral valgus osteotomy improves gait (**iii**), (**iv**) by repositioning the head more deeply into the acetabulum and moving the greater trochanter more distal improving leverage of the hip abductor muscles

3.12.11 Dyggve–Melchior–Claussen Dysplasia; Smith–McCort Dysplasia

Another subgroup with vertebral and epiphyseal abnormalities is the Dyggve–Melchior–Claussen and Smith–McCort dysplasia entity composed of patients with short stature, a short neck, barrel chest, lumbar lordosis and radiographs showing platyspondyly (flattened, shortened vertebrae), metaphyseal–epiphyseal irregularities, dysplastic hips, and a pathognomonic lace-like configuration of the iliac–crest cartilage–bone junction during the growth years (Fig. 3.21a–c). The classic DMC syndrome is accompanied by mental retardation while the Smith–McCort dysplasia has the same phenotype but the patients are mentally normal.

3.12.12 Pseudoachondroplasia

This disorder was defined by Maroteaux and Lamy to refer to patients with the body habitus of achondroplasia but normal facial features [265]. It is not a single disorder since there are both autosomal dominant and recessive types with considerable variability in both. In a large review, Wynne-Davies et al. concluded that they could not differentiate the two types by clinical–radiographic criteria [266]. Spinal and limb abnormalities are more marked radiographically than in achondroplasia leading to the awkward term pseudoachrondroplastic spondylo–epiphyseal dysplasia, usually shortened to pseudoachondroplasia (PSACH). Patients are described as appearing clinically normal at birth with dysplastic findings becoming apparent between 1 and 3 years of age. It evolves to a short-limb dwarfism with the spine relatively less involved than the limbs. Hips can be dysplastic with some coxa vara but the acetabulae tend to be flat or horizontal. The knees in particular are the site of major deformity worsened by ligamentous laxity which can involve varus, valgus, recurvatum, or rotational components and is often multiplanar. Each of hip, knee, and ankle subluxation can occur. There is considerable epiphyseal and metaphyseal irregularity seen on radiographs. Premature osteoarthritis results with most patients showing OA of the knee as early as 15 years of age. Platyspondyly with odontoid hypoplasia can be seen. Lateral spine radiographs show central, anterior tongue-like projections from the vertebral bodies. Scoliosis can occur, especially if there is pelvic obliquity, but it is readily manageable by bracing or posterior spinal fusion and is not as rigid or severe as in some other dysplasias. In some patients the spine is normal. The most valuable diagnostic radiograph is the pelvis where hip and pelvic maturation are markedly delayed. The triradiate cartilage remains widened and slowly developing as late as 12 years of age, the proximal capital femoral epiphysis appears late and remains small and often fragmented for most of the first decade, the femoral neck is short and beaked, and the pubic and ischial bones do not fully ossify until 8–10 years of age. In distinction to achondroplasia there is no caudal narrowing of the interpedicular spaces, no craniofacial abnormalities and considerably greater vertebral body, epiphyseal–metaphyseal, and joint space deformation.

3.12.13 Mucopolysaccharidoses

The mucopolysaccharidoses (MPS) represent the first group of skeletal dysplasia disorders for which biochemical abnormalities were detected. They are a group of lysosomal storage disorders caused by a deficiency of enzymes responsible for degrading glycosaminoglycans (formerly referred to as mucopolysaccharides). The enzyme deficiencies tend to block the normal catabolism of dermatan sulfate, heparan sulfate, or keratan sulfate, either individually or in combination, with chondroitin sulfate sometimes also involved. The glycosaminoglycan molecules accumulate in the lysosomes resulting in cell, tissue, and organ dysfunction. The glycosaminoglycan fragments generated by alternative pathways are then excreted in the urine. There are 10 known enzyme deficiencies giving rise to 7 distinct MPS disorders. The MPS disorders share many clinical features although to variable degrees. The course is chronic and progressive at variable rates with particular involvement of hearing, vision, cardiovascular function, musculoskeletal function, and mental capability. Severe mental retardation is

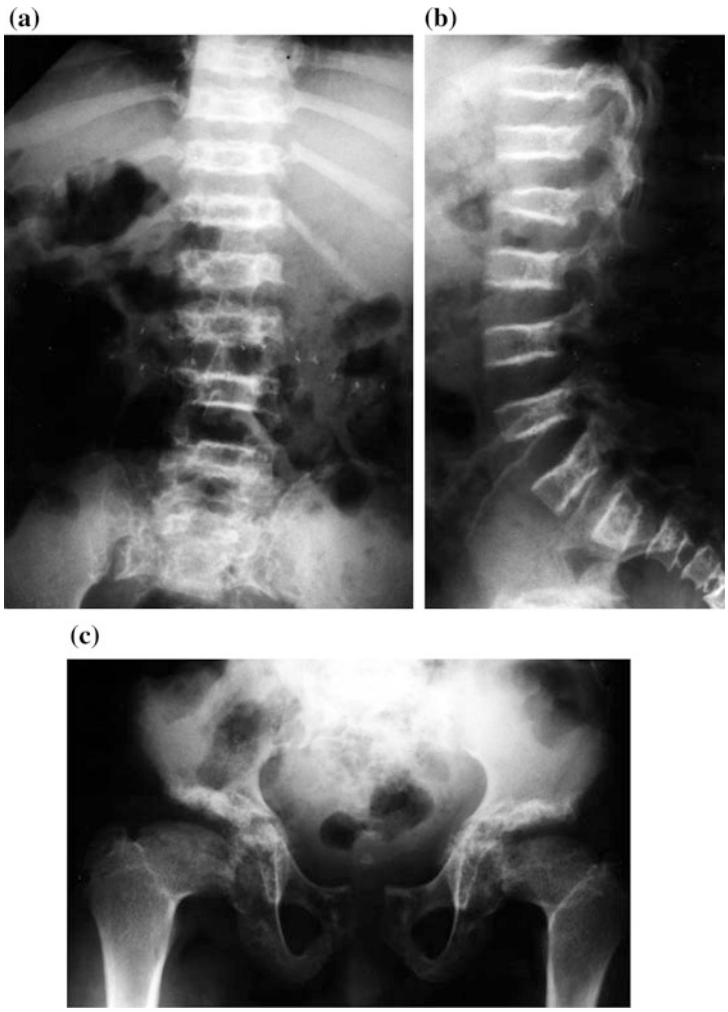


Fig. 3.21 Radiographic characteristics of Dyggve-Melchior-Claussen dysplasia or Smith-McCort dysplasia are shown. Platyspondyly is apparent in both AP (**a**) and lateral (**b**) projections involving thoraco-lumbar vertebrae. Anteroposterior radiograph of the hips **c** shows flattening and fragmentation of the bone of the femoral heads

characteristic of MPS1H, the severe form of MPS II, and all subtypes of MPS III. Normal intellect is usually retained in the other disorders. The skeletal disorders are particularly marked in MPS IV (Morquio syndrome) with many specific to that disorder. The large majority of MPS disorders are transmitted in an autosomal recessive manner, except for MPS II which is X-linked. Simple enzyme assays are available for the diagnosis of MPS using fibroblasts, leukocytes, or serum. Prenatal diagnosis following amniocentesis or chorionic villus biopsy is possible for all MPS disorders. The conditions are not yet curable but newer treatments have involved bone marrow transplantation and gene transfer into hematopoietic cells. They are characterized by increased urinary secretion of glycosaminoglycans. Several different types have been defined but it is the MPS IV Morquio disorder that requires the most frequent and extensive orthopedic management. From a radiographic perspective, Morquio's disease is a spondyloepiphyseal dysplasia but the biochemical abnormality has led to a specific grouping. Table 3.13 summarizes the MPS disorders in terms of clinical findings, enzyme deficiency, the glycosaminoglycan affected, inheritance, and gene locus [100, 101, 267].

3.12.13.1 MPS IH (Hurler Syndrome)

In this short stature disorder there is a deceleration of growth between 6 and 18 months of age with failure of advancement by 2–5 years. Death usually occurs in childhood and patients rarely live beyond 10 years of age. There is a prominent coarse facial appearance with flared nostrils, a low nasal bridge, and a tendency toward hypertelorism. The disorder was described in the early literature as gargoylism. Blindness occurs as the corneas become hazy and there is retinal pigmentation. Other abnormalities involve an enlarged tongue, hepatosplenomegaly, inguinal hernias, joint stiffness, a tendency to hip dislocation, and deafness. The bone radiographs are characterized by diaphyseal widening of the shortened and misshapened bones. There is frequently a short neck,

Table 3.13 Classification of mucopolysaccharidoses[a]

MPS type	Eponym	Clinical manifestations	Enzyme deficiency	Glycosaminoglycan affected	Inheritance	Gene locus
MPS I H MPS I S MPS I H/S	Hurler Scheie Hurler-Scheie	Diagnosis before 2 years of age, early corneal clouding, kyphoscoliosis, organomegaly, heart disease, mental retardation, death in childhood Late corneal clouding, stiff joints, normal intelligence, and life span. Phenotype intermediate between I H and I S, mild to severe skeletal involvement, corneal clouding, early death	α-L-Iduronidase α-L-Iduronidase α-L-Iduronidase	Dermatan sulfate, heparan sulfate Dermatan sulfate, heparan sulfate Dermatan sulfate, heparan sulfate	Autosomal recessive Autosomal recessive Autosomal recessive	4p16.3
MPS II (severe) MPS II (mild)	Hunter (severe) Hunter (mild)	Diagnosis before age 4 years, organomegaly, no corneal clouding or kyphoscoliosis, mental retardation, death before 15 years Normal intelligence, short stature, survival to 20–60 s	Iduronate sulfatase Iduronate sulfatase	Dermatan sulfate, heparan sulfate Dermatan sulfate, heparan sulfate	X-linked recessive X-linked recessive	Xq27.3
MPS III A MPS III B MPS III C MPS III D	Sanfilippo A Sanfilippo B Sanfilippo C Sanfilippo D	Profound mental deterioration, hyperactivity, relatively mild somatic manifestations Phenotype similar to III A Phenotype similar to III A Phenotype similar to III A	Heparan *N*-sulfatase α-*N*-Acetylglucosaminidase Acetyl CoA: α-glucosaminide acetyltransferase *N*-Acetylglucosamine 6-sulfatase	Heparan sulfate Heparan sulfate Heparan sulfate Heparan sulfate	Autosomal recessive Autosomal recessive Autosomal recessive Autosomal recessive	12q14
MPS IV A MPS IV B	Morquio A Morquio B	Distinctive skeletal abnormalities with extreme to mild short stature, corneal clouding, odontoid hypoplasia; milder forms exist Spectrum of severity as in IV A	Galactose 6-sulfatase β-Galactosidase	Keratan sulfate, chondroitin 6-sulfate Keratan sulfate	Autosomal recessive Autosomal recessive	3p21-cen
MPSV	No longer used					
MPS VI	Maroteaux-Lamy	Variable short stature, kyphoscoliosis, corneal clouding, normal intelligence; survival to teens in severe form; milder forms exist	*N*-Acetylgalactosamine 4-sulfatase (arylsulfatase B)	Dermatan sulfate	Autosomal recessive	5q11–13
MPS VII	Sly	Hepatosplenomegaly; wide spectrum of severity, including lethal neonatal form, infantile form with mental retardation and juvenile form with mild mental retardation	β-Glucuronidase	Dermatan sulfate, heparan sulfate, chondroitin 4-, 6-sulfates	Autosomal recessive	7q11.2–22

[a]*Derived from* Hopwood JJ, Morris PC (1990) Mol Biol Med 7:381–404; Neufeld E, Muenzes J (1995); and Whitley CB (1993) (Ref. [267])

kyphosis, and a thoraco-lumbar gibbus secondary to anterior vertebral wedging. The disorder is due to the absence of lysosomal-L-iduronidase in all tissues leading to accumulation of mucopolysaccharides in mesenchymal and other tissues including within neuronal tissues. There is increased secretion of dermatan sulfate and heparan sulfate in the urine and absence of L-iduronidase in cultured fibroblasts. There is relatively little need for orthopedic intervention owing to progressive systemic deterioration.

3.12.13.2 MPS IS (Scheie Syndrome)

The findings in relation to urine secretion and absence of L-iduronidase in cultured fibroblasts are the same as the MPS IH syndrome and differentiation is made on the basis of

the clinical course which is far more benign and of the phenotype in which the intelligence is normal, the facial features are much less coarse and the hepatosplenomegaly is not as marked. There are few orthopedic implications for this disorder.

3.12.13.3 MPS II (Hunter's Syndrome)

The disorder is somewhat milder than the MPS IH syndrome. It is a sex-linked recessive disorder with males only affected. Onset occurs between 2 and 4 years of age and leads to some growth deficiency. In the juvenile type mental and neurologic deterioration at 2–5 years of age leads to hyperactive behavior and spasticity while in those developing symptoms somewhat later the mental deficiency can be mild to absent. The coarsening of facial features, stiff and contracted joints in particular of the hand, and hepatosplenomegaly are also seen. There is urinary excretion of dermatan and heparan sulfate. The major clinical differences in contrast to the Hurler syndrome involve presence of clear corneas, a less severe gibbus, no affected females, and a more gradual onset of features. Deafness can occur as early as 2–3 years of age. Cardiac complications can lead to death prior to 20 years of age and in general the more severe juvenile patients frequently die between 4 and 14 years of age.

3.12.13.4 MPS III (Sanfilippo Syndrome)

This disorder is characterized by onset in early childhood with slowing of growth occurring after 2–3 years of age. Some appear normal until 4 or 5 years of age. There is slowing of mental development followed by rather marked deterioration including difficulties with gait, speech, and behavioral control. The usual result is severe mental deficiency although the syndrome may be compatible with long survival. Significant skeletal abnormalities do not occur. Urinary excretion studies reveal increased heparan sulfate. There are four subtypes—A, B, C and D—which have the same urine findings and clinical appearances but different biochemical abnormalities.

3.12.13.5 MPS IV (Morquio Syndrome)

This disorder was described independently by Morquio and Brailsford in 1929 and defined biochemically as a mucopolysaccharidosis in 1963 [268]. It represents a clear example of a short-trunk disproportionate dysplasia. It is autosomal recessive. Non-osseous problems include corneal opacities due to tissue accumulation of mucopolysaccharides and aortic damage. Morquio pointed out the short trunk with fingers reaching the knees, the prominent sternum, short neck, severe genu valgum, flat feet, hyperextensible thumb and, by radiographs, the epiphyseal abnormality, spacious acetabulae, and generalized platyspondyly. Clinical onset becomes evident between 1 and 3 years of age with severe early limitation of growth and eventual premature cessation of growth. Orthopedic deformities in the MPS syndromes are most extensive with this disorder and are of the spondyloepiphyseal type with diagnostic differentiation depending on biochemical testing [269]. A waddling gait develops along with a knock-knee deformity and flat feet around 3 years of age. The genu valgum becomes very marked if untreated by 8–10 years of age. There is marked involvement of the spine with flattening or platyspondyly of each vertebra with some subsequent ovoid appearances with central anterior bone projections of the vertebral body. The neck is short and there is anterior protrusion of the sternum. The incidence of kyphoscoliosis or scoliosis is high but major deformity infrequently occurs. Odontoid hypoplasia with or without transverse atlantal ligament laxity is always present and virtually all patients will develop signs of a cervical myelopathy of variable severity. Symptoms of cervical myelopathy tend to begin around 5 years of age. The hip and pelvis are abnormal with a flattening of the femoral head and shortened femoral neck. There is an invariable knock-knee deformity, short stubby hands, and joint laxity mostly evident at wrist, ankles, and small joints. Much of the knock-knee deformity is attributable to ligamentous laxity. There is an outward flaring of the rib cage and a prominent sternum. C1–C2 as well as C2–C3 subluxations are common. There is an excessive excretion of keratan sulfate in urine. There are two variants, types A and B, with type IV A due to a deficiency of *N*-acetylgalactosamine-4-sulfatase and type IV B due to deficiency of β-galactosidase. On occasion, the enzyme defects can be diagnosed from cultured skin fibroblasts. Maximum adult height is the range of 100 cm.

Orthopedic treatment involves atlanto-axial fusion or occipito-cervical fusion. Genu valgum often requires soft tissue releases and realignment with femoral or tibial osteotomy. Long leg bracing is usually required post-surgery for additional stabilization.

[The MPS V syndrome was formerly Scheie's disease but this has now been reclassified as MPS I S.]

3.12.13.6 MPS VI (Maroteaux–Lamy Syndrome)

This variant is distinct from the Hurler syndrome because mental deterioration does not occur during early childhood. Epiphyseal irregularity is seen in particular involving the femur and the vertebrae are flattened with anterior wedging in particular of T12 and L1. Odontoid hypoplasia, lumbar kyphosis, and genu valgum are seen. Increased urinary excretion involves predominantly dermatan sulfate.

3.12.13.7 MPS VII (Sly Syndrome)

This is a rare variant characterized by a deficiency of β-glucuronidase. There is moderate mental deficiency. This disorder can be recognized in the neonatal period and is associated with corneal clouding as early as 7 months of age.

Growth deficiency begins immediately post-natally and structural abnormalities involve odontoid hyplasia with atlanto-axial instability, shortening, and anterior inferior beaking of lower thoracic and lumbar vertebrae, a prominent sternum, acetabular dysplasia, and narrowed sciatic notches [270].

The high frequency of atlanto-axial structural abnormality and instability in the mucopolysaccharidoses was documented with 67 patients showing the phenomenon. In five patients there was complete absence of the odontoid process. There were 14 of 18 patients with a thoracolumbar kyphosis which measured from 14° to 53° and was invariably associated with 1 or more hypoplastic anterior vertebral bodies at the thoracolumbar junction. A scoliosis of more than 10° was seen in eight patients with the largest curve at 38°.

3.12.14 Metaphyseal Dysplasia

A group of skeletal dysplasias characterized by radiographic abnormalities most marked in the metaphyses is referred to as metaphyseal dysplasias, dysostoses, or chondrodysplasias. This group, which is relatively rare, represents an example where "fine-tuning" of descriptive entities has led to more confusion than clarity. If short stature is present the physeal regions of the epiphyses must be involved since growth occurs here, not in the metaphyses. The term metaphyseal dysplasia thus describes the most evident radiographic sequelae rather than the region of primary involvement. The three main entities are Schmid type, Jansen type, and McKusick type (or cartilage-hair hypoplasia) [238]. Other described metaphyseal disorders are associated with immunologic or endocrine abnormalities and have radiologic similarities with rickets, especially in relation to metaphyseal irregularities at the physeal–metaphyseal junction. The metaphyseal dysplasias tend to have bowing of the knees, mild short stature, and become evident after 2–3 years of age. Coxa vara is described in many of the entities, although this is clearly an abnormality of femoral neck physeal growth.

Schmid metaphyseal dysplasia. This is the most common entity and has been recognized on numerous occasions. The transmission is autosomal dominant and the disorder is characterized by genu varum, often coxa vara, and short stature. Expanded, irregular metaphyses are noted at hips and knees with the rest of the skeleton virtually normal. Manifestations develop after 2 years of age as bowing persists and short stature becomes more evident. In this "purest" variant of the metaphyseal dysplasias, skull, spine, epiphyses, and carpal and tarsal bones are normal radiologically; there are persisting bow legs with internal tibial torsion and coxa vara; and metaphyseal irregularities predominate.

Jansen metaphyseal dysplasia. The Jansen type of metaphyseal dysplasia is rare but eventually leads to severe dwarfism often with restricted joint movements and clubbed feet. Radiographic abnormalities are centered toward the middle part of the first decade and abnormal architecture of the metaphyses. Asymptomatic hyperglycemia is associated.

McKusick (cartilage-hair) metaphyseal dysplasia. This variant of metaphyseal dysplasia is particularly prevalent among the Amish in Pennsylvania and Finland. Short stature is moderate and the phenotype is characterized by thin sparse hair on the body and head. The finger joints are loose and the fingers have widened and shortened nails. Distal prolongation of the fibula can produce inversion deformity at the ankle. Metaphyses are radiographically irregular with cystic changes across the entire width of the bone.

3.12.15 Spondylometaphyseal Dysplasia

Another variant of descriptive localization in the metaphyseal dysplasias is the spondylometaphyseal group. Many variants have been described but some characteristic features include metaphyseal irregularities, bow legs, coxa vara, a horizontal acetabular roof (similar to achondroplasia), and platyspondyly with kyphoscoliosis. The epiphyses are normal.

Syndromal overlap with spondyloepiphyseal dysplasia and spondylometaphyseal dysplasia is high since there is rarely only epiphyseal or metaphyseal involvement in the latter 2. Joint laxity with spondyloepimetaphyseal dysplasia leads to severe clinical disability including death in the first decade.

3.12.16 Cleidocranial Dysplasia

Cleidocranial dysplasia (CCD) is one of the more commonly seen dysplasias with a characteristic series of changes. It is due to mutations in the transcription factor CBFA1 (core binding factor A1), now more commonly referred to as RUNX2. The disorder is autosomal dominant. The clavicles are hypoplastic and maldeveloped, in association with mild short stature, persistently open or delayed closure of the fontanelles and widening of cranial sutures, wormian bones of the skull, supernumerary teeth, wide symphysis pubis, and occasional coxa vara (Fig. 3.22a, b). Other findings can include mid-face hypoplesia, second metacarpal with two ossification centers, and multiple dental problems including malocclusion and delayed eruption of permanent dentition. The hip abnormalities are accompanied by widened triradiate cartilages during the first decade (Fig. 3.22b). The clavicular abnormalities are always seen but are variable and

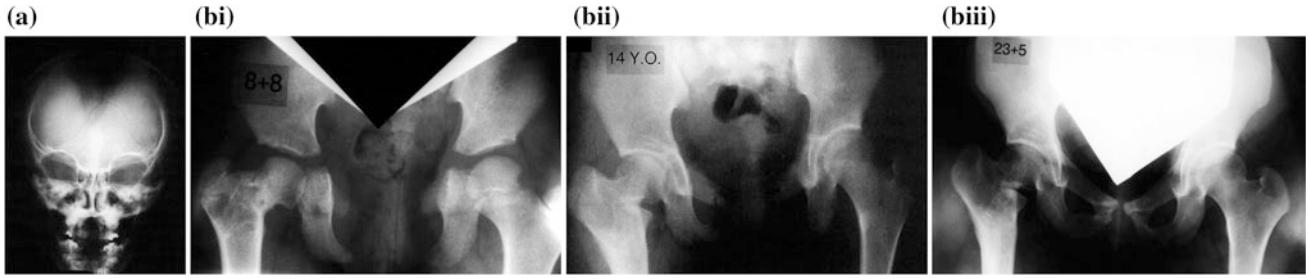


Fig. 3.22 Radiographic characteristics of cleidocranial dysplasia are shown. **a** Cranial X-rays show delayed closure and widening of the anterior fontanelle and cranial sutures. Wormian bones are present but not clearly seen. **b** Pelvic abnormalities are characterized by coxa vara, widened triradiate cartilages during the first decade, and delayed ossification of the pubic and ischial bones. Eventual ossification of the latter is complete. **i–iii** Note progressive ossification from age 8 to 14 to 23 years

may be asymmetric (Fig. 3.12). They include complete absence but there may be shortened medial segments present. The shoulders can generally touch anteriorly. Mutations in the coding region of the CBFA1 gene included frameshift, nonsense splicing, and missense mutations as well as novel polymorphisms [271]. The CBFA1/ RUNX 2 gene is a transcription factor with a major role in osteoblast differentiation as part of the intramembranous ossification system. Since the skull and clavicle form primarily by intramembranous mechanisms the effect of the mutations is understandable. Short stature and dental anomalies must also be accounted for in CCD [272]. Studies of clinical findings and gene mutations in many patients have allowed for further understanding based on the concept of the degree of persisting function allowed by a particular mutation.

All patients, mild to severe, had the classic CCD phenotype with hypoplastic clavicles and open fontanelles, abnormalities affected intramembranous ossification. Short stature however indicates associated involvement of the endochondral mechanism of development. A significant correlation was seen between short stature and the number of supernumerary teeth. These gene-phenotype correlations highlight a quantitative dependency on the gene dosage of RUNX2. This gene–dosage effect becomes evident with small reductions in the total RUNX2 activity, by approximately one-fourth of the normal. It has been suggested that cleidocranial bone formation mediated by intramembranous ossification may require a different functional level of RUNX2. They determined that heterozygous mice which had 79–84 % of normal Runx2 had a normal bone phenotype while those with less than 70 % had skeletal findings of the CCD syndrome with clavicle and calvarial defects but no growth plate abnormalities [273–275]. This study gave experimental support to the concept that there is a critical gene dose requirement of functional Runx 2 for formation of intramembranous bone. Null mutation of Runx2 in mice leads to neonatal death with a complete absence of bone tissue, defective hypertrophic chondrocytes, and no differentiated osteoblasts. Zheng et al., studying a severely involved 20-week fetus at autopsy, noted a markedly diminished zone of hypertrophic chondrocytes in long bone epiphyses along with disorganized growth cartilage above [276]. The Runx2 mRNA was about 50 % normal levels only.

3.12.17 Hereditary Progressive Arthro-Ophthalmopathy (Stickler Syndrome)

The Stickler syndrome involves joint problems, eye problems, hearing loss, and developmental facial anomalies. It is an autosomal dominant disorder. Since its initial description in 1965 it has become well recognized [277, 278]. The disorders are due to mutations of type II collagen COL2A1 or type XI collagen COL11A1 or COL11A2 [279].

Joint Involvement: Joint involvement occurs in 90 % of patients. In most, symptoms begin in the first decade of life with joint pain followed by swelling. Joint hypermobility in childhood is common. Hips and knees are most commonly affected with wrists and ankles also affected. Many have degenerative arthritis by mid-adult life [104]. Some eventually require joint arthroplasty. Hip involvement is characterized by coxa valga, widening of the femoral neck, and occasionally protrusion acetabuli.

Eye Involvement: Eye involvement occurs in 95 %. This includes myopia in 90 %, retinal detachment in 60 %, and blindness in 4 %. Cataracts are common. Retinal detachment can occur even in the first decade but is most frequent between 10 and 30 years of age. The myopia is congenital, of high degree, and non-progressive. The abnormalities of vitreous gel architecture are pathognomonic and used as a classification tool. The majority of patients have been suffering from a congenital anomaly of the vitreous correlating with defects in type II collagen. Others with collagen type 11 defects have a vestigial vitreous gel bordered by a distinct folded membrane.

Hearing Loss: Hearing loss is present in 70 % but rarely proceeded to complete deafness. This is multifactorial with conductive, sensorineurol, and mixed causes.

Facial Anomalies: Facial developmental anomalies are seen in 84 % involving some or all of flat face, small mandible, depressed nasal bridge, and midline clefting varying from high arched palate to cleft palate to a complete Pierre Robin sequence. (Some patients with a diagnosed Pierre Robin sequence will turn out to have Stickler disease as well.)

3.12.18 Dyschondrosteosis

The initial description and naming of dyschondrosteosis was in 1929 by Leri and Weill [280]. It is transmitted as an autosomal dominant disorder with females more frequently (4:1) and more severely affected than males. Dyschondrosteosis is a disproportionate skeletal dysplasia characterized by short stature with limbs more affected than trunk, Madelung's deformity at the wrist, and mesomelia involving shortening of the middle segments of the upper and lower extremities (Fig. 3.23) [281, 282]. The most shortened segments involve the radius, ulna, tibia, fibula, and sometimes the adjacent carpal and tarsal bones. Dyschondrosteosis is a specific skeletal dysplasia which although mild is generally characterized by the presence of Madelung's deformity of the distal forearm and wrist. When a Madelung's deformity is seen the patient should be carefully assessed as the large majority will have the deformity in association with either hereditary multiple extososis, Ollier's disease, or dyschondrosteosis. The disorder is caused in at least 60 % of patients by SHOX (short-stature homeobox-containing gene) heterozygous mutations, usually large-scale deletions. SHOX encodes a cell-specific homeodomain protein involved in cell cycle and growth regulation that acts as a transcription activator in osteogenic cells [98, 283, 284]. The deformity defined by Madelung in 1878 involved marked hypoplasia of the distal ulna along with its dorsal subluxation or dislocation and an ulnar drift of the wrist and hand [285]. There may be slight lateral diaphyseal bowing of the radius associated with the shortened ulnar component. If the ulna is particularly shortened, it causes a tethering effect medially on the distal radius and there is obliquity of the distal radial articular surface causing it to face in an ulnar and palmar direction and associated obliquity of the distal radial secondary ossification center and physis. In severe cases premature fusion of the medial half of the distal radial physis accentuates the deformity in adolescence. Radio-ulnar shortening can involve both bones equally or the radius predominantly.

It is extremely difficult to diagnose the disorder at birth but it is usually evident by the middle to the end of the first decade. Shortness of stature is an invariable occurrence although it is relatively mild. Adult height in dyschondrosteosis is mildly reduced and ranges from 137 to 163 cm. Most affected patients are within the normal range for height but at the lower margins.

Fig. 3.23 Anteroposterior radiograph of the forearm in a patient with dyschondrosteosis shows the characteristic Madelung's deformity at the wrist with the shortened and dorsally displaced ulna and the radial bowing

Beals and Lovrien documented shortening and mesomelia finding that radial length compared to humeral length was 65 % (normally 75 %) while the tibial length decreased to 70 % (normally 82 %) in relation to femoral length [286]. There can also be tibio-fibular disproportion with the fibula relatively longer either proximally (associated with tibia vara) or distally (without major ankle deformity). Hand radiographs in 39 individuals showed an early stable pattern allowing for diagnosis at any age; the metacarpophalangeal profile (MCPP) shows distal phalanx 2 disproportionately long and 2nd metacarpal disproportionately short [287]. There are relatively few reports of requirements for surgical intervention for the forearm, wrist, and hand deformities although with increasing sophistication of these procedures consideration for their use is increasing. Beals and Lovrien indicated however that patients with dyschondrosteosis

exhibited little functional impairment or cosmetic deformity and they felt that therapy was usually unnecessary. On occasion patients are seen with a genu varum severe enough to warrant surgical correction.

3.12.19 Other Mesomelic Dysplasias

Many disorders are characterized by the mesomelic pattern of forearm (radius–ulna) and leg (tibia–fibula) shortening. Langer mesomelic syndrome has a disproportionate short-limb dwarfism with mandibular hypoplasia, upper and lower extremity shortening with particularly marked shortening of the forearms and legs, and greater ulnar shortening compared to the radius and fibular compared to the tibia. Homozygous loss of SHOX (short-stature homeobox-containing gene results in the disorder. Nievergelt mesomelic syndrome presents with forearms and legs about one-third the lengths of arms and thighs. There is a characteristic rhomboidal shape of the tibia and a triangular fibula.

3.12.20 Acromesomelic Dysplasia

Dysplasias occur in which both progressively more extensive mid- and distal limb shortening occurs. Acromesomelic dysplasias refer to the presence of both distal (acromelia) hand and foot shortness and shortness of the forearm and leg (mesomelia). The commonest variant is acromesomelic dysplasia Maroteaux (AMDM) due to mutations in the transmembrane natriuretic peptide receptor gene NPR-2. Two specific variants are Grebe dysplasia and Hunter–Thompson dysplasia.

Grebe Chondrodysplasia. A marked variant of an acromesomelic syndrome is Grebe chondrodysplasia with profound upper and lower extremity shortening concentrated in forearms, legs, and digits. In this disorder there is a normal axial skeleton, relatively normal humerus and femur but markedly shortened and deformed forearms (radius/ulna) and legs (tibia/fibula) and even more severe abnormalities of the hands and feet with fused carpal and tarsal bones, several metacarpal and metatarsal bones absent, proximal and middle phalanges of the fingers and toes invariably absent, and distal phalanges present. The digits are reduced to mere appendages and there is often postaxial polydactyly [288].

Hunter–Thompson acromesomelic dysplasia. This variant is milder than the Grebe disorder with mildly shortened forearms and legs, fibulae represented by distal triangular remnants, metacarpals extremely short, several finger phalanges absent, variable hypoplasia of the metatarsals and single phalanges of the toes [289].

3.12.21 Acromelic Syndromes (Acrodysplasias)

There are literally dozens of syndromes with digital anomalies leading to shortness and malformation present either exclusively or predominantly in the hands and feet. These most distal abnormalities are included in limb shortening disorders referred to as acromelic or as the acrodysplasias. The short hands and feet are usually associated with shortened stubby digits. Although many of the disorders are isolated to the hands and feet many are also associated with craniofacial abnormalities, ectodermal abnormalities including the nails, teeth, gums, and hair, and other organ abnormalities including in particular structural cardiac problems. It is perhaps not surprising that these regions are subject to considerable developmental malformation since there are numerous bones present within a relatively restricted region. With the recent deciphering of gene and molecular abnormalities of skeletal development, many of these disorders are being defined in relation in particular to abnormalities of patterning genes active in early limb bud formation. Even in the relatively pure syndromes limited to hands and feet there are almost always subtle abnormalities detected elsewhere. The classic forms of acrodysplasia however involve shortening of the tubular bones of the hands and feet, cone shaped diaphyses and virtually no changes elsewhere. The most prominent shortening is seen in the metacarpals and metatarsals. Amongst the earliest descriptions of this particular disorder is one by Brailsford who referred to the disorder as peripheral dysostosis.

Ellis-Van Creveld syndrome. The Ellis-Van Creveld (EVC) syndrome is characterized by acromelic limb shortening, polydactyly primarily of the hands and ectodermal dysplasia involving the nails, teeth and gums. Congenital heart disease is present in approximately 50 % of patients, most commonly a single atrium with a cleft mitral valve. The face is characterized by hypertelorism. Also seen is sparse, absent or silky hair, variable tooth abnormalities involving either early or late presentation but always pegged and hypoplastic appearances, and gums adherent to the lips. The nails of the hands and feet are always deformed. In the upper extremity there is an extra digit always on the ulnar side and an occasional extra digit on the radial side leading to 6 or 7 digits overall. The clavicles are abnormal, the radial heads usually dislocated, and a knockknee deformity almost always develops in the first decade. The genu valgum that results is due to a defect to the lateral portion of the proximal tibia. The Ellis-Van Creveld disorder is now more commonly referred to as chondroectodermal dysplasia. The abnormality is detected in the newborn.

Tricho-rhino-phalangeal syndrome. In the TRP syndrome the peripheral dysostosis is associated with short hair, mild short stature and a large pear shaped nose. The major

orthopedic disorder associated with TRP is a Perthes-like hip involvement which often heals with marked deformation [290, 291]. The trichorhinophalangeal dysplasia syndrome has been increasingly recognized over the past few decades since its original description in 1966. The affected individuals have fine, sparse and brittle hair; a pear shaped bulbus nose and long philtrum; and cone-shaped epiphyses in the phalanges. Most patients are also short and many show hip abnormalities characteristic of either unilateral or more often bilateral Leg-Perthes disease. The hip abnormalities however are almost invariably of the more severe gradient of the Perthes disorder and tend to lead to flattening and widening of the head with hinge abduction phenomena. Premature osteoarthritis occurs and many patients have considerable discomfort even in adolescence. The disorder is autosomal dominant and it is increasingly suspected that it is more common than previously recognized. Shortening of the fingers and toes generally accompanies the cone shaped epiphyses and may be particularly apparent in metacarpals and metatarsals. Cone-shaped epiphyses are present in many skeletal dysplasias having been described in over 20 disorders and must not be considered as diagnostic of TRP dysplasia alone. The most serious complication is the hip disorder although the avascular necrosis is variable. It tends however to the more severe variants. Eventual changes of coxa magna, coxa plana, coxa vara, and a short neck are described. A wide variety of bone and ligament abnormalities have been reported including joint laxity, scoliosis, dislocatable and even absent patellae, delayed tooth eruption, and spondylolisthesis. It is the hip disorder however which is most commonly seen and the most severe skeletal aspect of the disorder. Progressive degenerative arthritis almost invariably occurs in the hips but can also affect the spine, knees, and elbows. It has been suggested that early diagnosis and more vigorous containment therapy might help improve the end results. In one study however all patients eventually evolved to a Stulberg class IV deformity [290, 291].

Craniofacial dysostoses. Many of the digital abnormalities are associated primarily with major craniofacial developmental abnormalities. Many of these have been found associated with molecular abnormalities of FGFR2 [59]. Craniosynostosis syndromes are increasingly linked to abnormal gene loci [292]. Some of the more frequently seen disorders follow [17].

Apert syndrome. Amongst the commonest disorders is the Apert syndrome (acrocephalosyndactyly). The main clinical features are a high forehead, flat occiput, mid facial hypoplasia, and fusion of the second, third, and fourth fingers and toes.

Pfeiffer syndrome. Pfeiffer reported a family with mild acrocephaly in association with cutaneous syndactyly of the second and third fingers and marked deviation of broadened thumbs and great toes.

Crouzon syndrome (craniofacial dysostosis). The Crouzon syndrome is associated with craniostenosis with mid facial hypoplasia, hypertelorism, nasal beaking, prominent eyes, dental malocculsion and deafness. Other of the craniofacial disorders can also be associated with digital abnormalities.

Polydactyly syndromes. Preaxial polydactyly involves a unilateral extra thumb or big toe and can be seen as isolated autosomal dominant disorders. Postaxial polydactyly is more common with 6 digits present and can be seen either as an isolated syndrome or more commonly in association with multiple other disorders.

Syndactyly. Syndactyly refers to bone or soft tissue union of 2 or more digits. A multiplicity of forms and variants has been described. These can occur as either an isolated phenomena or more frequently as components of well established genetic disorders such as the acrocephalosyndactylys.

Digital dysplasia syndromes. In the final group of disorders many digital abnormalities are associated with malformations of other organs of other parts of the musculoskeletal system. Amongst the 3 most common of these are the Holt-Oram syndrome in which unilateral dysplasia of the thumb is associated with malformations of the heart. In some the thumb is totally absent and limb defects particularly on the radial side can be extensive. There can also be extra or abnormal bones in the carpus.

Poland syndrome. In this disorder there is the association of unilateral cutaneous synbrachydactyly with ipsilateral absence of the pectoralis minor muscle and the sternal portion of the pectoralis major. Rib defects together with absence of part or all of the hand is an occasional component. Dextrocardia can also be associated. Brachydactyly refers to shortening of a single or multiple digits due to bony malformation.

Other deformities involving increased or decreased length of individual or groups of digits as well as rectangular deformations have been described.

3.12.22 Larsen Syndrome

3.12.22.1 Overview of Syndrome

Larsen syndrome is characterized by multiple congenital large joint dislocations and characteristic craniofacial flattened midface, depressed nasal bridge, widely spaced eyes (hypertelorism) and a prominent forehead [293]. While not all joints are affected in each patient, several regions of abnormality must be present for the diagnosis to be made and the knee with rare exceptions is always involved. Knee involvement ranges from recurvatum to subluxation to

complete dislocation [294]. As well as knee involvement the multiple joint dislocations include the hips (dislocatable, subluxed, dislocated), elbows (dislocation, proximal radioulnar synostosis), hands and wrists (radiocarpal dislocation, digital dislocations/subluxations, polydactyly). Equinovarus foot deformities are common along with metatarsus adductus and flat feet. Spinal problems are extremely prominent with such deformities as C1–C2 instability, cervical spinal bifida, and a mid cervical kyphosis owing to underdevelopment of the anterior parts of the vertebral bodies [295]. Associated myelopathy can occur. There is a tendency to decreased interpedicular distance in the thoracic region and mild to moderate thoracolumbar scoliosis without bony deformity. There is a large extra (bifid) ossification center in the calcaneus seen in early childhood in the first decade. The thumb is widened and flattened, as are some of the other digits with particular shortening of the distal phalanx. Supernumerary carpal bones and short broad (spatulate) fingers are seen. Short stature, cleft palate and hearing loss due to malformations of the auditory ossicles can be associated.

3.12.22.2 Molecular Defects

Autosomal dominant variants are more common. They are due to mutations in FLNB, the cytoskeletal protein filamin B [296]. These can be missense mutations or small inframe deletions. Autosomal recessive Larsen syndrome is caused by carbohydrate sulfotranserase 3 mutations (CHST3). Chondroitin sulfate proteoglycans show markedly decreased 6-0-sulfation but enhanced 4-0-sulfation confirming functional impairment of CHST3 [297]. The disorder is distinct from diastrophic dysplasia sulphate transporter (DTDST)-deficient cells. Phenotypic characteristics of dominant and recessive variants are similar but recessive Larsen, humero-spinal dysostosis and spondyloepiphyseal dysplasia Osman form a phenotypic spectrum.

3.12.22.3 Knee Abnormalities

In a review of 38 cases there were 12 grade 1 tibiofemoral dislocations, 5 grade 2, and 18 grade 3 (using the Leveuf-Pais classification) [294]. There were also isolated dislocations or subluxations of the patella and dislocatable patellas. The grade 1 disorders were treated with progressive casting in flexion and grade 2 also with casting with surgery reserved for patellofemoral dislocations. The severe grade 3 were best treated with early open surgical correction which usually entailed resection of medial and lateral retinacula and iliotibial fascia, V-Y reconstruction of the external apparatus, medial transfer of one-third of the patellar tendon, capsulorrhaphy and casting.

3.12.22.4 Vertebral Abnormalities

The cervical spine is the most often and most severely affected in Larsen syndrome. Cervical kyphosis is present in about 50 % with subluxation or fusion of the C2–C3–C4 vertebral bodies. There was often posterior vertebral arch spina bifida (cervical) with dysplastic laminae and hypoplasia of the lateral processes of all cervical vertebrae. Spinal instability with myelopathy and quadriparesis often developed. Anteroposterior spinal dissociation must be looked for in Larsen syndrome with CT study particularly valuable for demonstration [298]. There can be gross dissociation between anterior and posterior cervical spinal elements owing to multiple vertebral body hypoplasia and associated posterior spinal dysraphism. This can also cause a collapsing cervical lordoscoliosis. There can also be multiple levels of cervical spondylosis with a fibrocartilagenous anteroposterior defect. At surgery Luk and Yip described the unstable cervical spine as showing either complete dissociation of laminae from the vertebral bodies at the pedicle region or the spondylolysis area filled with fibrocartilage. Often halo traction followed by lengthy cervical fusion anteriorly and posteriorly are needed [299].

In summary, descriptions of vertebral abnormality include, in varying combination from patient to patient: cervical kyphosis or lordosis, subluxation or fusion of vertebral bodies, posterior vertebral arch dysraphism (spina bifida with failure of fusion of posterior arches), dysplasia of the laminae, hypoplasia of lateral processes of cervical vertebrae, spondylolysis at pedicles to enhance dissociation, and thoracolumbar scoliosis without vertebral anomalies.

3.12.22.5 Frequency of Clinical Findings

In a study of 20 families with 52 affected children in an autosomal dominant group all families had dislocations or subluxations of the large joints (65 % elbow, 80 % hip, 80 % knee dislocations) along with clubfoot 75 %, anterior chest wall deformities (pectus excavatum or carinatum) 55 %, short stature 70 % below the 10th percentile but rarely below the first centile), characteristic facial findings (50–60 %), spatulete finger especially the thumb (all but 1), conductive deafness (20 %), and all with supernumerary carpal and tarsal ossification centers [296]. The disorder is more characteristic of a hyperlaxity syndrome than a primary skeletal dysplasia.

3.12.23 Ollier's Disease

3.12.23.1 Terminology

Ollier's disease is a rare, non-hereditary skeletal condition characterized by persisting cartilage masses in the metaphyses and diaphyses, subperiosteal deposition of cartilage, and asymmetrical involvement of the limbs, with 1 side being either exclusively or predominantly involved. The affected bones often are shortened and deformed (Fig. 3.24). In childhood they are subject to pathological fractures and in adult life to malignant degeneration. This bone disease, defined initially by Ollier, is included by some in the condition referred to as multiple or general endochondromatosis, but it is topographically separate from the condition of bilateral multiple enchondromas, in which involvement of the short tubular bones of the hands and feet is greater [300–303].

3.12.23.2 Disease Profile

A study assessed 21 patients with Ollier's disease in relation to angular deformities, pathological fractures and limb-length discrepancies and their orthopaedic treatment [304]. Seventeen patients had exclusively unilateral involvement while 4 had predominantly unilateral involvement. There was equal distribution between the sexes (11 male, 10 female) and between the left and right sides. The femur and tibia were the bones involved most frequently. The pelvis, in particular the iliac crest, and the fibula also were affected commonly. The metaphyses were the main sites of involvement, although diaphyseal involvement was seen as well in the more severe cases. Epiphyseal irregularities were seen in the patients with the most extensive involvement, usually becoming apparent radiographically after the age of 5 years but significant epiphyseal deformity did not occur. In the proximal end of the femur the initial focus of abnormality was usually the lesser trochanter, with involvement seen toward the greater trochanter and inferiorly in more severe cases. The femoral neck was relatively spared. In all patients, the region of involvement did not change with time. Pelvic and fibular involvement did not pose any clinical problems in these patients, and lesions of the hand and foot posed relatively few problems. Although the shortening and deformities were progressive, the positions and radiographic features of the lesions did not change with growth, with rare exceptions. As the metaphyseal lesions matured, punctate calcifications were seen in them quite often. The youngest patient showing this characteristic radiographic finding was 6 years old; such changes sometimes were not seen until the age of 13 years. Fairbank described a severe case in which calcification was seen at the age of 2 years and 8 months [303]. Dense calcification in cartilage lesions is considered to be a feature of benign processes, whereas the disappearance of calcified masses may be a sign of malignant change. The radiographs in the series showed increasing and more-normal bone density after skeletal maturation. Normal trabeculation did not occur in any site where there was a lesion.

Anthropometric measurements were available for 18 patients. All measurements of height were within the normal range. Two children were 1.5 standard deviations above the mean; 2 were 1 and 2, 0.5 standard deviation above the mean; 8 patients had height measurements at the mean; and 3 were 1 and 1, 2 standard deviations below the mean.

3.12.23.3 Clinical Sequelae

The important clinical problems were progressive shortening of the involved extremity, angular deformity, and pathological fracture. Malignant degeneration to chondrosarcoma was not seen but this should not be considered a definitive observation, because the patients were not followed into adult life. Malignant change in Ollier's disease generally occurs in the adult years.

Angular deformities. The location and degree of angular deformity were closely related to the position and extent of enchondromas. When a metaphyseal area was involved uniformly across the width of the bone, there was no deformity other than shortening. Epiphyseal plate growth tended to be slow adjacent to metaphyseal enchondromas. Deformity invariably occurred when metaphyseal involvement was not uniform across the entire width of the bone. Angulation was associated in all instances with non-uniform enchondromatous metaphyseal involvement. The concavity of the angular deformity always was adjacent to the more extensive endochondromatous involvement. Angular deformity was common, most often in the distal part of the femur, and was most severe there. Repeated osteotomy often was required to achieve good alignment at skeletal maturity. Although instances of proximal and distal tibial angulation also occurred, a single osteotomy performed toward the latter part of the growth period generally was sufficient in those patients. Growth is slower adjacent to the enchondromas, either because epiphyseal cartilage is abnormal or because there is a tethering effect on the epiphyseal cartilage tissue by an abnormally thick periosteal sleeve in reaction to the lesions. Any non-uniform involvement with enchondromas indicates the direction the deformity will take, and the more extensive the involvement the more likely it is that there will be recurrent deformity after osteotomy. Spontaneous correction of deformity, either partial or complete, was not seen.

Involvement of the lower extremity. Of the 20 patients with involvement of the lower extremity, each of the 6 with proximal femoral lesions had coxa valga, but that deformity

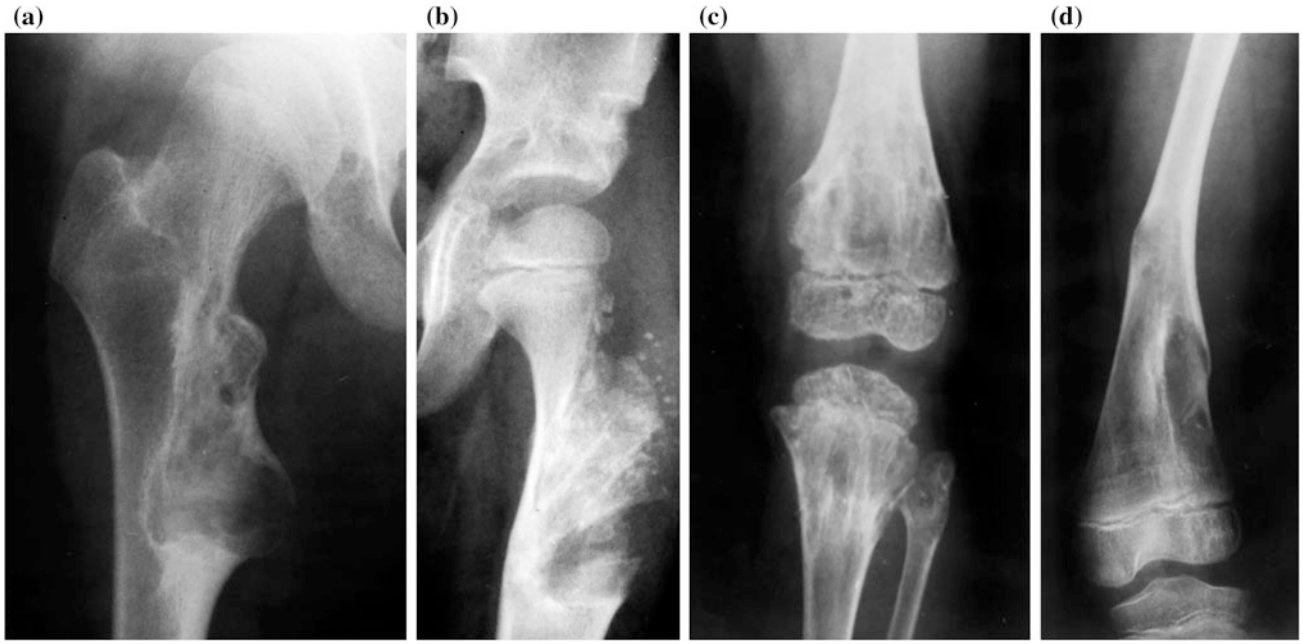


Fig. 3.24 Radiographic findings in Ollier's disease are shown. **a** A characteristic localized focus of cartilage is seen in the proximal femur in the area of the lesser trochanter and proximal medial diaphysis. (Reprinted with permission from Shapiro F, Ollier's Disease. J Bone Joint Surg Am. 1982: 64A: 95–103). **b** Slightly more extensive area of involvement affects the greater trochanter and proximal diaphysis. The cartilaginous tissue is concentrated laterally. Punctate foci of calcification are characteristic of this disorder. **c** Shortening, often of several centimeters, occurs when there is involvement of the distal femur and proximal tibia. Radiolucencies in the metaphyseal region are characteristics. If the involvement is uniform across the diameter of the bone in both anteroposterior and lateral projections shortening is present but is not complicated by angular deformity as in this case. **d** Angular deformity occurs when uniform involvement across the diameter is not seen. There is a considerable valgus deformation of the distal femur leading to obliquity of the knee joint. The cartilaginous focus (radiolucent area) is concentrated at the distal lateral femur impacting negatively on the adjacent lateral femoral physeal growth

always was mild and virtually non-progressive. There were no instances of subluxation, dislocation, or dysplasia of the hip, and corrective osteotomy never was required. Coxa vara was not seen. Fifteen of the 19 patients with distal femoral involvement had an angular deformity, 8 showing varus and 7 valgus angulation. Two patients also had anterior angulation because of prominent posterior enchondromas. One patient had posterior bowing because of an anterior enchondroma. Of the 8 patients with varus deformity, 5 required an osteotomy. There were 11 osteotomies in all, ranging from 1 to 4 per patient. Of the 7 patients with valgus deformity, 5 required osteotomy, for a total of 13 osteotomies. One patient had 6 osteotomies. The need for repeated osteotomies was manifest primarily in the distal end of the femur, especially with valgus deformity. Eight patients had angular deformities in the tibia, 6 proximally and 2 distally. Proximally, only tibia valga was seen. Of the 6 patients, 4 had an osteotomy. A single procedure was sufficient to provide and maintain correction in each. Distally, 2 patients had a varus deformity, and 3 osteotomies were required.

3.12.23.4 Distal Femoral and Tibial Deformities

Of the 8 patients with a varus deformity of the distal end of the femur, 5 had osteotomies. The first patient had 35° of varus angulation and underwent 4 medially based opening-wedge osteotomies, at the ages of 9, 11, 12, and 15 years. In retrospect, all of the wedges were insufficient, and the final varus angle was 20°. The second patient had an osteotomy at the age of 4 years for a 20° deformity. By the age of 8 years, 20° of deformity had recurred, but it was balanced by 20° of proximal tibia valga. Both deformities then remained virtually unchanged well into adult life. The third patient had a distal femoral varus opening wedge osteotomy at 9 years of age with repeat procedure for final straightening at 15 years of age. The fourth patient had 25° of varus angulation; 2 osteotomies were done, at the ages of 8 and 12 years, and a straight femur was evident at skeletal maturity. The fifth patient had a 20° varus deformity, corrected by osteotomy at the age of seventeen years. Of the 3 patients who did not have surgical intervention, one was 7 years old, with a 25° deformity; one 15 years old, with a 10° deformity balanced by proximal tibia valga; and one was

an adult with a 20° deformity in a severely shortened limb that required a prosthesis.

Five of the 7 patients with a distal femoral valgus deformity had osteotomies. One had a 25° deformity. At the age of 6 it was corrected to 10° with an opening-wedge procedure. At the age of 13 years the deformity was 15° and full correction was then attained with another osteotomy. The second patient had a 35° deformity for which 6 osteotomies were done, at the ages of 4, 7, 9, 11, 13, and 14 years. At maturity the femur was straight. The third patient had 2 distal femoral opening-wedge procedures, one at 9 years for a 25° deformity and one at 13 years for a 30° deformity. The fourth patient had a distal femoral osteotomy at the age of 4 years for a 30° angulation but was lost to follow-up. The fifth patient had 2 distal femoral opening-wedge procedures, one at 9 years old for a 20° deformity and one at 15 for a 30° deformity. In the 2 patients with valgus deformity who did not have an osteotomy, one was an 8-year-old child with a 15° angulation and the other was 13-year-old with only 8° of deformity.

Eight patients had an angular deformity of the tibia. Of the 6 with proximal tibia valga, 4 had a laterally based opening-wedge osteotomy: at 14 years old (an 18° deformity), at 8 years old (for a 25° deformity), at 12 years old (for a 20° deformity), and at 14 years old (for a 15° deformity). The angulation had developed relatively slowly in each patient. The 2 patients with proximal tibia valga who did not have an osteotomy also had a varus deformity of the distal end of the femur, so that alignment of the 2 long bones was nearly normal although the articular surfaces at the knee in both patients were slightly oblique.

The 2 patients with varus deformity of the distal tibia each had a closing-wedge osteotomy. In one this was performed at the age of 6 years, correcting a 15° tilt to neutral, but by the age of 15 the deformity had recurred (to 25°) and the osteotomy was repeated. A closing-wedge osteotomy also was required on the opposite ankle although there was no radiographic evidence of endochondromatosis on that side. The second patient still had a 20° varus tilt at skeletal maturity, despite early osteotomy but the angle had not changed greatly over a decade. The involved side was extremely short and a prosthesis was needed. All femoral and tibial osteotomies healed normally, whether the osteotomy was above or through enchondromatous lesions. Acetabular or other pelvic deformities never were of clinical significance. Angular deformity associated with enchondromas was not seen in the fibula; any fibular deformity appeared to be secondary to tibial involvement. Although the proper timing for an osteotomy depends on many variables, the procedure generally is indicated when the weight-bearing alignment of the extremity is altered significantly. As a rough guide, an angular deformity of 20° or more, not balanced by a reverse deformity, is an indication for osteotomy. If possible, procedures should be delayed to limit the number required.

There were 3 causes of recurring angulation after osteotomy: 1. The persistence of the disease at the epiphyseal growth plate and metaphysis. The osteotomy is directed at the deformity and not at its primary cause. 2. Inadequate correction of the deformity at the time of operation. Careful review of the immediate postoperative radiographs showed that under-correction had been accepted. 3. Loss of correction post-operatively. If possible, the osteotomy should be made on the diaphyseal side of the enchondromatous area, so that the bone wedge will rest on normal corticocancellous bone. However, an intralesional osteotomy often is required because the lesion is so extensive and because maximum correction is achieved when the osteotomy is performed at the apex of the deformity. Frequently neither the bone wedge nor the metallic fixation had good inherent stability and collapse did occur. The patients must be monitored carefully by radiographs.

Although it might seem that overcorrection of the deformities could decrease the likelihood of the need for reparation, overcorrection rarely is done, since few patients or families readily accept the substitution of one deformity for another. In addition, it is difficult to know how much overcorrection is desirable.

3.12.23.5 Involvement of the Upper Extremity

One patient had bilateral upper-extremity involvement, with the left side much more extensively involved. The lower extremities were normal radiographically. The proximal end of the humerus was bowed markedly (50° of valgus angulation) and an osteotomy to correct the deformity was considered, although not done. A distal ulnar-resection osteotomy was done at the age of 13 years to correct radial deviation due to relative ulnar lengthening.

3.12.23.6 Lower Extremity Length Discrepancy

The extremity with the enchondromas always was shorter than the opposite one. The extent of the shortening paralleled the radiographic involvement. There was no correlation between degree of angulation and extent of shortening. If the entire width of the distal femoral metaphysis was involved with enchondromatous tissue, the shortening was severe but angulation was absent. The maximum discrepancy reached prior to any surgical treatment for correction of discrepancy ranged from 4.3 to 35.7 cm (average, 9.8 cm). There was a progressive increase in the discrepancy in all patients throughout the growth period. The rate of inhibition of growth appeared to be constant in all patients. These observations allow for accurate estimates of the ultimate discrepancy. After the first few years of life the need for

osteotomy and perhaps repeat osteotomy will have become apparent. Although the epiphyseal arrests in this series did not always equalize the limb lengths, retrospective assessment indicates that growth-remaining charts are useful; but even when the actual amount of correction needed from an arrest is known precisely, it is the deformed limb that must make up the deficit and its growth rate is slow. The affected bones often are so short that their length is at or below the second standard deviation below the mean. Therefore, the amount of correction to be gained must be extrapolated from the charts, and the arrests may have to be performed at an early age. If the projected discrepancy is 5 cm or less, well-timed epiphyseal arrest alone can produce excellent results, but when larger discrepancies exist the loss of height and the uncertainty of correction invite the use of other techniques. Diaphyseal lengthening of some of the involved long bones is a feasible alternative in some patients even though those with the greatest amount of shortening, who would benefit most from a bone-lengthening, often cannot undergo the procedure since the bulbous enchondromatous metaphyseal diaphyseal involvement does not provide a stable site for the distraction device to pull against. In patients in whom the projected discrepancy is 5 cm or more, however, diaphyseal lengthening for partial or full correction warrants strong consideration.

Unsatisfactory results may be seen when, in particular in the last few years of the growth period, combinations of osteotomy, epiphyseal arrest, and diaphyseal lengthening are used. Imperfect results from one procedure, in particular diaphyseal lengthening, may require that an epiphyseal arrest be done, but may obscure the appropriate timing for that procedure. If done too late, an arrest will not be fully effective. The bone-lengthening operation is technically difficult at any age, but a bone studded with enchondromas and perhaps deformed distally or proximally, or predisposed to recurrent deformation, compounds the problems. A lengthening procedure may have to be coordinated with an epiphyseal arrest on the opposite side.

Epiphyseal arrest. Twenty standard epiphyseal arrests were performed for limb-length discrepancy. When patients were too old to obtain full correction, only limitation of discrepancies was attainable. Three one-sided hemiphyseal stapling (medial or lateral) procedures were done in an effort to correct angular deformity, but each was ineffective. Retrospective reviews of the results achieved with epiphyseal arrest indicate that the corrections gained were what would have been expected based on the growth charts.

Diaphyseal lengthening. Five patients had 6 diaphyseal lengthening procedures, 5 tibial and 1 femoral. Lengthening was performed where the actual or projected discrepancy was considerable (6 cm or more). Five lengthenings were done in mildly to moderately involved bones and one was done in a normal tibia, originally the same length as the one on the opposite side. The femoral lengthening (Wagner technique) achieved a 9.0 cm increase. Two tibial lengthening were done by the Wagner method and the other 3, by the Anderson method. The 5 tibial lengthenings achieved an average gain 4.8 cm (range, 4.0–5.1 cm). Fourteen additional operative procedures associated specifically with the lengthening were required. With the Anderson technique, each patient had a tibiofibular synostosis several months before lengthening, and the pins were removed when healing was well advanced. With the Wagner technique, secondary plating and bone-grafting always was done and the plates were removed when healing was complete. In 1 patient a tendo Achilles lengthening was needed, and in another the plate fractured and had to be replaced. There were no instances of failure of consolidation of the bone after lengthening. Data on limb-length discrepancy are presented in Table 3.2b. The cases of 5 patients who did not have surgical treatment were not tabulated. One had so short an affected limb (35.7 cm at maturity) that he required a prosthesis. Three were young (4–8 years old) and were under observation, with discrepancies measuring 3.4, 1.3, and 1.0 cm. The fifth patient died of neuroblastoma at the age of 11 years. His discrepancy was 4.0 cm.

3.12.23.7 Pathological Fractures

Seven of the 21 patients (33 %) had an average of 2 pathological fractures each, with a range from 1 to 4. The femur was the site of fracture on 10 occasions and the tibia, on 4 occasions. All fractures healed with conservative treatment in the usual amount of time. The fractures occurred throughout the period of childhood. Operative intervention should not be used simply because a pathological fracture is seen since the cartilage provides good stability, displacement is almost always slight, and healing occurs readily.

3.12.23.8 Malignant Transformation

A major concern in any patient with Ollier's disease is malignant transformation of cartilage tissue at one site to a chondrosarcoma. The frequency of this occurrence is difficult to determine but is considered to be quite high in most studies. Certain guidelines are available. Malignant transformation essentially never occurs until after skeletal growth has ceased and very few cases are reported under 20 years of age. The commonest sites of occurrence, as for all other chondrosarcomas, are the proximal regions involving in particular the proximal humerus, pelvis, and proximal femur. Histopathology alone is not a particularly reliable method of diagnosis since the light microscopic appearance of an enchondroma in Ollier's disease even during the growing years is extremely abnormal with some fearing that essentially all lesions represent at least a pre-sarcomatous appearance. The more convincing findings of malignant transformation involve an increase in size of a lesion after

skeletal maturity, discomfort at the site of the lesion when none was previously present, and the radiographic appearances of increased lysis of bone and disappearance of any calcification previously seen. Treatment involves the current protocols for chondrosarcoma. There is also an increased incidence of intracranial tumors, some of which are localized cartilage growths but gliomas have also been described [305].

3.12.24 Maffucci Syndrome

The Maffucci syndrome is characterized by multiple enchondromas and soft tissue hemangiomas both cutaneous and of internal organs. The enchondromas are usually noted in childhood or adolescence and are structurally similar to those in Ollier's disease. It is not a genetic disease. Lower extremity length discrepancy occurs in many. A major additional concern is malignant degeneration with a predilection for intracranial neoplasms in about 15 %. These can be chondromas or chondrosarcoma but other neoplasms such as glioma, pituitary adenoma or chordoma are seen [306].

3.12.25 Hereditary Multiple Exostoses: (Hereditary) Multiple Osteochondromas

3.12.25.1 Overview

Hereditary multiple exostoses is one of the most common of the skeletal dysplasias. It is an autosomal dominant disorder characterized by widened metaphyses and multiple exostoses or osteochondromas throughout the skeleton specifically positioned at the periphery of the growth plates and metaphyses where the endochondral sequence of bone formation and the intramembranous sequence of bone formation are in close relationship [307–316]. The disorder was referred to as diaphyseal aclasia in the older British literature [317] and other common terms have included multiple hereditary osteochondromata, and multiple cartilaginous exostoses [318]. It does not to affect bones formed exclusively by the intramembranous mechanism such as the cranium and face or exclusively by the endochondral mechanism such as the carpal and tarsal bones. The disorder rarely becomes evident clinically before 2 years of age. Its clinical and pathologic features were well described in the late 19th and early 20th centuries; as early as 1915 Ehrenfried of the Children's Hospital, Boston was able to review over 300 articles presenting about 600 cases [309, 310]. The main differential diagnosis is with trichorhinophalangeal syndrome (Langer-Giedon syndrome) [although facial, ectodermal, and mental symptoms in L-G make differentiation easy] and with metachondromatosis [318]. A large number of entities have exostoses but not to the extent of hereditary multiple exostoses [318]. The disorder was described well in a case in Lancet in 1825 [319].

Virtually all patients require orthopaedic surgical intervention during the growing or young adult years mostly to remove troublesome exostoses or to correct characteristic deformities [320, 321]. Although exostoses are seen at the metaphyses of almost all of the long bones, the severe and clinically significant deformities involve the forearm and the leg, regions characterized by 2 bones in close longitudinal relationship. The elbow, wrist, knee, and ankle are particularly vulnerable to deformity. In the majority of cases the ulna and fibula are disproportionately short in relation to the radius or tibia. The longer of the 2 bones is concave toward the interosseous membrane and toward the shorter bone, so that it seems reasonable to ascribe a tethering effect of the interosseous membrane and ligaments in association with a disparate growth rate as causative factors in deformation. The epiphyseal changes at the distal ends of the tibia and radius are analogous, with the distal articular surfaces tilted toward the shorter bone and the epiphyseal shape secondarily altered.

3.12.25.2 Histopathology

The exostoses are invariably broad based in association with a widened metaphysis. When the exostoses are present as elongated projections, the tips invariably are directed towards the diaphysis and away from the epiphysis (Fig. 3.25a). The exostoses and the widened metaphyses enlarge with growth coming via the endochondral mechanism from the cartilage cap. The cartilage covering is fibrocartilaginous at its surface but forms a physis immediately adjacent to the bone it is producing (Fig. 3.25b). The endochondral bone and marrow of the exostosis merges with that of the adjacent metaphysis without cortical intervention. The cartilage cap stops growing at the same time that the adjacent growth plate fuses. At that time, the cartilage cap thins and involutes, the exostosis is now covered by a thin rim of cortical bone and any persisting cartilage is converted to a fibrous tissue covering. The close relationship of the exostoses to the physeal growth mechanism is further shown by the fact that the largest and most numerous exostoses are found at the most rapidly growing bone regions, the distal femur, proximal tibia, proximal humerus and distal radius and ulna. Any increase in size of an exostosis occurring after skeletal maturity raises a high level of concern about malignant transformation.

3.12.25.3 Pathogenesis; Molecular Disorder of EXT 1 and EXT 2

Almost 90 % of patients with HME demonstrate germline mutations in the tumor suppressor genes EXT 1 (exostosin-1) or EXT 2 (exostosin-2) [322–329]. For both genes a mixture of nonsense, missence, frame shift, splice

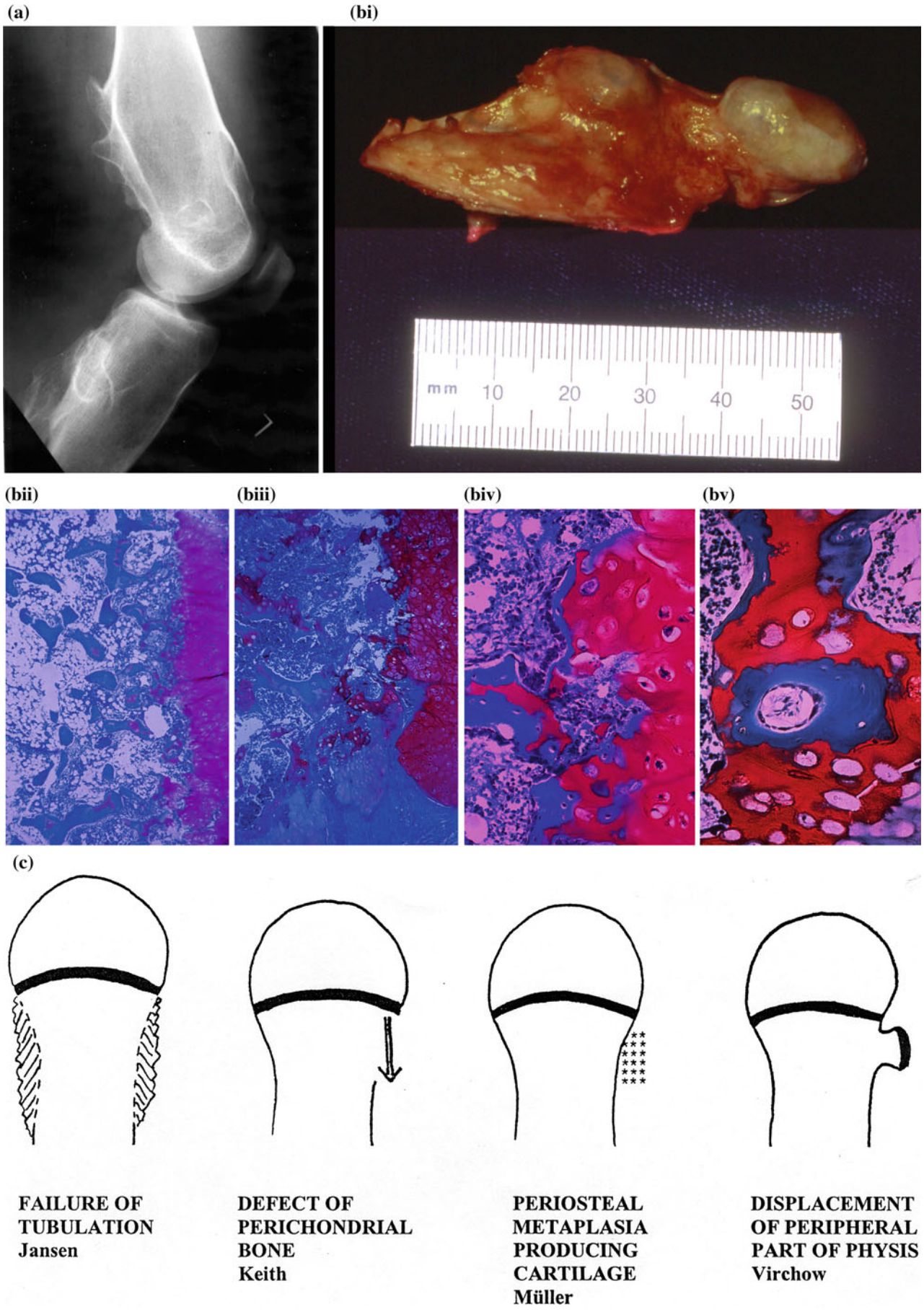
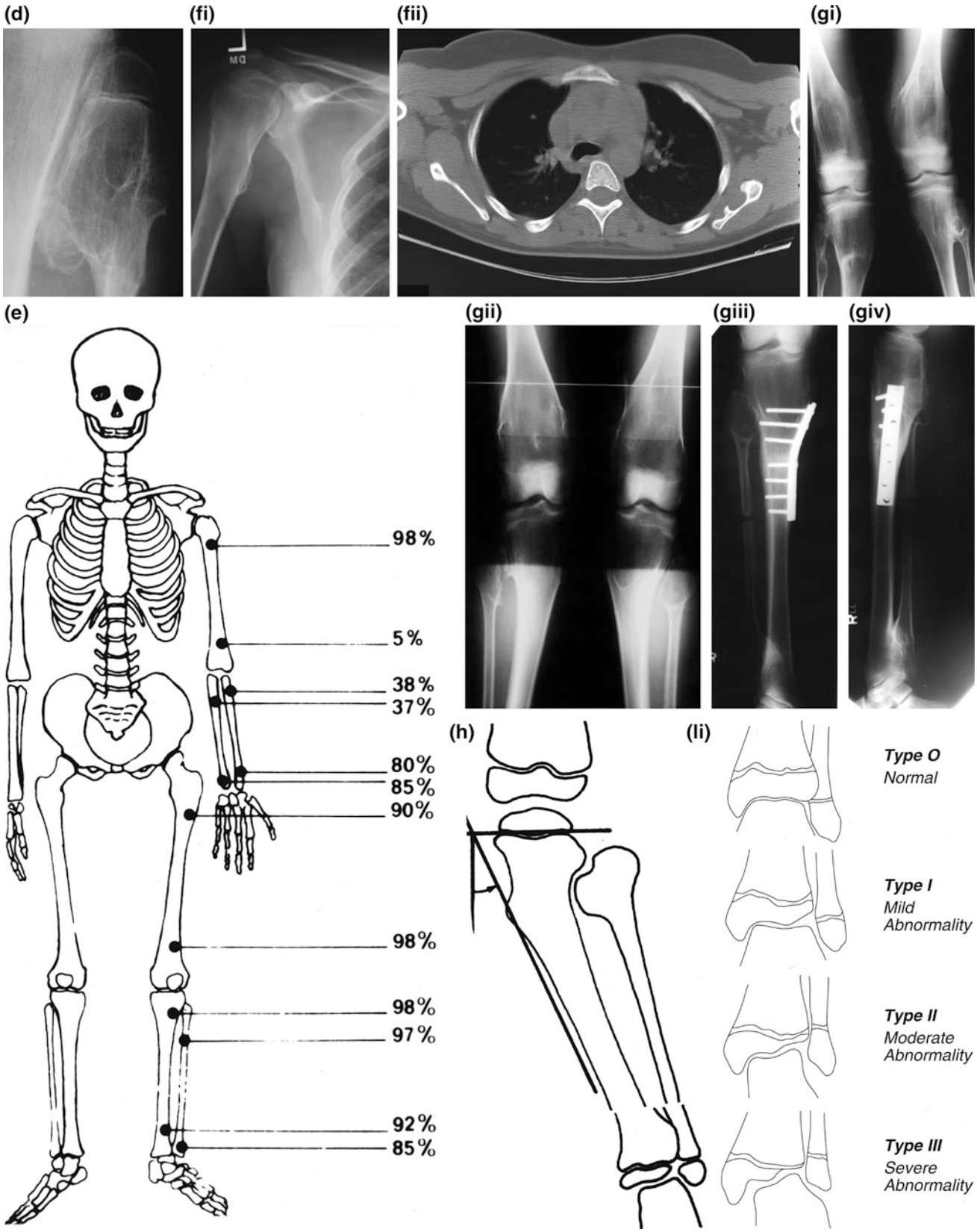


Fig. 3.25 (continued)



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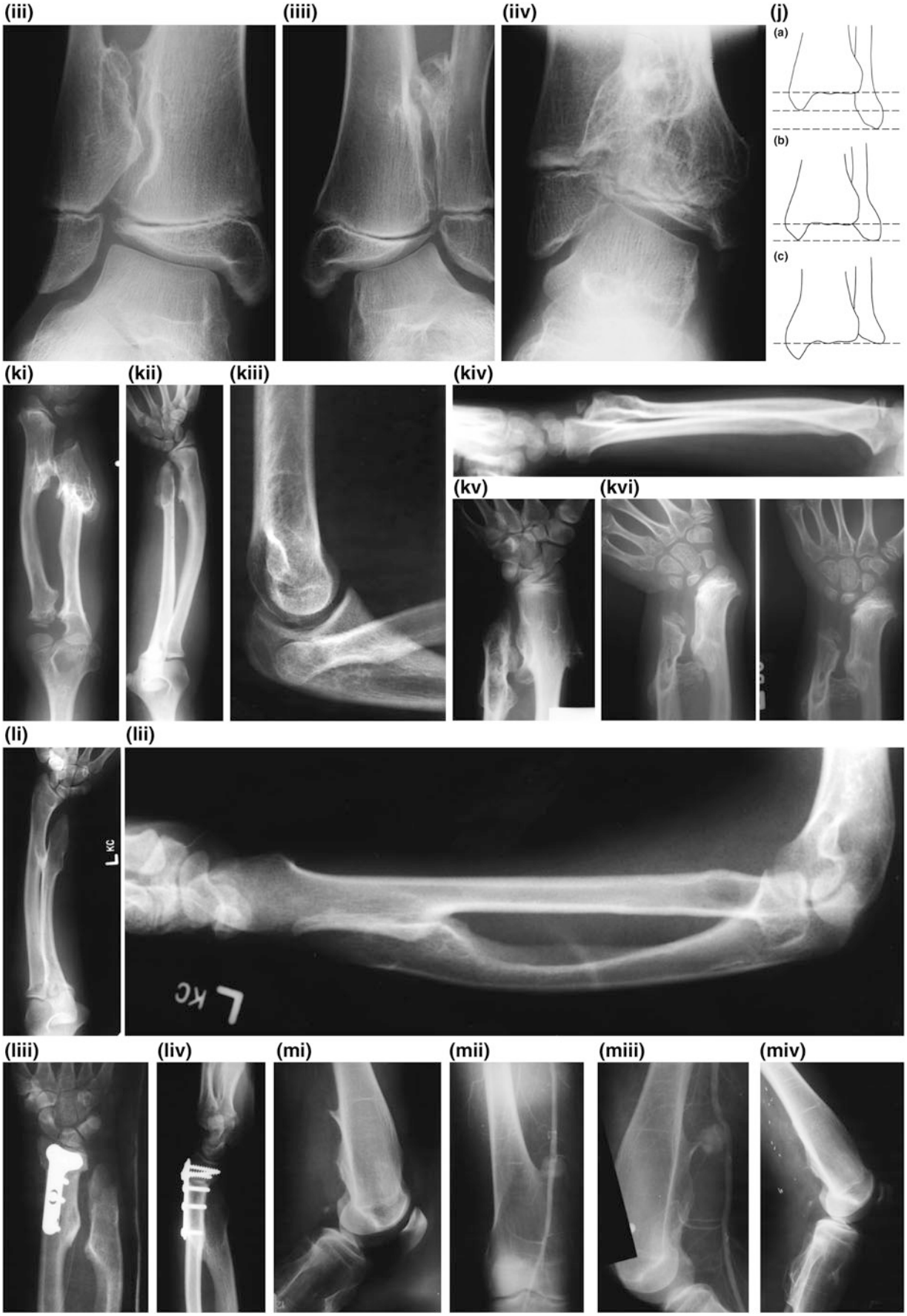


Fig. 3.25 (continued)

site and in-frame deletions are found [328]. The EXT genes encode glycosyltransferases involved in the adhesion and/or polymerization of heparan sulfate (HS) chains at HS proteoglycans (HSPGs) [325, 327, 329]. The EXT 1 mutations are detected in about 65 % of cases with EXT 2 in about 35 %. Heparan sulfate proteoglycans play a role in the diffusion of Ihh (Indian hedgehog) thereby regulating chondrocyte proliferation and differentiation. In a study of 172 patients those with mutations of EXT1 had a significantly worse condition than those with EXT2 mutations in regard to stature, deformity, functional parameters and development of sarcomas [323]. A more severe phenotype for EXT1 mutations has also been found in other studies [324].

The osteochondroma lesions: (i) invariably occur in bones which develop by both endochondral ossification and intramembranous bone formation, (ii) are initiated at the periphery of the growth plate region where the intramembranous sequence relates most closely to the endochondral sequence, and (iii) cease growing at the same time the growth plate fuses. They are closely related to the growth plate apparatus and are considered as perversions of its normal state.

Five main theories of pathogenesis (Fig. 3.25c) have been advanced: (i) Virchow proposed that some growth plate cartilage becomes split off but continues to grow in its abnormal position [312, 330]. Growth of the exostosis therefore occurs perpendicular to the long axis of the bone; (ii) Mueller considered that a periosteal metaplasia in the periphyseal/perimetaphyseal area produced the characteristic lesions such that cells normally defined as bone producing were acting as chondrocytes; (iii) Keith alluded to inadequacies of the periosteal bone sheath which he felt allowed for greater than normal outward expansion of endochondral bone; (iv) Jansen noted that the lesion was most marked by a broadened metaphysis which indicated a failure of tubulation (resorption); and (v) Langenskiold felt that perichondrial bone of the groove of Ranvier, normally derived in his opinion from tissue within the epiphysis passing outwards and forming an osteogenic layer, failed to form since that tissue pathologically retained its chondrogenic properties and was abnormally deposited as a cartilaginous and not osseous mass [331].

The failure of deposition of normal groove of Ranvier tissues leads to failure of the normal processes of periphyseal-perimetaphyseal bone formation, tubulation and remodeling. Elements of all 5 theories could theoretically contribute to the pathogenesis although the pathoanatomy is consistent with Mueller's theory as the primary cause and those of Keith, Jansen and Langenskiöld accounting secondarily for failure of metaphyseal remodeling. Proximal fibular exostoses (Fig. 3.25d) demonstrate structural abnormalities well.

Leveuf and Ogden in separate works studied pathologic tissue from osteochondromas along with adjacent physeal

◀ **Fig. 3.25** Radiographic examples of hereditary multiple exostosis are shown. **a** The characteristic abnormalities in hereditary multiple exostosis comprise not only widening of the metaphysis but its association with randomly placed exostoses (osteochondromas) whose tips point away from the epiphysis. **b(i)** Photograph of a large osteochondroma removed from a patient with hereditary multiple exostoses. At surgery there are many undulations noted at the periphery of the metaphysis and adjacent to the largest of the exostoses. In the growing child these are covered by thick cartilaginous caps and are generally more prominent to gross inspection at surgery than was apparent radiographically since the plain radiograph shows only the underlying bone. + **ii–v** Histologic sections of the cartilage cap and underlying bone it has synthesized are shown. The cartilage stains red with safranin O and functions as a growth plate. The bone stains green with the fast green counterstain. Endochondral bone formation occurs. In **v** conversion to a lamellar bone segment has occurred. **c** Theories of pathogenesis of the hereditary multiple exostosis lesions are illustrated. **d** Proximal fibular exostosis which led to a gradual but complete peroneal nerve compression is shown. This resolved slowly but fully after surgical debulking of the osteochondromatous region and to release pressure on the peroneal nerve. **e** The occurrence of exostoses throughout the skeleton in a study of 32 patients from the Children's Hospital, Boston is shown. (Reprinted with permission from Shapiro et al. Hereditary multiple exostoses. J Bone Joint Surg Am. 1979:61A:815–824). **f(i)** Exostosis of the medial border of the scapula is shown on radiograph. **ii** These are best demonstrated by CT scanning. **g(i, ii)** Characteristic *lower* extremity deformities in hereditary multiple exostosis include proximal tibia valga. Correction is by proximal tibial-fibular varus osteotomy as seen in **iii** and **iv**. Osteotomy site must be below the expanded metaphyses to prevent peroneal nerve damage. **h** Determination of the degree of tibia valga in hereditary multiple exostosis is shown. **i** Progressive degrees of obliquity in hereditary multiple exostosis at the ankle are shown (**i**) along with corresponding radiographs of 3 relatively severe cases (**ii–iv**). **j** Altered relationships of the distal fibula to the distal tibia at the ankle in hereditary multiple exostosis are shown. Normally the distal end of the fibula is distal to the distal end of the tibia, a position that helps stabilize the ankle. **k(i–iv)** Characteristic deformities of the *upper* extremity in hereditary multiple exostosis involve primarily the forearm. The ulna is relatively more shortened than the radius and its distal end has a Madelung like deformation. Dislocation of the radial head is common as the radius is longer. Multiple radiographs show the variation in deformity which occurs. Image **vi** shows the range of wrist motion with the deformity. **l(i–iv)** Correction of angular deformity of the distal forearm was performed with distal radial closing wedge and derotation osteotomy. Regional exostoses were also removed. This improved both the clinical appearance and function of the forearm and wrist. **m** A pseudoaneurysm resulting from pressure from a distal posteromedial femoral exostosis is shown. Most of these vascular lesions develop in mid adolescence and early adulthood when involution of the cartilaginous cap of the osteochondroma leaves the underlying bone spicule more prominent. **i** Lateral radiograph shows the prominent bone spur at the posteromedial aspect of the distal femur in a 17-year-old boy who had discomfort and gradually increased swelling of the posterior thigh over the previous 6 weeks. **ii, iii** Anteroposterior and lateral arteriograms show the femoral artery and a circular collection of dye at the tip of the exostosis at the site of the pseudoaneurysm. Surgery removed the exostosis followed by segmental excision of the pseudoaneurysm and arterial repair with a venous graft. **iv** A postoperative radiograph shows the operative site

tissue obtained from growing children by biopsy [332, 333]. The photomicrographs show structural differences in physeal and exostosis lesional cartilage even when those are juxtaposed. The perichondrial groove tissue is absent from its normal position adjacent to the physis and metaphysis. It remains unclear whether the osteochondroma cartilage is present due to uncontrolled lateral growth of peripheral physeal tissue or whether groove tissue has differentiated fully to cartilage rather than to bone as it normally does but the latter interpretation seems more likely. The osteochondroma cartilage cap tissue undergoes the endochondral sequence merging lesional bone tissue with endochondral bone from the regular physis thus causing the widening of the metaphysis. The abnormally structured groove region prevents both normal physeal control by the periosteal tissue and resorption by osteoclasts. Ogden has shown that the groove tissue is normal in those parts of the perimeter of the physis that are not involved in the osteochondromas and Leveuf has shown that the normal groove tissue is reconstituted well below the physis where metaphyseal widening is no longer present and appropriate tubulation has been re-established.

Leveuf obtained 2 large biopsies from the distal femur and proximal tibia of a 7-year-old child with hereditary multiple exostoses [332]. The biopsy removed a tissue segment in continuity from the periphery of the physis and the widened metaphysis down to the region of the diaphysis where normal tubulation was re-established. The tissue segment included the exostosis and the normal adjacent physeal and metaphyseal tissue. The histologic and radiographic study noted that there was a considerable distance between the growth cartilage and the origin of the diaphysis since the widened metaphysis was the site not only of the exostosis but of the failure of remodeling. Leveuf noted that 2 types of exostosis could develop, the wide flattened sessile variant which tended not to elongate with bone growth and the narrow pedicle type of exostosis which did increase its length with bone growth. Between the physis and the beginning tubulation of the diaphysis the wall of the metaphysis was malformed and composed of cartilaginous plaques which gave rise to endochondral bone on their inner surface. It was not until the ossification groove of Ranvier was reestablished distal to the widened metaphysis that normal remodeling occurred and the groove tissue synthesized cortical bone. The most characteristic finding between the normal growth plate cartilage and the normal diaphyseal cortex which was a considerable distance from the physis, was the metaphyseal wall filled with cartilaginous inclusions which were thin and flat. The cartilaginous wall was covered by a perichondrium continuous without transition from the perichondrium of the epiphysis above and the periosteum of the diaphyseal cortex below. The metaphyseal wall cartilage was immediately adjacent to the growth plate cartilage but was separated from it by a segment of connective tissue formed of fibers seemingly detached from the perichondrium and oriented in a transverse dimension. Below the cartilaginous metaphyseal wall was contiguous with the origin of the diaphyseal cortex and at their point of union a normal appearing perichondrial Ranvier ossification groove was seen. He felt that the cartilage in the metaphyseal wall was certainly the developing point of the sessile exostoses. On the inner surface of this cartilage growth was occurring by the endochondral mechanism which merged with the adjacent metaphyseal bone.

Leveuf's description of a well-oriented biopsy from a child with hereditary multiple exostoses in the active growth phase shows absence of the normal perichondrial ossification groove and its replacement by cartilaginous tissue with endochondral growth function. The groove is repositioned at a greater distance from the physis than normal and where it is present metaphyseal widening abruptly ceases, tubulation or funnelization begins and normal cortical bone is formed. Although the physeal cartilage which is normal is immediately adjacent to the cartilage of the exostosis they are separated by a thin patch or region of connective tissue. [Leveuf used this histopathologic example to support the bone growth theory of Policard that growth in length of a long bone was triggered primarily by the periosteal bone in particular at either end by the ossification groove bone tissue and that the physeal tissue merely elongated secondarily. This view has never been widely accepted and indeed appears inaccurate but this does not negate his highly accurate description of the periphyseal and perimetaphyseal tissues in hereditary multiple exostosis and the interpretation of the pathogenesis of those specific lesions].

Ogden studied a proximal fibula surgically removed from a 4-year-old girl with hereditary multiple exostoses in the course of treatment of a peroneal nerve palsy [333]. The juxtaposed regions of the normal physis and the cartilage of the osteochondroma were studied. A normal growth plate was found under the lateral 75 % of the chondroepiphysis of the proximal fibula at which point an abnormal physis of the osteochondroma appeared adjacent to the cartilage of the epiphysis. In different sections "this osteochondroma was directly juxtaposed to the normal growth plate, separated from the normal growth plate by a fibrous (never bony) zone or separated from the normal growth plate by an area of abnormal cartilage proliferating into the epiphyseal cartilage." The abnormal osteochondroma or exostosis cartilage "continued under the medial 25 % of the epiphysis and then turned 90° to course distally along the metaphysis." The osteochondroma was always separated from the epiphysis by an intervening fibrous or fibrocartilaginous zone. The cartilage of the exostosis had a considerable increase in the amount of intercellular substance throughout the various zones and the cells tended not to be arrayed in normal columnar fashion. Despite this,

endochondral ossification proceeded in a relatively normal fashion from the cartilage cap.

Milgram also demonstrated that the osteochondroma was derived from aberrant cartilaginous growth plate tissue which appears to proliferate independently and separates from the growth plate near its edge. The cartilage remains subperiosteal and may continue to proliferate as an osteochondroma perpendicular to the growth plate from which it derived [334]. He illustrates the distal radial growth plate from a 12-year-old boy with HME. Other examples show the lesional osteochondroma cartilage to be clearly differentiated from normal physeal cartilage, although it is immediately juxtaposed to it.

There is clearly a mechanical and biological controlling function for the periosteum and its bony ring in relation to the physis and metaphysis. In an effort to assess the control features of the perichondrial sleeve a series of experiments were done in our laboratory [335]. The osteochondromas were caused experimentally from defects created by entirely removing relatively large periosteal flaps or windows in 10 day to 6-week-old rabbits. The defects were made at the lateral aspect of the distal femoral growth plate and metaphysis. A transverse cut was made in the periosteum parallel to and 1 cm from the growth plate on its metaphyseal side. Two incisions, 0.5 cm apart passed from the transverse incision to the plate. The periosteum was lifted and easily peeled towards the plate. The growth plate cartilage was uncovered and the fibrous attachment into the epiphysis beyond the plate was found to stop further periosteal displacement. The periosteal flap was removed by sharp dissection at this site, creating a large window-like defect. Histological sections were made on the removed periosteal flap. The Safranin O stain of the removed flap shows the green staining layer of fibrous connective tissue, the green periosteal membrane bone and flecks of metaphyseal bone-central red cartilage core surrounded by green staining bone. The tissue remaining was shown to be devoid of its periosteal sheath and of the bony ring. On some occasions, careful dissection still showed periosteal tissue present which probably accounts for the failure to induce osteochondromas on all occasions. Times of sacrifice varied from 3 to 8 weeks and tissue created in response to the defects was assessed by gross inspection, radiography and histological sections.

In hereditary multiple exostoses all cases show metaphyseal widening due to a failure of funnelization as well as localized broadly based osteochondromas standing out from the bone. In our experiment 41 of 62 defects (66 %) resulted in osteochondromas. The animal lesions and radiographs are similar to the human cases. The histological appearance of the induced lesions is crucial to their interpretation. Human exostoses are covered with hyaline cartilage, their metaphyseal bone is continuous with the primary metaphyseal bone (not positioned against cortical bone, and the bone develops by endochondral ossification. Histological sections of the induced lesions show 3 specific responses: (i) at the defect site the metaphysis has not been remodeled but has remained wide and blunt. The endochondral bone has persisted and the non-remodeled area is composed of metaphyseal bone showing central cartilage cores. Funnelization has occurred normally, however, around the rest of the circumference of the distal femur where the periosteum is intact; (ii) many of the osteo-chondral lesions possess cartilage "caps" which are composed of hyaline cartilage. This cartilage is producing bone by evolving into a well-defined endochondral sequence; and (iii) the true cortex is absent between the metaphysis and the osteochondral lesion. The cancellous metaphyseal bone from the growth plate is in continuity with the new endochondral bone of the lesion. Comparable experimental findings in the rabbit were described by Hwang and Park [336].

Experiments like this attempt to demonstrate the pathogenesis of a developmental abnormality using a surgically created defect in a young otherwise normal animal. The response to what is a traumatic lesion is understandably intense. Nevertheless the responses unleashed result in the formation of osteochondromas histologically similar to those seen in humans. The postulate that the osteochondromas of hereditary multiple exostoses occur secondary to a physical or functional defect in the periosteal tissue which normally ensheathes the entire growth plate appears to have good experimental as well as theoretical backing. The sequence of events is such that (i) the defect allows the endochondral sequence to "escape" since the physical controlling effect of the periosteal sheath including the bony ring and its cellular resorptive effect are both lacking; (ii) further endochondral growth of the osteochondroma lesion occurs secondary to the adjacent periosteal reaction which in response to the defect has undergone a metaplastic change into cartilage; and (iii) continuity between the normal cancellous metaphyseal bone and the cancellous bone of the lesion occurs since cortical periosteal bone formation at the defect site is prevented owing to the local absence of the periosteum. The induction of osteochondromas by a simple interference defect experimental method serves both to define some of the normal biological functions of the periosteum and to account for the pathogenesis of a well-known entity.

Human specimens from distal femurs and proximal tibias in which the osteochondroma was excised with a thin margin of the peripheral physis and adjacent metaphyseal cortex show tissue consistent with a metaplasia of the groove of Ranvier cells towards a chondrogenic pathway [337].

3.12.25.4 General Stature

The anthropometric data indicate that persons with hereditary multiple exostoses are of shortened stature but that they

almost all fall within the normal range, with actual dwarfism being rare. The short stature is mildly disproportionate, with limb involvement greater than spinal involvement. The outstretched fingers reach to just below the trochanters in moderate and severe cases, rather than to the mid thigh region as in the normal. There is no inconsistency between skeletal age and chronological age during development. The distribution of general stature in 30 patients documented in the series is shown [320]. In only 2 of the 30 patients was the general stature less than the second standard deviation below the mean, and one of these patients was skeletally immature at the time of final assessment, with a skeletal age 2 years less than chronological age. An individual whose stature is below the second standard deviation below the mean is considered as abnormally small or dwarfed, since stature within the range of 2 standard deviations is considered arbitrarily to be normal. Seven of the patients were of average height, 17 were below the mean, and 6 were above the mean. Thus, the majority of patients were below average in height but almost all remained within the normal range, and only 1 was outside the normal distribution with a final height at 2.5 standard deviations below the mean. Ehrenfried noted that "a shortness of stature is practically constant. The patients are always of medium height or below, and sometimes they are … dwarfed…" "The lack of growth is in the legs, and not the trunk… The upper limbs are also short [309]."

Sitting height. Separate growth charts that depict sitting height and over-all height are available. In 26 of 30 patients, the sitting height was greater than the over-all height in terms of the standard deviation as related to the mean. In 3 patients both values were along the same standard deviation and in one, over-all stature was relatively greater than sitting height. The sitting height averaged 1.0 standard deviation above over-all height. These findings also indicate a mildly disproportionate short stature, with the limbs involved to a greater extent than the spine.

3.12.26 Clinical Problems in Hereditary Multiple Exostoses

There are 6 main groups of clinical problems that may be seen in patients with hereditary multiple exostoses [315–317, 321]. These include: (i) the exostoses, which can be uncomfortable or unsightly or both; (ii) angular deformities of the limbs; (iii) length discrepancies of lower and upper limbs; (iv) pressure phenomena caused by the exostoses; (v) fracture of the exostoses; and (vi) malignant degeneration of the exostoses. Although this skeletal dysplasia does not shorten life expectancy, except in rare patients with malignant degeneration, it does cause considerable difficulty. In the 32 patients in one study [320], approximately 2.7 surgical procedures per patient had been performed before the age of 20 years. This number is considered to be on the low side, as some of the children with large exostoses and considerable deformities were still being followed at the time of assessment and others had moved. It was the exostoses themselves that led to the greatest number of operations, especially at the knee, wrist, and shoulder. The exostoses of the hand and foot rarely presented sufficient clinical symptoms to warrant excision.

Occurrence of exostoses: The exostoses are present bilaterally in virtually all long tubular bones and frequently in the pelvis, scapula, ribs, and short tubular bones of the hand and foot (Fig. 3.25e). They occur at the periphery of the epiphyseal growth plate and metaphysis, which is the region of intimate relationship between the intramembranous and endochondral developmental sequences. The epiphyses and round bones of the carpus and tarsus, which develop exclusively by endochondral ossification, are not involved primarily. In the upper limb, all lesions were metaphyseal [320]. Exostoses appeared almost invariably at the proximal end of the humerus (49/50, or 98 %); at the distal end of the radius (36/45, or 80 %); and at the distal end of ulna (35/41, or 85 %). Lesions of the distal end of the humerus were quite rare, appearing in only 2 (5 %) of 39 humeri, and lesions of the proximal end of the radius (14/37, or 38 %) and proximal end of the ulna (14/38, or 37 %) were relatively infrequent. In the lower limb, all lesions were also metaphyseal [320]. They occurred almost invariably at the proximal end of the femur (56/62, or 90 %), distal end of the femur and proximal end of the tibia (in both cases in 61/62, or 98 %), proximal end of the fibula (60/62, or 97 %), distal end of the tibia (57/62, or 92 %), and distal end of the fibula (53/62, or 85 %).

Roentgenograms of other regions showed exostoses in the scapula, ribs, pelvis, vertebral spinous processes, metacarpals, and phalanges. The pelvis, scapula (Fig. 3.25f) and ribs are commonly affected. Large exostoses frequently emanate from the iliac crest. CT scanning is advisable pre-pregnancy in affected females to assess for any pelvic canal lesions. Lesions on the anterior scapula commonly at the medial or vertebral border often are symptomatic impeding smooth passage over the adjacent ribs and must be removed.

Deformities of the lower limb: All roentgenograms were examined for the presence or absence of deformities found in hereditary multiple exostoses: coxa valga, femora vara, tibia valga (Fig. 3.25g), obliquity of the articular surface and subchondral bone of the distal tibial epiphysis, and obliquity of the superior articular surface of the talus. Each of these deformities was assessed along with the lengths of the tibia and fibula, the relationship of the distal end of the tibia (medial malleolus) to the distal end of the fibula (lateral malleolus), and limb-length discrepancies. Although the Green-Anderson table of normal values was used as a

standard for limb lengths (femur and tibia) no normal values have been reported for the lengths of the tibia and fibula including the malleoli, or for the various angles that we wished to measure to assess deformity. Lower-extremity orthoroentgenograms from 50 patients with fractured femora who were being followed for limb length discrepancies were used to obtain normal values for the lengths of the tibia and fibula and the associated bone relationships and angles.

The degree of tibia valga was assessed as the angle formed between the epiphyseal growth plate and the long axis of the medial cortical surface of the tibia (Fig. 3.25h).

The obliquity of the subchondral surface of the distal tibial epiphysis was noted not to involve the entire surface but usually to begin in its mid-portion. Where obliquity was noted the medial half of the surface was level while the lateral half was found to slant upward and outward. The degree of obliquity was graded as Type O, I, II, or III (Fig. 3.25i). When the entire surface was perfectly level, as in the normal state, the classification was Type O. Type I indicated that the obliquity from the central portion of the articular surface of the distal tibial epiphysis angled upward and laterally but the lateral margin of the subchondral bone remained well within the epiphyseal side of the growth plate. Type I appeared as a minimal deformity but was seen commonly enough to be considered a mild variation of normal. This group was a transitional group, with some ankles so graded being very close to Type O and others approaching the Type II pattern. For purposes of grading, however, since the deformity was quite small it was included with Type O and was defined as normal. Type II deformities were those in which the distal subchondral bone sloped into the lateral margin of the epiphyseal growth plate. Type III lesions were those in which the subchondral bone slanted into the epiphyseal growth plate in its lateral third rather than at its lateral edge.

Obliquity of the superior surface of the talus was considered to be either present or absent. Normally, the surface is flat; with obliquity the lateral aspect of the surface is more superior than the medial aspect. This assessment was made to distinguish between a talus that was tilted in the ankle mortise and one with obliquity of the superior articular surface.

Tibia-fibula relationships. The tibia was measured from the plateau to the distal tip of the medial malleolus and the fibula was measured from the most proximal portion of the head to the most distal tip of the lateral malleolus. The total fibula-tibia length ratio was calculated. This measurement was done on all the exostosis patients and on the 100 normal control legs from the patients with fractures. The tibial measurement in this instance differed from that used on the Green-Anderson charts, as we wished to include the malleoli. The relationship of the lateral malleolus to the medial malleolus was assessed in 100 normal ankles and in 64 patients with hereditary multiple exostoses. The distal end of the fibula were graded as distal to, at the same level as, or proximal to the distal end of the tibia (Fig. 3.25j).

Since the proximal ends of the fibula and tibia are at different levels, it was necessary to assess both the tibia-fibula length ratio and the relationship of the lateral to the medial malleolus. We wished to establish whether the differences at the ankle were due solely to altered position of the 2 bones or whether relative shortening of the fibula was also a factor. A correlation was also made between the relationship of the distal ends of the tibia and fibula and the degree of obliquity of the articular surface at the distal end of the tibia.

The deformities of the lower limb noted follow.

Coxa valga: The proximal end of the femur was assessed in 64 patients, and there were 16 cases of coxa valga (25 %). On occasion acetabular dysplasia was associated with the coxa valga. In 46 patients the head-neck-shaft relationship was normal despite the presence of exostoses. Coxa vara was not seen.

Femora vara: There were 4 instances of distal femora vara. Femora valga did not occur.

Tibia valga: This deformity occurred within the tibia; the term does not refer to femoral-tibial valgus angulation. The apex of the tibial valgus deformity was metaphyseal, just below the growth plate. The measurement of deformity refers to deviation into valgus. Normally, with no deformity the long axis of the medial tibial cortex is parallel to a line drawn perpendicular to the proximal tibial growth plate; that is, 0°. In the normal-patient controls, 4 (8 %) of 50 had minimum deviation of 5° and none had values greater than 5°. Thirty had no deviation (0°) and 16 had values between 1 and 4°. In the patients with hereditary multiple exostoses, 20 (33 %) of the 60 tibiae had a tibia valga of 5° or greater. In these 20, the tibia valga ranged from 5° to 25°, with a mean of 10°. Tibia vara was not seen.

Obliquity of the distal tibial epiphysis: This obliquity refers to the articular surface and subchondral bone of the distal end of the tibia, and not to the epiphyseal growth plate. The growth plate itself was perpendicular to the long axis of the tibia in both normal and exostosis patients. A classification of the degree of obliquity and associated abnormality of the ankle mortise was outlined. Of 61 ankles assessed in the patients with hereditary multiple exostoses, 5 were Type O (normal), 23 were Type I, 20 were Type II, and 13 were Type III. Thus, 54 % were moderately to markedly abnormal (Types II and III). In Type III ankles in exostosis patients, lateral talar subluxation was seen occasionally. Of the normal ankles, 73 were Type O, 25 were Type I, and only 2 were Type II.

Intrinsic obliquity of the superior talar articular surface: This term does not refer to a tilt of the talus but to an intrinsic obliquity of the superior talar articular surface. In

the exostosis patients, the lateral region of the talar articular surface was more superior than the medial region in 42 (70 %), while in 18 (30 %) the surface was level. In the normal patients the lateral surface was superior in only 20 (20 %) with the other 80 (80 %) level.

Length and distal-position relationship of tibia and fibula: The fibula-tibia length ratio was 1.00 in the normal group of 58 legs (range, 0.98–1.03) and 0.94 in the exostosis group of 64 legs (range, 0.86–1.01). The numerical ratios were determined prior to any corrective osteotomies and prior to the one proximal tibial-fibular epiphyseal arrest. This ratio documents the shortness of the fibula relative to the tibia. In the normal controls, the lateral malleolus was distal to the medial malleolus in all (100 %) of the 100 ankles. The fibular growth plate was at the level of the tibiotalar joint space. In the patients with hereditary multiple exostoses, the fibula was distal to the tibia in 28 (44 %), at the same level in 23 (36 %), and proximal to it in 13 (20 %). There was a good but not absolute correlation between the obliquity of the articular surface of the distal end of the tibia and the relative position of the 2 malleoli. Type II deformities predominated when the fibula equaled the tibia in length and Type-III deformities predominated when the fibula was shorter than the tibia.

In this series [320] neither the coxa valga nor the femoral vara presented clinical problems. Weiner and Hoyt described development of the proximal femur in HME [338] and noted valgus configuration of the proximal femur was seen in each of 50 hips in 25 patients with hereditary multiple exostoses. Porter et al. [339] studied 24 hips in patients with HME by anteroposterior radiographs. Coxa valga and dysplasia were common with a median neck-shaft angle 156° and a median center-edge angle of 23°. Shenton's line was frequently broken. They felt that HME itself caused developmental anomalies of the hip due to the generalized defect but that any proximal femoral osteochondromas themselves could precipitate structural worsening. They had not studied symptoms and management but noted that only 1 of their 200 patients with HME had, as of 2000, needed total hip replacement. Felix et al. [340] however reported sufficiently severe acetabular dysplasia in a 12 year old girl with bilateral groin pain that bilateral hip surgery proved beneficial. This involved proximal femoral varus derotation osteotomy, removal of the medial osteochondroma, and triple pelvic osteotomy. Malagon [341] also described a mechanically progressive insufficiency of the acetabular cavity together with the coxa valga deformity which was symptomatic in some.

Tibia valga was considerable in the study and 20 % of the patients had varus osteotomies of the proximal end of the tibia and fibula. This operation is always a source of potential difficulty owing to the closeness of the vascular trifurcation and the peroneal and posterior tibial nerves to the osteotomy site. The risk is further increased in patients with hereditary multiple exostoses, as the exostoses themselves frequently compromise the space available for the neurovascular structures. One transient peroneal-nerve palsy occurred in this series. In HME the tibial osteotomy is performed at a more distal level than normal because of the metaphyseal widening, a closing wedge procedure with slight shortening is favored, and gentle debulking of the proximal fibula is considered based on concern about the size, shape and position of any exostoses there. Nawata et al. also showed tibial valgus angulation increasing with growth in HME [342]. Lateral subluxation of the patella was also seen in a few instances.

The degree and frequency of altered bone relationships at the ankle were documented. The ankle abnormalities that present clinically as a pes valgus are associated with shortness of the fibula relative to the tibia, the more proximal relationship of the lateral malleolus to the medial malleolus, obliquity of the distal tibial epiphyseal surface, and occasionally lateral subluxation of the talus. Partial compensation to help to form a more regular ankle joint was provided by developmental obliquity of the superior talar articular surface. The pes valgus was often roentgenographically marked, and 2 patients had a clinical problem severe enough to warrant a supramalleolar varus osteotomy at the distal end of the tibia and fibula in the first 2 decades of life. It would be expected that other patients with tibia valga plus a marked valgus deformity at the ankle may have difficulty with this during later years but symptomatic and functional problems in the first 2 decades of life are generally not seen. Some control of deformity can be expected from stapling of the distal medial tibial epiphyseal growth plate once there is early indication that a deformity appears likely to occur.

Snearly and Peterson have reported on operative procedures for ankle deformity in 9 patients [343]. The indications for intervention were pain, angular deformity and limitation of motion. Procedures used include removal of the osteochondroma, which eliminated discomfort and improved appearance but could not be counted on to correct deformity; lengthening of the fibula; and asymmetric medial stapling of the distal tibial growth plate. Fibular lengthening was a one-stage step-cut lengthening in severe cases with gains of 12 and 17 mm. Asymmetric medial stapling allowed for a mean correction of tibial-talar tilt of 10.3° in 3 cases. With this approach distal tibial osteotomy was not needed.

Deformities of the upper limb: Deformities of the forearm in hereditary multiple extososis are primarily related to the shorting of the ulna referable to the length of the radius and the position of the exostoses of either bone. Characteristic deformity involves a relative shortening of the ulna with malformation of its distal end leading to an ulnar drift of the wrist and hand, obliquity of the distal radial articular surface with angulation towards the shortened ulnar side, bowing of

the radius with the concavity towards the shortened ulna and, in many instances, subluxation or dislocation of the radial head at the elbow and dorsal subluxation of the distal end of the ulna in a Madelung like deformation (Fig. 3.25k). The tendency to radial head dislocation is increased in those where there is more extensive shortening of the ulna and minimal to absent bowing of the radius. Pronation and supination are variably affected depending on the presence and size of ulnar and radial exostoses, the degree of bowing of the radius and the presence or absence of radial head dislocation. Burgess and Cates quantified ulnar and radial lengths, distal radial articular angle, radial bow, carpal slip (of the lunate), and ulnar variance on forearm radiographs from 49 forearms with HME but no dislocation of the radial head [344]. They concluded that there was a proportional suppression of the growth of the radius and ulna throughout the range of involvement and that the radial articular deformity did not correlate with the degree of negative ulnar variance. With HME, therefore, the forearm bone deformities involved intrinsic proportional shortening of radius and ulna such that wrist deformities were not due to extrinsic ulnar tethering of distal radial growth.

In one series there were 8 dislocations of the radial head in the 37 elbows that were assessed (22 %) [320]. In the 37 roentgenograms of an entire forearm that were available for review, the degree of deformity was normal or mild in 12 (40 %), moderate in 6 (20 %), and severe in 12 (40 %). The distal end of the ulna was invariably more seriously involved than the distal radius.

Measurements of pronation and supination were available in 26 forearms. Pronation and supination were normal or only mildly restricted (0°–70° or more) in 33 (63 %) of 52 instances; moderately restricted (0°–30°–60°) in 11 (21 %); and severely restricted (0°–30°) in 8 (15 %). These ranges of movement refer to pronation and supination separately, and not to their total range. Usually either pronation or supination was affected, with the movement in the other direction fairly free. Pronation was the restricted direction of movement more frequently than supination by a margin of 2–1. Radial deviation was limited and ulnar deviation was increased. In those individuals for whom values were recorded, radial deviation averaged 12° and ulnar deviation 45°.

The deformities present at the various regions are quite consistent, the main difference being one of degree. Some progress slowly while others remain stationary. No deformity, once identified, improved with growth. Over half of the patients with hereditary multiple exostoses had moderate to severe deformity of the forearm, and one-third had significant restriction of either pronation or supination. The characteristic deformities of the upper extremity were treated surgically by excision of dislocated radial head at the time when skeletal growth had terminated and by occasional osteotomy at the distal end of the radius. The excision of distal osteochondromas in an effort to increase rotation was sometimes highly effective but tended to result in limited improvement. No patient in this series underwent stapling of the lateral half of the distal radial epiphyseal growth plate to prevent ulnar drift. On one occasion, excision of the radial head in a forearm in which the distal end of the ulna was severely shortened and malformed resulted in marked instability, which was eventually treated by a mid-shaft radio-ulnar synostosis.

Taniguchi has shown how the severity of the forearm lesions correlates with the overall severity of the HME [345]. He assessed the forearm appearance in 41 patients and divided them into 3 groups: group 1, no involvement of the distal forearm ($N = 8$); group 2, involvement of the distal forearm without shortening of radius or ulna ($N = 11$); and group 3 involvement of the distal forearm with shortening of the radius or ulna ($N = 22$). He then compared each group in relation to the number of lesions throughout the entire body, the age of onset, patient height and the presence of valgus deformity of the ankle. Correlations show quite nicely that the mild, moderate, and severe appearances at the distal forearm and wrist correlated with similar findings throughout the rest of the skeleton. The number of lesions in group 1 was 5.8 ± 7.4, group 2, 28.5 ± 10.4, and group 3,45.7 ± 10.2. Involvement of each region of the body also correlated well with the grouping system. For example, involvement in the proximal humerus was 31 % in group 1, 77 % in group 2 and 95 % in group 3. In the proximal femur the percentages of involvement were 6, 73 and 95 %. Excellent correlations were seen in all other regions of the body using this system. The age of onset, by which is meant the age at which the parents or physicians first noted exostoses, was 10.3 ± 4.0 years in group 1, 4.6 ± 4.5 years in group 2, and 2.8 ± 1.8 years in group 3. It is very rare to diagnose this condition before 1 year of age, although detailed radiographic surveys beginning at the newborn period have not been done. Height correlations showed group 1 at 0.3 ± 0.6 standard deviations above the mean, group 2 at -0.3 ± 1.5 standard deviations below the mean, and group 3 at -1.1 ± 1.0 standard deviations below the mean. Correlations continued with valgus deformity of the ankle greater than 10° showing no instances in group 1, 1 in group 2 and 12 in group 3. In addition the only 3 cases of the dislocation of the radial head occurred in group 3.

Considerable controversy persists regarding the long-term need and value of upper extremity surgery to correct the deformities associated with hereditary multiple exostoses. Arms et al. did a retrospective study on 37 patients who had had various forms of operative intervention relating to osteochondromas and associated deformities of the forearms [346]. Their questionnaire sought specifically to determine patient responses to the value of various forearm interventions. The surgeries performed included 36 osteochondroma

excisions, 6 radial head excisions, 5 distal radial hemi-epiphysiodeses, 2 distal radial osteotomies and 4 ulnar lengthenings. They concluded that early aggressive intervention of a surgical nature may not always be needed since most of the patients after reaching skeletal maturity functioned very well with minimal concerns regarding esthetic appearance despite significant deformity. They concluded that simple excision of symptomatic osteochondromas or symptomatic dislocated radial heads at skeletal maturity would suffice for the large majority of patients. They were not supportive of early radical intervention during the growing years to prevent problems since they felt that problems at skeletal maturity were not overly great. Other studies had also concluded that although cosmesis was markedly improved function improved to a much less extent. Stanton and Hansen showed that meaningful function was preserved in the presence of great deformity on many occasions [347].

More patients are currently undergoing upper extremity surgery. It remains extremely important to define the reasons for intervention and to be aware of the benefits and limitations of the procedures. Masada et al. have classified the forearm deformities in hereditary multiple exostoses into 3 types [348]. Type 1. The main area of osteochondroma formation is in the distal ulna. The ulna is relatively short with lateral bowing of the radius, the radial head located, tapering of the distal ulna and ulnar tilt of the distal radial epiphysis. In their series 61 % of forearms were of this type. Type 2. In addition to ulnar shorting the radial head is dislocated but bowing of the radius is less severe because of the dislocation than in the type 1 deformity. In type 2A the radial head is dislocated because of an osteochondroma at the proximal metaphysis of the radius while in type 2B there is no osteochondroma of the radius. Type 2A accounted for 6 % of the forearms and type 2B for 14 %. Type 3. The main osteochondroma formation is in the metaphysis of the distal radius and there is relative shortening of the radius. This was seen in 19 % of patients. Masada et al. have summarized their recommended surgical procedures as follows: Type 1. Excision of osteochondroma, radial osteotomy, immediate (one-stage) ulnar lengthening. Type 2A. Excision of osteochondroma, radial osteotomy, immediate ulnar lengthening, excision of radial head. Type 2B. Excision of osteochondroma, radial osteotomy, gradual ulnar lengthening; and Type 3. Excision of osteochondroma only.

The operative approaches to forearm deformities in hereditary multiple exostoses have been well summarized by Fogel et al. [349], Masada et al. [348], and Peterson [350]. The procedures used involve excision of the osteochondromas, lengthening of the ulna, corrective osteotomy of the distal radius, stapling of the distal physis of the radius, excision of the radial head, and open reduction of the dislocated radial head. The epiphyseal stapling of the distal radius described by Siffert and Levy in 1965 involves a hemi-epiphyseal approach with stapling on the lateral radial side allowing some growth medially to continue [351]. This represents an early example of “guided growth”.

The most common procedure is excision of the osteochondroma. This can improve rotation and will also improve appearance in many. It will also tend to normalize the relationship of the radius to the ulna at either end of the forearm and minimize tendencies to subluxation and dislocation. Ulnar lengthening reduces the tethering force on the growing radius thus encouraging it to continue to grow straight or to minimize its curvature and protect against dislocation of the radial head. The ulnar lengthening will also minimize ulnar drift. It is evident that the relationship of the distal ulna to the carpus will still not be normal. Correction of the angular deformity of the distal radius can be achieved either by hemi epiphyseal lateral stapling or wedge osteotomy (Fig. 3.25l). Hemi-epiphysiodesis is minimally invasive but the result can be difficult to project because of uncertainty regarding how the tethering on the ulnar side has damaged the medial physis.

Peterson recommends excision of the osteochondroma once the growth pattern on the involved bone is clearly being altered by its presence [350]. Ulnar lengthening is generally performed if the radial-ulnar length discrepancy exceeds 1 cm. Up to 2 cm of length can be gained in a one stage procedure although removal of the soft tissue interosseous ligament tether is usually needed. Transverse osteotomies can be fixed with bone graft and plates although occasionally oblique step-cut osteotomies are done. Length greater than 2 cm can be gained using gradual distraction lengthening with external fixators. In general resection of the dislocated radial head is not recommended in particular if there is growth remaining and efforts to relocate it are generally followed by stiffness. Efforts are directed to early excision of osteochondromas at the proximal radial-ulnar area and minimization or prevention of the radial head dislocation by ulnar lengthening. Finidori et al. commented that the radial head was at high risk of dislocation when the affected ulna was greater than 1 cm shorter than the radius [352]. Irani and Petrucelli agreed [353]. Burgess and Cates also concluded that ulnar variance with shortening greater than 8 % predisposed to radial head dislocation [344].

Long term results of surgery for forearm deformity in HME were assessed in 31 forearms at a mean follow-up of 13 years [354]. The mean age at surgery was 11 years. At follow-up some of the deformities had recurred even if initially corrected. They concluded that “corrective osteotomy and/or lengthening of the forearm bones was not beneficial.” The most beneficial procedure was excision of the exostoses. The best indications for surgery were to improve rotation and appearance. Most complications were related to the ulnar lengthening (non-union, re-fracture, nerve palsy).

Waters et al. outlined their approach to forearm correction with these deformities [355]. The average lengthening in 24 patients (of whom 17 had HME) was 1.5 cm (range 1.0–2.3) which was 9 % of total length.

When the deformities in the forearm are great or when surgical intervention has been less than fully effective Rodgers and Hall have reported creation of a 1 bone forearm as an effective salvage procedure for recalcitrant forearm deformity [356]. The radial-ulnar fusion is combined with removal of the proximal radius to allow the ulna alone to function as the elbow hinge and removal of the distal ulna to allow the radial-carpal joint to function singly. This surgical procedure can be combined with a forearm lengthening.

Lower Extermity Length Discrpancies: The femoral-tibial limb length discrepancy measurements indicated a range from 0.1 to 4.0 cm [320]. In 2 patients, femoral and tibial shortening were equal; in 20, femoral shortening was greater than tibial; and in 10, tibial shortening was greater than femoral shortening. On occasion, the shortening was limited to either the femur or the tibia.

Of the 22 patients who had reached skeletal maturity, 11 (50 %) had limb length discrepancies that were in the range for which limb-length equalization would normally be recommended. Of these, however, only 5 (23 %) actually had the procedure. The limb length discrepancies at the termination of growth in those who did not undergo growth-arrest procedures measured 2.1, 2.4, 2.3, 2.6, 3.1, and 3.5 cm. The following reasons were: subsequent planned correction of discrepancies with associated opening-wedge osteotomy for deformity on the short side or closing-wedge osteotomy on the long side; difficulty of performing epiphyseal arrests in regions where large exostoses are present; clinical impression of an acceptable situation despite the roentgenographic measurement; and reluctance of patients and their families to undergo yet more procedures.

When we take into consideration all 22 patients who had reached skeletal maturity and also the 7 who were old enough that it was possible to say whether they would or would not require an arrest, there were 29 patients, of whom 12 (41.2 %) had discrepancies within the recommended range for operative intervention.

All 5 patients who were operated on had distal femoral epiphyseal arrests, and one had a proximal tibial-fibular epiphyseal arrest as well. The limb length discrepancies at the time that the arrest was performed and the eventual limb length discrepancy at the termination of growth were as follows: 2.9 cm, to 1.2; 2.4 cm, to 1.3; 2.3 cm, to 0.5; and 4.0 cm, to 4.0. There were no over-corrections, and although 4 of the 5 limbs were corrected into an acceptable range, all were short of perfect equalization. The last patient was operated on too late by all criteria. In the other 4, however, the question arose as to whether growth anomalies in hereditary multiple exostoses might make prediction from the normal charts slightly unreliable. We therefore plotted femur-tibia length ratios along the appropriate percentile distribution in all the patients with hereditary multiple exostoses and compared them with the standard charts. The mean value for this length ratio in the patients with hereditary multiple exostoses was 1.27, which was exactly the same as the value from the charts for normal subjects with the same size distribution. There had been considerable difficulty in assessing the skeletal age from the roentgenograms of the wrists. The pattern of limb length discrepancy that can occur in this condition is variable. The discrepancy can remain unchanged for several years; it can increase at slow or moderate rates, which is the usual pattern; or it can, on occasion, decrease spontaneously. The growth-study data did not support the belief that there is an increase in longitudinal growth in an affected bone following removal of an exostosis. In addition, no correlation was seen between the degree of shortening in a particular bone and the number or size of the exostoses present. Limb-length discrepancies in our series were frequent, and in approximately one-half of the patients they were great enough to warrant epiphyseal arrest. These discrepancies point to the asymmetrical growth pattern in patients with hereditary multiple exostoses. The previously expressed belief that the growth retardation in a bone is directly related to the size and number of the exostoses is inaccurate. The discrepancies present in patients in our series were mild to moderate and were readily managed by appropriately timed epiphyseal arrests. Extremely careful observation is required, however, as the discrepancies can remain stable, increase at varying rates, or even, on occasion, spontaneously decrease. Corrective osteotomies can also alter limb-length relationships. Some difficulties were encountered in determining skeletal age accurately due to the associated wrist and knee anomalies, but the Green-Anderson charts were appropriate for predicted corrections in this condition. The limbs were more affected than the spine, both the femur and the tibia were involved, and the limb involvement was not invariably rhizomelic.

Pressure phenomena caused by exostoses: Pressure phenomena in relation to the spinal cord, nerves, vessels, and viscera can occur. Although these are relatively infrequent they can have serious consequences and patients must be followed at regular intervals and informed about reporting abnormal findings once noted. The pressure phenomena tend to become most apparent around 15 years of age or later as skeletal maturity is associated with thinning and eventual disappearance of the cartilage cap leaving the underlying often pointed segments of bone more prominent. Pressure phenomena on nerves, spinal cord, adjacent vessels and viscera were recognized early with many reports reviewed by Gibney as long ago as 1876 [311].

Peripheral nerve compression/stretching. The most commonly affected nerve is the peroneal owing to expansion of proximal fibular exostoses (Fig. 3.25d) [357].

Spinal cord compression. Spinal cord compression is possible owing to exostoses growing within the canal from points of junction of the endochondral and intramembranous systems [185]. Roach et al. studied the spinal canal in 44 patients with HME by advanced imaging (43 MRI, 1CT) [358]. They noted a 27 % incidence of exostoses inside the spinal canal although the large marjoity of patients were asymptomatic and neurologically normal. Their study was triggered after seeing 3 patients with neurologic findings due to exostoses of the spinal canal. Plain radiographs were poor in their ability to detect the lesions and sometimes identified lesions that turned out not to exist on the more sensitive imaging. The lesions were usually solitary but on occasion there were 2 several vertebrae apart. Each spinal region had exostoses seen with cervical the most common. The lesions derived from either the posterior vertebral bodies on the lamina. Some osteochondromas (not part of the 27 %) were outside the canal on the spinous or transverse processes. The paper also did an extensive review of the literature concerning spinal cnal osteochondromas. Overall, approximately 55–80 % were in the cervical region, 20–36 % thoracic and relatively few lumbar. The C2 vertebra seemed particularly prone to involvement and to symptomatic expression.

Vascular compromise. The commonest pressure anomaly is formation of pseudoaneurysms in post-adolescent, early adult life and the commonest region affected is the postero-medial aspect of the distal femur producing lesions of the femoral or popliteal artery (Fig. 3.25m). Vasseur and Fabre reviewed 103 cases of vascular complications of osteochondromas having sufficient detail, 97 from the literature [359]. Cases with HME accounted for 33 % and solitary exostoses for 67 %. The mean age of vascular lesions in their 6 patients was 22.5 years (range 14–46 years) and in the literature review the mean age was 22.6 years. Complaint of a hard swelling related to the osteochondroma but pain was an indicator of incipient vessel damage. Clinical findings included: pulsatile mass 39 %, non-pulsatile mass 24 %, distal ischemia 22 %, and phlebitis 2 % but also lower limb edema or parasthesia. The lower limb was affected 83 % of the time with predominance of lesions of distal femur. Rib osteochondromas occasionally caused hemothorax. The popliteal artery at the distal level of Hunter's canal in relation to distal femoral or proximal tibial osteochondromas was the most damaged artery. Arterial damage occurred 91 % of the time with isolated vein lesions or combined lesions causing the others. Of the 103 cases, false aneurysm was most common (59 or 57 %) followed by aneurysm 7, vascular compression 15, arterial thrombosis 13, false aneurysm +venous thrombosis 2, venous thrombosis 4, arterial and venous thrombosis 1, and arterial trauma 2. Surgical vascular management is needed along with resection of the osteochondroma. Vascular repairs can include closure of arterial defect, end to end anastomosis, autologous saphenous vein graft, synthetic vein graft, and thrombectomy.

Visceral pressure. Virtually all internal viscera have been the subject of case reports of abnormal extrinsic pressure or rupture including trachea, lung, esophagus, all other parts of the gastrointestinal system, the urinary bladder and the uterus.

Bursa formation. The commonest and most benign sequel of an exostosis is bursal irritation.

Fracture of exostoses: Fracture of exostoses can occur. They are commonest at the distal femur and proximal tibia and usually heal uneventfully.

Malignant degeneration of exostoses: Malignant degeneration to a chondrosarcoma of one of the exostoses is a well-known complication [312, 360–363]. The transformation almost invariably occurs in the adult age group especially after the 3rd decade. Virtually all tumors are chondrosarcomas derived from remnants of the cartilage cap. Concern is raised about malignancy whenever there is increase in size of an exostosis after skeletal maturity, pain at the site of an exostosis or radiographic evidence of increased bony radiolucency suggestive of local bony invasion. Some physicians recommend performing a bone scan at skeletal maturity and repeating it every few years to try to diagnose malignant transformation sooner than relying on clinical awareness. Approximately 2/3rd of the exostoses that undergo malignant transformation are of the scapulae, proximal humerus, pelvis or proximal femur with most of the others at the knee. The true incidence of malignant change has been difficult to determine since it requires a several decade study of a large group of patients. Original estimations of 10–25 % of transformation appear far too high and more recent reports tend to place the rate at 2.5–5 % [321, 360–363]. In 217 individuals with HME, 9 (4.1 %) developed chondrosarcoma, all of which were associated with EXT1 mutations [363].

3.12.27 Metachondromatosis

Metachondromatosis is a rare autosomal dominant skeletal dysplasia characterized by: (i) multiple metaphyseal juxtaepiphyseal exostoses that primarily involve the hands and feet, point towards the joint, and may spontaneously resolve; (ii) multiple enchondromas usually involving the iliac crest and long bone metaphyses of the lower extremity; (iii) periarticular radiodensity representing spicules of bone formation in expanded juxtacortical enchondromas; and (iv) frequent femoral head AVN [364–366]. Histologic

studies show a characteristic cartilage cap with endochondral bone formation on the inner surface, a sessile exostosis resembling a juxtacortical chondroma with spicules of endochondral bone formation, and intramedullary lesions of well circumscribed islands of cartilage. Cases of AVN of the femoral head associated with sessile femoral neck expansile enchondromatous lesions have been described. Shortening and deformity of the long bones do not otherwise occur and all patients with this disorder are of normal stature. The disorder was defined and named by Maroteaux in 1971 who stressed that attention was drawn to the disorder in the majority of cases because of deformation of the metacarpals, metatarsals or phalanges of the fingers or toes [364]. Management is by surgical removal of clinically bothersome exostoses and nonoperative containment or surgical treatment for the femoral head AVN as indicated.

3.12.28 Osteopetrosis

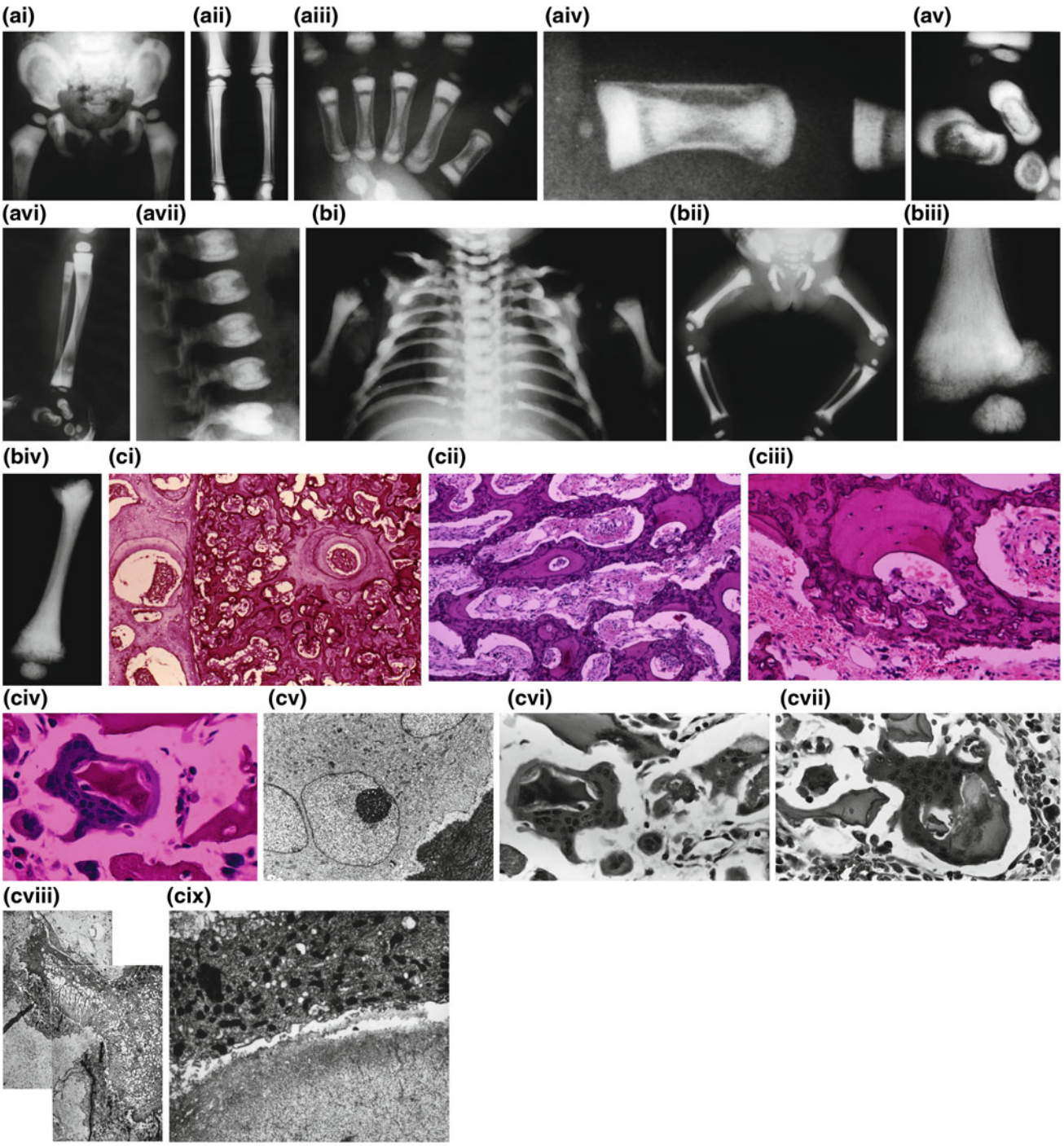
3.12.28.1 Overview

Osteopetrosis is an inherited condition characterized by increased bone radiodensity and widened metaphyses throughout the skeleton owing to a failure of normal osteoclast mediated bone and cartilage resorption. It was initially recognized and described by Albers-Schönberg, a German radiologist, in 1904 [367]. It is not a single disease but a syndrome with several variants initially defined on clinical criteria. There are 3 clinical groups: infantile-malignant autosomal recessive (ARO), fatal within the first few years of life (in the absence of effective therapy); intermediate autosomal recessive (IRO), appearing during the first decade of life but not following a malignant course; and autosomal dominant (ADO), with full-life expectancy but many orthopaedic problems [368]. The most common variant is autosomal dominant osteopetrosis, type II (ADO II), also referred to as Albers Schönberg disease since it represents the variant described in his initial report. The infantile variant shows a myelophthisic anemia, granulocytopenia, and thrombocytopenia, and patients eventually die from infection or bleeding or both. Neurologic sequelae include cranial nerve compression (optic nerve, blindness; auditory nerve, deafness; facial nerve, paresis), hydrocephalus, convulsions, and mental retardation. Radiographs show uniform bone density without corticomedullary demarcation, broadened metaphyses, "bone within a bone" or endobone phenomena (tarsals, carpals, phalanges, vertebrae, ilium), and thickened growth plates if there is superimposed rickets (Fig. 3.26a). Transverse pathologic fractures occur, often followed by massive periosteal bone formation. Computed tomographic scans, magnetic resonance imaging, and bone scans provide specific information. Iliac crest bone biopsy is valuable to quantitate osteoclast and marrow changes by light and electron microscopy. Medical treatments for the severe lethal autosomal recessive variants (ARO) currently involve bone marrow (hematopoietic stem cell) transplantation to provide monocytic osteoclast precursors. Orthopaedic problems in the intermediate and autosomal dominant forms include increased fractures, coxa vara, long-bone bowing, hip and knee degenerative arthritis, and mandibular and long-bone osteomyelitis. Osteotomy, plating, intramedullary rodding, and joint arthroplasty can be done, but are extremely difficult because of bone hardness.

3.12.28.2 Types of Osteopetrosis

Infantile-malignant autosomal recessive osteopetrosis (ARO). Most patients with infantile osteopetrosis are initially diagnosed within the first year of life. There are 2 modes of presentation. In one, the dense structure of the bones and the absence of a medullary canal leads to increased fragility and pathologic fracture. When the involved individual is assessed for limb pain, the radiograph shows increased bone density and a pathologic transverse or short oblique fracture. The second mode involves failure to thrive with frequent upper respiratory infections. When a detailed pediatric assessment is performed, a chest radiograph reveals the radiodense pattern of the ribs, vertebrae, and adjacent long bones; frequent concurrent pneumonia; and a hematologic picture characterized by anemia, granulocytopenia, and thrombocytopenia. Clinical examination reveals a marked hepatosplenomegaly. Further clinical manifestations of the condition also evident within the first year of life involve decreased function of the auditory and optic nerves, leading to progressive hearing and visual loss. These latter 2 conditions are associated with narrowing and sclerosis of the auditory and optic canals but visual problems can also be due to primary retinal degenation. Virtually all affected children will die during the first few years of life because of progressive worsening of the hematologic picture leading to massive problems with infection or bleeding or both. Two forms can be distinguished based on the presence or absence of osteoclasts as seen on bone biopsy: the much more common osteoclast-rich form in which osteoclasts are present in normal to increased numbers (but ineffective in resorbing bone) and variants which are osteoclast-poor [369].

Intermediate mild autosomal recessive osteopetrosis (IRO). Patients with this form of osteopetrosis tend to be diagnosed toward the end of their first decade of life [370]. Often a fracture brings about the diagnosis owing to radiographs characterized by increased density and decreased metaphyseal remodeling. At the initial diagnosis, the patient has some or all of the following conditions: mild disproportionate (short-limb) short stature, macrocephaly,



recurrent fractures, mandibular osteomyelitis, dental abnormalities, and mild to moderate anemia. Hepatosplenomegaly is either slight or absent. Relatively few patients have been described, and virtually all patients have survived into adulthood. Mandibular osteomyelitis can be extremely troublesome.

A subset of the intermediate form of osteopetrosis is associated with renal tubular acidosis, intracerebral calcification visible in plain radiographs, and a carbonic anhydrase II enzyme deficiency [371].

Benign autosomal dominant osteopetrosis (ADO). The autosomal dominant variant of osteopetrosis, sometimes referred to as the adult form, is a much more benign condition, and, in general, patients have a full-life expectancy [372–374]. Hepatosplenomegaly is not seen. Almost half of the individuals diagnosed with this condition are

asymptomatic. This number is determined on the basis of family studies initiated by discovery of a member with the condition. Two types of the autosomal dominant disorder are described. Type I patients have a generalized increase in bone mass but are unlikely to experience fractures whereas type II patients show sclerosis of the skull base and pelvis and the characteristic "rugger jersey" spine along with multiple fractures. ADO II represents Albers-Schönberg. Some have discontinued use of the ADOI term based on studies that the increased bone density is due to excess osteoblast function rather than decreased resorption [375]. The major symptom is pathologic fracture in approximately 40 % of patients involved. Although extreme fragility with multiple fractures has been reported, in general, the fractures are single isolated occurrences. The fractures are often transverse, demonstrating the characteristics of fractures through pathologic bone. Bone pain, especially in the lumbar area, is reported in 25 % of patients. Two other specific problems are cranial nerve palsies and osteomyelitis. A common focus of osteomyelitis is the mandible, although long-bone infections also occur. Coxa vara is typical, and cases of anterolateral bowing of the femur have been described. A gene for autosomal dominant osteopetrosis has been localized to chromosome 1p21 [376] and subsequently recognized as a mutation in ClCN7.

Animal models. There are several animal models which have a naturally occurring osteopetrosis. Those cited in most detail are murine variants although less typical rabbit and chicken models have also been described. The murine models in the rat include the *ia* (incisor absent), *tl* (toothless), *op* (osteopetrosis), and in the mouse the *gl* (gray-lethal), *mi* (microphthalmia), *oc* (osteosclerosis), and *op* (osteopetrosis) variants [377, 378]. Molecular defects in murine forms closely parallel specific clinical variants in children [375].

3.12.28.3 Histopathology

The histological appearance of the skeletal tissues and the results of studies on experimental animals with disease similar to human osteopetrosis are consistent with the conclusion that the skeletal lesions result principally from a marked decrease in the rate of bone and cartilage resorption with little or no change in the rate of bone and cartilage formation [379–381]. Failure to resorb the calcified cartilage formed during endochondral ossification leads to progressive filling of the metaphyseal region, and eventually of the marrow cavity of the diaphysis, with a tissue composed of cores of calcified cartilage surrounded by new bone. In the most severe cases the unresorbed tissue extends the full length and width of the bone, completely obliterating the marrow spaces and excluding the blood-forming marrow cells. Failure of osteoclasts to resorb bone at the periphery of the metaphyseal-diaphyseal junction at the distal end of Ranvier's ossification groove leads to the widened, abnormally shaped metaphyses. In the diaphysis, failure of resorption inhibits normal remodeling and cylindrization and leads to a thicker cortex [381].

Gross morphology: All bones are affected. The metaphyses and diaphyses of the long bones are increased in diameter. The epiphyses are normal in shape. Coronal sections and specimen roentgenogram show that the secondary centers of ossification, although more radiodense than normal, are appropriately positioned and of the same size and shape as the secondary centers of ossification of normal children. The time of appearance of the secondary centers is normal. Healing epiphyseal displacements are seen.

◀ **Fig. 3.26** Characteristic findings in osteopetrosis are reviewed. **a(i–vii)** Radiographic findings of osteopetrosis include uniform radiodensity without corticomedullary demarcation, broadened metaphyses and the "bone within a bone" or endobone phenomenon. The latter is seen most characteristically in the tarsals, carpals, phalanges, vertebra, and ilium. These findings can be seen in the newborn or early months of life in the malignant recessive variant but also characterize the benign dominant forms. (Reprinted with permission from Shapiro F, Osteopetrosis: Current clinical considerations. Clin Orthop Rel Res. 1993; 294: 34–43. Copyright 1993 Wolters Kluwer Health). **b(i–iv)** Periosteal elevation is often seen in patients with osteopetrosis. This can occur in relation to undisplaced or unrecognized metaphyseal fractures and also with epiphyseal growth plate fracture separations. Bleeding is often magnified by the thrombocytopenia. **i** Note extensive soft tissue early bone formation around humeri. Increased density affects all bones. **ii** *Lower* extremity radiograph shows bone density, periosteal new bone formation and multiple pathologic metaphyseal fractures owing to bone fragility. **iii** Higher power view of transverse metaphyseal fracture of distal femur is shown. **iv** Tibial specimen shows periosteal elevation (*white arrows*) associated with proximal and distal metaphyseal fractures (*curved dark arrows*). (Reprinted with permission from Shapiro et al. Human osteopetrosis: a histological, ultrastructural, and biochemical study. J Bone Joint Surg Am. 1980;62A:384–400). **c** Histopathologic findings characteristic of osteopetrosis. are shown **i–iii**. The characteristic matrix finding is the persistence of cartilage in the marrow (*far right*) with continuing new bone formation. In addition woven bone also persists with lamellar bone deposition proceeding. This is seen in thickened periosteal bone at *left*. Failure of absorption leads to the density of the bones both histologically and on radiographic representation. Sections can be found from the metaphyseal region in which cartilage cores persist surrounded by woven bone with that mass then surrounded by lamellar bone. **iv–vi** At the light microscopic level early in the disorder the osteoclast number is markedly increased and the osteoclasts are usually quite large with far more nuclei than normal. The osteoclasts position themselves appropriately in relation to bone and cartilage but function poorly since those tissues remain unresorbed. In older cases, the osteoclast number dramatically diminishes. **viii–ix** Both qualitative and quantitative ultrastructure of the osteoclast can be performed. The characteristic finding in most instances is a markedly diminished to absent ruffled border adjacent to bone and cartilage indicating diminished function of the osteoclast. The cartilage is at top and the osteoclast at bottom. In **vii** a normal osteoclast shows an intense ruffled border reaction adjacent to the cartilage. (Reprinted with permission from Shapiro et al. Variable osteoclast appearance in human infantile osteopetrosis. Calcif Tissue Int 1988;43:67–76. Copyright 1988 Springer Science + Business Media)

Cross sections of the diaphyses show the increased diameters to be due to an increased thickness of the true cortices as well as to the accumulation of a large amount of subperiosteal new bone in which small amounts of red marrow tissue are seen. Compact osseous tissue is seen in the medulla rather than cancellous bone. Cortical-medullary demarcation is indistinct. Long bones show extensive diaphyseal new-bone accretion. The calvarial diploë are increased in thickness, with little marrow space between them.

Light microscopy: A longitudinal section of an entire phalanx demonstrates well the contribution of the endochondral sequence and of the intramembranous-periosteal sequence to long bone development, as the synthesis pattern is preserved in the absence of effective resorption.

i. *Epiphysis and metaphysis*: The epiphyses are normally shaped. The cells in the articular cartilage and in the cartilage of the epiphyseal growth area are normal except for a few regions of the proliferative and hypertrophic zones of a few of the epiphyseal growth plates, which contain irregularly clumped chondrocytes between the vertical bars of extracellular matrix and irregular and somewhat widened columns of cells. Bundles of fibrous tissue extend between the hypertrophic zone and the zone of provisional calcification and interrupt the normally smooth, homogeneous appearance of the extracellular matrix. Except for these latter regions, the extracellular organic matrix of the articular cartilage and the epiphyseal growth cartilage appear normal. Since there can be a number of Type-I epiphyseal fractures and fracture-separations observed clinically and roentgenographically, one cannot be certain whether these regions of irregularly dispersed columns of cells are an inherent part of osteopetrosis or whether they represent responses to the epiphyseal fractures. The latter seems more likely.
The most striking and characteristic histological feature of osteopetrosis is observed at the metaphysis: the persistence of large amounts of calcified cartilage surrounded by bone, principally woven bone but in a number of instances lamellar bone. The cement lines are thicker and more prominent than usual. This endochondral tissue is present throughout the metaphysis and in many instances it fills the medullary canal of the diaphysis. The tissue remains organized as thickened primary trabeculae, consisting of a central core of calcified cartilage surrounded by new bone. Toward the diaphysis the trabeculae are densely packed, with virtually no marrow tissue present. In none of the major long bones studied is the regular columns of cartilage cells constituting the epiphyseal growth plate extend to the periphery of the epiphyseal cartilage. Moreover, at the periphery the germinal layer of the epiphyseal cartilage is often observed to be immediately adjacent to newly formed endochondral bone, without the interposition of the regularly ordered columns of cartilage cells. This most likely represents a repair response to the epiphyseal fracture-separations rather than an inherent feature of osteopetrosis.

ii. *Cortical and subperiosteal bone*: At the periphery of the metaphysis and diaphysis, the persisting remnant of the original cortical bone of the primary center of ossification can still be recognized, as it has not been resorbed. Peripheral to this, large masses of periosteal bone are seen, of a thickness wider than the original central medullary cavity and center of primary ossification. The pattern formation within this subperiosteal bone is not uniform. Adjacent to the primary center of ossification, true lamellar haversian bone is present. Peripherally, woven bone that is beginning to transform into true lamellar bone is seen. The woven bone looks normal under light microscopy, although there are some central areas of more primitive-appearing bone. Adjacent to some areas of woven bone, however, thick accumulations of acellular cartilage are present, sometimes lying free and at other time surrounded by coarse and fine woven bone. Safranin-O staining of this cartilage is normal. Scattered lamellar bone is also seen adjacent to cartilage and woven bone. The subperiosteal accumulation of bone and cartilage is not as dense roentgenographically as the intramedullary tissue. Moderate vascularity and considerable fibrous tissue are seen histologically. The irregular histological pattern of bone and cartilage is not analogous to that seen in the normal reaction to fracture, when the cartilage is cellular and a more ordered sequence of repair is noted. The appearance of this tissue indicates that resorption has not occurred or has occurred only incompletely, and that the regular temporal and spatial sequence of events has been disturbed.

iii. *Joint cavities*: The joint cavities appear normal grossly and histologically.

iv. *Secondary centers of ossification*: The tissue in the secondary ossification centers has the same structure as that seen in the metaphyses. The central cores of cartilage persist and are surrounded by woven bone. Isolate spicules of mature haversian lamellar bone are seen. There are many osteoclasts in the secondary ossification centers.

v. *Cell populations (cytology)*: In most variants numerous osteoclasts are present in close relationship to both cartilage and woven bone. Biopsies or variants with this finding are now referred to as osteoclast-rich. On

occasion, sections are seen in which spicules of bone and cartilage are entirely surrounded by huge osteoclasts. Osteoclast profiles with as many as 80 nuclei are noted. The osteoclasts are most abundant in the metaphysis adjacent to the growth plate and in the extracortical, subperiosteal region. They are infrequently seen in the lower metaphysis and diaphysis, among the persisting thick cores of cartilage and bone. In the subperiosteal tissue, plump osteoblasts cover the surface of both woven and young lamellar bone, and osteocytes are seen. The bone in the lower part of the metaphysis and diaphysis contains osteocytes, but osteoblasts are seen only occasionally. More recently, some variants are seen with very few osteoclasts. These are referred to as osteoclast-poor.

C. Electron Microscopy: In the osteopetrotic iliac-crest bone in ARO, there is almost always a marked increase in the number of osteoclast profiles and marked ultrastructural abnormalities of the osteoclasts compared with those in normal bone obtained from the iliac crest of a normal 2-year-old child. The osteoclasts from normal bone have many nuclei, an abundance of mitochondria, lysosomes, a Golgi apparatus, scattered ribosomes, and a well-structured endoplasmic reticulum. Ruffled borders and a surrounding clear zone are frequently observed in the portion of the osteoclast adjacent to the bone surface. The ruffled border is composed of the cell membrane thrown into many folds. The clear zone, also part of the osteoclast cytoplasm, is peripheral to the ruffled border and is free to organelles. The lamina limitans, an electron-dense, osmiophilic layer on the surface of bone, is also present. There is a close spatial relationship of the osteoclasts to the surfaces of bone and cartilage and to the blood vessels. Nineteen osteoclast profiles were counted in the normal cortical bone, 13 (68 %) of which were adjacent to the bone and 6 (32 %) of which were free. Six of the osteoclasts (32 %) had ruffled borders and 10 (53 %) had clear zones.

In the osteopetrotic bone, 86 osteoclast profiles were examined. Owing to the numerous osteoclasts present, profiles were quite easy to locate, whereas considerable sectioning was required to find such cells in the normal control. Sixty-three (73 %) of the cells were on the bone or cartilage surface and 23 (27 %) were free (Table 3.1). Thus, the osteoclasts, as well as being more numerous, were still appropriately positioned to perform their resorptive functions.

The most striking ultrastructural characteristic of osteoclasts in the osteopetrotic bone is the absence of ruffled borders and except in a few instances, of clear zones as well. Even osteoclasts that are adjacent to the surface of bone show no evidence of a change in their surface membranes. In a few instances, small cytoplasmic processes, which are often present along the portion of the cell away from the bone surface, are observed in that portion of the cell adjacent to the bone. The osteoclasts adjacent to cartilage have the same ultrastructural characteristics as those adjacent to bone.

Osteoclasts in the osteopetrotic bone contain more nuclei than osteoclasts from normal bone but the nuclei appear normal in shape, position, and appearance. Mitochondria, lysosomes, Golgi apparatus, and a well-developed endoplasmic reticulum are also present in the osteopetrotic osteoclasts. The endoplasmic reticulum, however, is situated in the portion of the osteoclast most distant from the surfaces of bone and cartilage. All of the organelles appear Ultrastructurally normal. The lamina limitans, the electron-dense, osmiophilic layer present on the surface of both bone and cartilage, is much more prominent in the osteopetrotic specimens. When present in cartilage it does not inhibit the formation of bone matrix, which frequently overlay it. In certain sections large amounts of normal-appearing collagen are present on the surface of the bone trabeculae. These are osteoid seams.

3.12.28.4 Diagnostic Criteria

(a) *Hematologic studies*: Extensive hematologic abnormalities characterize the infantile-malignant variant. The routine hemogram yields important information concerning the compromised hematologic status. The patients have a myelophthisic anemia. The marrow-forming regions of the bone are unable to function normally because they remain plugged with calcified cartilage and woven bone that persists due to failure of resorption. The eventual hematologic picture is characterized by anemia, granulocytopenia, and thrombocytopenia. The patients rely on extramedullary sources of hematopoiesis primarily from the enlarged liver and spleen for production of blood cells.
The anemia is associated with macrocytosis, reticulocytosis, circulating erythroblasts, and tear-drop erythrocytes. Stress erythropoiesis leads to production of fetal hemoglobin. The initial white-blood cell count is often elevated with the differential showing a leukoerythroblastic reaction. Hepatosplenomegaly accompanies the extramedullary hematopoiesis, and the subsequent hypersplenism produces the thrombocytopenia, leukopenia, and hemolytic anemia.
The susceptibility to infection has led to studies of neutrophil competence. Reeves et al. assessed monocytes and granulocytes in 5 osteopetrotic patients and suggested that abnormal function of these cell types diminished host resistance [382]. More recently, Beard et al. documented decreased neutrophil, monocyte, and

granulocyte-macrophage colony responses to stimulation that pointed to expression of the osteopetrotic defect at or before the progenitor cell level [383].

Mild to moderate anemia with evidence of extramedullary hematopoiesis is seen in the intermediate forms. There are no specific hematologic problems in patients with the benign autosomal dominant form.

(b) *Gene Mutations*: Six genes have been identified in which mutations are associated with osteopetrosis. Approximately 20 % of cases have no mutation identified so there are almost certainly other genes involved. The mutations are in TCIRG1 [384], ClCN7 [385], OSTM1 [386], RANKL [387], RANK [388], and PLEKHM1 [389]. Mutations have also been identified in the carbonic anhydrase (CA-II) dependent form of osteopetrosis with renal tubular acidosis and cerebral calcification [390]. The mutations have been related to specific phenotypes and to the outcomes of bone marrow transplantation.

Autosomal recessive osteopetrosis (infantile malignant osteopetrosis). TCIRG1 is the most frequently mutated gene in ARO accounting for 50 % of cases. This gene was previously described as the ATP6i gene. This variant of ARO is osteoclast-rich. The enzymatic reaction catalyzed by carbonic anhydrase provides protons which are extruded by the vacuolar proton pump (VPP) which acidifies the extracellular microenvironment. The VPP is a complex of several subunits among which the a3 subunit is specific for osteoclasts. The a3 is an isoform of subunit of the Vo domain in the VPP and it is encoded by the TCIRG1 (ATP6i) gene. Failure in the vacuolar pump disrupts the resorbing function of the osteoclasts [369, 384]. A similar inactivating deletion occurs in the TCIRG1 gene in the murine osteopetric model oc/oc. The next most frequently mutated gene in ARO is the ClCN7 gene which causes 15 % of cases. The ClCN7 gene is active in chloride channels, providing the chloride conductance needed for the proton pump to function well. ClC-7 is a late endosomal/lysosomal Cl^- channel that is highly expressed in osteoclasts where it can be inserted into the ruffled border [385]. Mutations in the ClCN7 gene are also responsible for intermediate osteopetrosis and all recognized cases of autosomal dominant osteopetrosis (ADO) [391–393]. The abnormalities are point mutations in the gene but there is no apparent correlation between the mutations and disease severity.

Mutations in OSTM1 [386] display the most severe recessive osteopetrotic phenotype and die at early ages. The murine variant OSTM1 gene is present in the grey lethal (gl) mouse. This is also an osteoclast-rich variant. It accounts for about 5 % of cases of ARO. The severity is associated with severe brain abnormalities and epilepsy.

Other osteoclast rich variants are due to PLEKHM1 mutations (analogous to the incisor absent (ia) rat) involved in less than 1 % of families with ARO and CAII dependent osteopetrosis associated with renal tubular acidosis and the CA enzyme deficiency.

All the osteoclast-rich forms account for about 70 % of cases. Osteoclast-poor forms have been detected more recently and are due to either RANKL [387] or RANK [388] dependent mutations. The RANK mutations and RANKL mutations account for about 4 % of cases each.

Autosomal Dominant Osteopetrosis. All cases of ADO, type II are due to mutations in the ClCN7 gene.

(c) *Blood chemistry studies*: In the infantile-malignant variant at the time of diagnosis, the serum calcium, phosphorus, and alkaline phosphatase values are normal, but acid phosphatase is elevated. Development of a low-calcium level is indicative of superimposed rickets, which is a well-documented phenomenon in some patients. The mid-molecular parathyroid hormone level is usually normal or slightly elevated, but the levels of 1,25 (OH) vitamin D are invariably markedly elevated. Over time, most ARO patients show increased alkaline phosphatase levels although this is considered to be due to osteoblastic response to the high number of osteoclasts, even if the latter are dysfunctional.

In the intermediate form, the calcium and phosphorus levels are also normal, and the acid phosphatase levels are markedly elevated. Blood chemistry values are normal in the autosomal dominant form except for the markedly elevated acid phosphatase levels. Bollerslev has provided a detailed study of several biochemical variables in 2 variants of the autosomal dominant condition [373]. Acid phosphatase was markedly increased in what he refers to as Type II; Type I was normal.

Tartrate resistant acid phosphatase (TRAcP) is always elevated in ADO II [391] and in many cases of ARO [394].

3.12.28.5 Normal and Abnormal Osteoclast Function and Bone Resorption

Bone resorption is mediated via multinucleated cells called osteoclasts [395, 396]. These cells form by fusion of circulating monocytes derived from hematopoietic stem cells (HSC). The stem cells differentiate through a series of steps involving commitment of HSCs into the monocyte/macrophage lineage, proliferation of pre-osteoclasts, differentiation into osteoclasts, and cell polarization enabling resorptive activity. Machrophage-colony stimulating factor (M-CSF) and RANKL are essential for osteoclast cell dif-

ferentiation expression of tartrate resistant acid phosphatase (TRACP) occurs. Polarization of the cell adjacent to bone (and cartilage) occurs via a circular clear zone which provides a tight attachment to bone; the osteoclast cell membrane within the circular clear zone is thrown into multiple folds, seen on transmission electron microscopy, referred to as a ruffled border. This serves to greatly increase the cell surface area allowing transfer into the region of adjacent bone surface where resorption occurs (forming Howship's lacunae). Osteoclasts express several molecules prominent in the resorption process including TRACP, matrix metalloproteinase 9 (MMP-9), cathepsin K, carbonic anhydrase II (CA II), the a3 subunit of the V-ATPase, the chloride channel 7 (ClC-7) and osteoporosis associated transmembrane protein 1 (OSTM1). Within the sealed ring (i.e., clear zone in electron microscopic terminology) bone resorption via acidification is induced by active secretion of hydrochloric acid across the ruffled border which lowers the pH to 4–5 leading to dissolution of the inorganic hydroxyapatite and then via enzyme of the collagen fibers. The osteoclasts use CA II to eventually lead to exchange of Cl^- into the resorption cavity to acidify it. CAII generates a proton and bicarbonate from carbon dioxide and water. The proton is actively transported across the membrane of the ruffled border through the action of the osteoclast specific vacuolar-type H+ATPase proton pump. A chloride channel coupled to the proton pump facilitates balancing the charge of ions across the membrane.

Regarding gene mutations causing osteopetrosis: (i) CAII defects limit the appropriate formation of carbonic acid and thus its dissociation into bicarbonate and a proton (H^+), limiting proton transport through the ruffled border; (ii) mutations of the a3 subunit of the osteoclast H^+-ATPase proton pump (TClRG1 or ATP6i) more directly limit active secretion of protons and (iii) abnormalities of the ClCN7 chloride channel gene negatively affect passive transfer of chloride which also limits the acidification within the resorption lacuna.

3.12.28.6 Imaging Studies. Plain Radiographs and Skeletal Survey

Radiographic features in the infantile form are illustrated. A skeletal survey reveals increased radiodensity of the bones throughout the skeleton. In the more advanced cases, there is absence of corticomedullary demarcation with uniform cortical density seen across the entire diameter of the bone. The metaphyses are wider than normal because of a failure of metaphyseal remodeling. This feature becomes more prominent after several months. In certain individuals, the "bone within a bone," or endo-bone phenomenon, can be seen particularly in the tarsal bones, vertebral bodies, phalanges of hands and feet, and pelvis (iliac wings). The metaphyseal regions often show alternating transverse radiodense and radiolucent bands, indicative of periods of exacerbation and remission. Thickening of the growth plates can be seen in patients that have rickets superimposed. Periosteal elevation caused by trauma and bleeding can be inferred from the longitudinal peridiaphyseal alternating bands of radiodensity and radiolucency, often referred to as the "onion-skin" phenomenon (Fig. 3.26b). Correlative radiographic and light microscopic pictures of osteopetrotic bone have been presented by several authors. In a rare autosomal recessive variant, osteopetrosis is associated with renal tubular acidosis, carbonic anhydrase II deficiency, and intracranial calcification. A characteristic finding in many adult autosomal dominant patients is the rugger-jersey spine appearance caused by thick radiodense accumulations at the superior and inferior vertebral body surfaces with relatively radiolucent areas in between.

Bollerslev and Andersen studied 35 patients with autosomal dominant osteopetrosis and described 2 types based on radiographic variations [373]. Both types have osteosclerosis throughout the skeleton, but in Type I patients, there is prominent sclerosis and increased thickness of the cranial vault, diffuse sclerosis of the spine without preferential end-plate thickening, and no bone-within a bone (endobone) phenomenon in the pelvis. In Type II patients, sclerosis of the skull is marked at the base, vertebrae show end-plate thickening (rugger-jersey spine), and the endobone phenomenon is almost always seen in the pelvis.

CT-Scan: For diagnosis and determination of the effects of management, the CT-scan assessment of the diameter of the auditory and optic canals is of great importance. It provides a baseline quantitative documentation of canal diameter that is helpful in observing patients over time, especially after treatments such as surgical decompression, bone marrow transplantation, or high-dose calcitriol. Optic canal tomography was used widely before the CAT-scan.

Magnetic resonance imaging: Magnetic resonance imaging has been used in osteopetrosis primarily as an indicator of marrow activity. The infantile-malignant forms demonstrate a complete lack of signal from the marrow in the vertebral bodies. The bodies appear "black", because of an absence of signal that contrasts sharply with the presence of signal from the adjacent intervertebral disks. Marrow elements are demonstrated, however, in benign forms and after successful bone marrow transplantation.

Bone scan: Bone scans have been used in osteopetrosis to show focal increased bone uptake in cases where osteomyelitis and occult fractures are being considered [397]. A Tc-99m methylene diphosphonate scan in an adult

with the benign dominant form shows increased uptake at sites of pathologic fracture, but normal generalized uptake even with significant increased bone density on plain radiographs. Thus, periosteal reactivity can be assessed. When specific studies of the reticuloendothelial system are performed using Tc-99 human serum albumin millimicrospheres, complete absence of bone marrow activity has been noted. The human serum albumin studies also document increased splenic uptake and hepatosplenomegaly. Because of relatively poor resolution, scintigraphy is not routinely performed in patients with osteopetrosis, although in selected cases it has valve. Magnetic resonance imaging is a more precise indicator of marrow function.

3.12.28.7 Iliac Crest Bone Biopsy

Iliac crest bone biopsy can help assess the biologic state of the condition and monitor specific therapies. Shapiro et al. have documented a variable osteoclast appearance in 9 patients with infantile-malignant osteopetrosis studied between 1 and 12 months of age before any therapy [380]. Owing to the risk of infection and bleeding, a cautious approach to biopsy is needed. Biopsies are performed in the operating room with antibiotic coverage to minimize risk of infection. Preoperative investigation involves a careful hematologic assessment. A biopsy is not performed if the platelet count is under 50,000. If the count is in that region or lower, preoperative platelet transfusion is recommended as long as it does not compromise subsequent therapy such as bone marrow transplantation. Biopsy should be performed only after prior consultation with the hematology service. Iliac crest biopsy can be done either through a small open incision or through a percutaneous incision using a bone biopsy needle.

We have performed biopsy to quantitate osteoclast number and bone surface coverage at the light microscopic level, to assess the ruffled border-clear zone relationship to bone and cartilage cores by transmission electron microscopy, and to assess the marrow contents (Fig. 3.26c) [380]. Osteoclast numbers, size and nucleation were always increased and the cells were always appropriately positioned in relation to bone and cartilage. In those patients with only a mild-to-moderate osteoclast increase, the marrow had an otherwise near-normal appearance with a good complement of hematopoietic cells. Light microscopic histomorphometry documented the percentage of bone and cartilage surfaces covered by osteoclasts. The controls from the areas of greatest osteoclast presence showed a 5 % coverage. One osteopetrotic patient showed a coverage of 4.8 % with all other patient values elevated from 7.6 to 27.9 %. The authors have proposed that an index of 5 to 9 % surface coverage is indicative of a mild increase, 10 to 19 % a moderate increase, and greater than 20 % a marked increase. Quantitative electron microscopy showed the ruffled border-clear zone complex to be absent or markedly diminished in 7 of the 9 patients. In 2, however, osteoclast profiles had abundant ruffled border-clear zone complexes. Patients with the hyperosteoclastic bone marrow were more severely affected clinically. The bone marrow quantitation does not yet establish absolute diagnostic criteria, but is helpful in monitoring the biologic response to disease and therapy.

3.12.28.8 Specific Orthopaedic Concerns in Osteopetrosis

a. *Fractures*: Two types of fractures are seen in children with infantile osteopetrosis. These involve either diaphyseal or metaphyseal fractures that are generally transverse and minimally displaced or epiphyseal fracture-separations that are also minimally displaced and often difficult to detect radiographically. Delay in recognition of such fractures and the difficulty of immobilization in the small, sick infant often lead to extensive periosteal elevation and extracortical new bone formation. On occasion, the entire shaft from growth plate to growth plate is surrounded by exuberant periosteal new bone formation. The reaction may be enhanced by increased subperiosteal bleeding associated with thrombocytopenia. The possibility of an occult osteomyelitis must also be considered.

Fractures also occur with increased frequency in patients with intermediate autosomal recessive and benign autosomal dominant osteopetrosis. In general, they can be treated effectively by nonoperative means. The fractures heal although the time to healing is often prolonged. There is a high incidence of hip and proximal femoral fractures, particularly in the autosomal dominant group. These can undergo successful internal fixation, but comment is invariably made on the extreme hardness of the bone and difficulty of the intervention. Both intramedullary rods and side plates have been used.

Bollerslev and Andersen documented fracture patterns in autosomal dominant osteopetrosis [398]. Of 35 patients studied, fractures occurred in 12. Only 2 of 20 had Type I osteopetrosis, whereas 10 of the 15 fractures were in Type II patients. A wide variety of bones were involved, including tibia, femur, patella, scaphoid, ribs, scapula, and transverse spinous processes. Ten of 12 patients had only 1 fracture, and each of the other 2 had only 2 fractures. Milgram and Jasty noted fractures in 9 of 21 patients. In 2 of the children, epiphyseal fracture

separations with abundant periosteal new bone formation had occurred. Compression fractures of the spine have not been reported.

b. *Coxa vara*: Many patients develop a coxa vara deformity, some in the first few years of life [372]. This deformity is seen in the intermediate and autosomal dominant types and is the most common deformity in these groups by far. The coxa vara appears to be caused by stress fractures of the femoral neck, with gradual deformity ensuing. The deformity can be treated by osteotomy, but the hardness of the bone makes internal stabilization difficult.
c. *Long bone deformity*: Long-bone deformity other than coxa vara is occasionally seen in the autosomal dominant type. There is lateral bowing, which usually involves the femur, but has also occurred in the tibia, humerus, and radius and ulna. The deformity may be secondary to malunion after diaphyseal and metaphyseal fractures, but generally is of slow onset and not associated with gross trauma.
d. *Osteomyelitis*: Because of the diminished vascularity of the bones and impaired white cell function, osteomyelitis is seen frequently with osteopetrosis. The most common site of involvement is the mandible. The teeth are impaired frequently by osteopetrosis, and mandibular osteomyelitis is associated with dental caries. Long-bone infections occur and must be treated vigorously because chronic foci have been established in many patients and are difficult to eradicate.
e. *Back pain*: Back pain is mentioned in most reports of benign autosomal dominant osteopetrosis. This rarely requires surgical intervention, but can be persistent. Bracing and conservative medication regimens are often required.
f. *Osteoarthritis*: Degenerative arthritis of the hip and knee is seen with increased frequency in mid-adult life in patients with the autosomal dominant form [399]. Total hip and total knee arthroplasties have been performed with good results, but the difficulty of reaming and instrumentation in association with the extremely hard bone, and narrowed to absent intramedullary canals, must be anticipated. It is theorized that the increased stiffness of the dense subchondral bone predisposes to premature cartilage degeneration.

A survey in the Pediatric Orthopedic Society of North America detailed results obtained in 79 patients with osteopetrosis the vast majority having the autosomal dominant variant [400]. The major orthopedic complication of the disorder was fracture with a high level of involvement of femoral neck, intertrochanteric proximal femur, subtrochanteric proximal femur and femoral shaft. There were also many tibial fractures and lesser numbers of upper extremity fractures. The major hip deformity requiring treatment was coxa vara. In 6 patients with femoral neck fractures the best results were obtained with closed or open reduction and internal fixation using either pins or compression screws. Neither infection nor delayed union occurred. On the other hand, those treated with cast therapy alone invariably developed varus and nonunion. Intertrochanteric fractures were best treated with internal fixation although considerable difficulty owing to hardness of the bone was generally noted. Subtrochanteric fractures healed with both operative and nonoperative methods. Femoral shaft fractures were generally treated successfully with nonoperative methods. Intramedullary rodding was both extremely difficult and in each of 3 patients 3, 5 and 7 years of age further surgery was needed. Tibial fractures treated with casting alone tended to heal successfully. Coxa vara was best treated operatively with valgus osteotomy preferably during childhood. Surgery was particularly valuable for coxa vara and the femoral neck fracture but for most long bone fractures nonoperative management worked well.

3.12.28.9 Specific Neurologic Concerns in Osteopetrosis

Although optic and auditory nerve dysfunction have been recognized in osteopetrosis, more detailed studies indicate a broader spectrum of neurologic involvement. In the infantile-malignant variant, the most common neurologic problems are optic atrophy with blindness, nystagmus, deafness, facial paresis, hydrocephalus, macrocephaly, and convulsions [401]. The optic atrophy with blindness is believed to result primarily from direct compression of the optic nerve within the narrow optic canal. Other hypotheses have been advanced, however, including hydrocephalus, increased intracranial pressure, primary retinal degeneration, and primary demyelination of the optic nerve. It is now believed that there may be primary involvement of the central nervous system parenchyma, as well as changes secondary to skeletal abnormalities. A large number of patients with the infantile variant have delayed motor development, and, in some, mental retardation develops. Ventricular hypertrophy and cortical atrophy have been defined by CT-scans. In 1 study, CT-scans showed hydrocephalus in 5 of 6 infantile patients.

Neurologic sequelae also occur in the intermediate and benign autosomal dominant forms, but are progressively less severe. In the benign form, about 20 % of patients have readily detectable neurologic manifestations, with the large majority optic, trigeminal, facial, and auditory nerve compression syndromes. When specific studies looking for cranial nerve compression sequelae were done on 14 patients recently, all but 1 had neurologic problems involving at least 1 of these nerves.

A neurosurgical procedure involving optic nerve decompression for osteopetrosis in early childhood has been reported to provide either improvement of visual capability or at least stabilization of function [402]. Electrophysiologic studies such as visual-evoked responses help quantitate the sequelae of optic nerve compression and the results of decompression. Auditory evoked potentials help document delays in nerve conduction associated with heaving defects. Surgical decompression of the facial and auditory nerves with some good results has also been reported.

3.12.28.10 Current Systemic Management Options for Osteopetrosis

Treatment protocols aiming to cure osteopetrosis are based on current understandings of etiology. Since failure of osteoclasts to resorb normal amounts of calcified cartilage and bone underlies the condition, therapeutic efforts have been directed either at stimulating host production of osteoclasts or providing an alternate source of osteoclasts to augment those not performing effectively. The osteoclast has its origin from circulating monocytes that fuse to form the multinucleated cell.

a. *High dose calcitriol*: This approach was based on the experimental finding that high-dose calcitriol (1,25-dihydroxyvitamin D) stimulates osteoclast formation and bone resorption [403]. The amounts given are extremely high, with several cases treated at dose levels of 1.5 ug/kg per day. It is important to note that in infantile-malignant osteopetrosis, the serum 1,25-dihydroxyvitamin D level is always markedly elevated, with a mean level of 193 pg/ml in 8 patients with the normal range 15–60. The massive pharmacologic doses are believed to induce bone resorption by stimulating quiescent osteoclasts or enhancing differentiation of precursors to the monocyte-osteoclast line. An integral part of this therapy is the use of a low-calcium diet that itself may potentiate a resorptive phase. Cases indicating stabilization or reversal of key osteopetrotic parameters have been reported but this approach is not curative.
b. *Recombinant Human Interferon Gamma*: Key et al. utilized recombinant human interferon gamma-1b in 8 patients with osteopetrosis and subsequently expanded the study to 14 with the severe malignant infantile variant [404]. Treatment was by subcutaneous injection. After 6 months of therapy all 14 patients had decreases in trabecular bone area and increase in bone marrow space as determined by marrow imaging. This improvement was sustained in 11 patients treated for 18 months. The long-term therapy was shown to both increased bone absorption and hematopoiesis and improve leukocyte function. This method is also not curative.
c. *Hematopoietic Stem Cell Transplantation*: Hematopoietic stem cell transplantion (HSCT) evolved from experimental work by Walker in the grey-lethal and microphthalmic osteopetrotic mouse in which he demonstrated that splenic transplants and parabiosis with normal litter mates induced normal bone resorption and reversal of the osteopetrotic state by providing large numbers of osteoclast precursors [405]. The multinucleated osteoclast is formed by fusion of circulating monocytes. Bone marrow transplant is the only curative therapy [406–409]. Successful allogeneic human bone marrow transplant for osteopetrosis was reported in a 5-month old child, and subsequent reports of successful transplantations have appeared [406]. In a review of European experience, 9 cases of HLA-identical transplants were reported, 6 of which were surviving disease free, and 2 HLA-mismatched transplants were reported, 1 of which was surviving disease free [407]. Gerritsen et al. studied 65 patients receiving myeloablative pretreatment [410]. Recipients of a human leukocyte antigen (HLA) identical bone marrow transplant had a probability for 5 year survival with osteoclast function of 79 %; recipients of a phenotypically HLA-identical bone marrow graft from a related or unrelated donor or 1 HLA-mismatched graft from a related donor had a probability for 5 year survival with osteoclast function of 38 %; while those who received a graft from a HLA-haplotype mismatched related donor had a probability for a 5 year survival of only 13 %. Osteoclast function developed in all patients with engraftment. In 25 % of patients however recovery of osteoclast function was associated with severe hypercalcemia especially in those older than 2 years of age. Only some of the patients experienced visual improvement in the group with impairment at the time of transplant even with engraftment. Solh et al. reported on 8 patients with malignant osteopetrosis who underwent bone marrow transplant [409]. Median age at transplant was 9 months with 6 patients receiving marrow from HLA-identical sibling donors, one from a phenotypically matched father and one from a 1 antigen mismatched father. Two patients died without engraftment. Three out of 6 who engrafted were alive and well at 48, 63, and 81 months. Those patients showed full bone marrow reconstitution. In the youngest patient vision improved dramatically with successful bone marrow transplant. The best results overall were obtained with the best matches and in the youngest patients. Rappaport has commented on the use of bone marrow transplant, indicating that one problem is hypercalcemia with abrupt onset of massive bone resorption. A review of the entire field of bone marrow transplantation provides details of possible benefits but

also of extensive complications that can occur with these procedures [411]. At present, bone marrow transplantation is considered only for the clear cut infantile-malignant form.

A retrospective analysis was made of 122 children who had received an allogenic hematopoietic stem cell transplantation (HSCT) for autosomal recessive osteoporosis between 1980 and 2001 [412]. It included 65 patients from a previous report [410] published in 1994. Five year disease free survivial for recipients of a genotype HLA-identical HSCT (n = 40) was 73 %, with decrease to 43 % for recipients of a phenotype HLA-identical or one HLA-antigen mismatch graft from a related donor (n = 21), 40 % for recipients of a graft from a matched unrelated donor (n = 20), and 24 % for patients who received a graft from an HLA-haplotype-mismatch related donor (n = 41). Severe visual impairment was present in 42 % before HSCT but the majority of the children, after successful transplant, had no further deterioration of vision with conservation best in children transplanted before 3 months of age. Short stature and severe hypercalcemia were also better limited by earlier transplantation. Most children attended regular school or schools for the visually handicapped. There was no fall-off in survival between 5 and 10 years post-transplant. Common causes of death were graft failure, septicemia, pneumonia, GVHD, veno-occlusive disease or neurological degeneration. The median age at HSCT was 6 months (range 1–105 months) with recommended time less than 3 months of age. All patients received myeloablative conditioning using such agents as busulphan and cyclophosphamide with efforts to improve engraftment including other cytotoxic drugs and immunosuppressive antibodies. Of the total 122 patients, 46 % were alive with osteoclast function at last assessment with the longest being 16.5 years post-transplant.

d. *Molecular Diagnosis of ARO and the Outcome of Bone Marrow Transplantation*: Over the past decade it has become possible to further evaluate the results of HSCT to the molecular cause of the ARO. ARO is genetically heterogenous and certain subsets of patients do better than others [413]. The osteoclast-rich variants are due to mutations in TClRG1, ClCN7, OSTM1, and PLEKHM1 and osteoclast-poor due to RANKL and RANK. Villa et al. related their HSCT experience to underying molecular defect in 230 ARO patients. They concluded that patients with mutations in the TClRG1 gene responded well to HSCT with a suitable donor. Cases of ARO due to the ClCN7 gene had a greater likelihood of retinal degeneration and cerebral atrophy and the authors expressed concern that even in cases of engraftment the neurological deficits were not improved. Cases due to the OSTM1 gene had even more severe neurological defects and HSCT had not been done in their group. Mutant ClCN7 or OSTM1 patients also show lysosomal storage disease in the brain and retina which is responsible for the degeneration of these nervous tissues [375]. The infrequent PLEKHM1 cases were relatively milder and also had not undergone transplant. In the osteoclast-poor RANKL gene mutation variants, HSCT patients did not do well since, in this variant, the affected protein came from osteoblasts of mesenchymal cell origin, not from hematopoietic cells. HSCT is not recommended for this variant, but theoretically they might benefit from mesenchymal stem cell transplantation (MSCT).

e. *Hematopoietic Stem Cell Transplantion in utero*: The partial effectiveness of post-natal HSCT led to the investigation of possible value of in utero transplantation (IUT). Frattini et al. treated ATP6a3-deficient mice by in utero heterologous HSC transplant from GFP transgenic mice. They noted that "dramatic phenotype rescue by GFP osteoclasts was obtained with engraftment…" Recipients were not immunosuppressed and graft-versus-host disease was not observed in pups born after in utero treatment. They concluded that IUT could bypass some of the problems seen with conventional bone marrow transplantation [414].

f. *Mesenchymal Stem Cell Transplantation*: This has been suggested for types of osteopetrosis, such as those with RANKL gene mutations not primarily due to hematopoietic stem cells but originating from mesenchymal cells.

g. *General Supportive Measures*: Supportive measures must be used to stabilize patients before other therapies or to serve as palliation if patients fail to respond. The hematologic picture of symptomatic anemia, granulocytopenia, and thrombocytopenia can be treated by blood and platelet transfusions. Splenectomy can be done for hypersplenism, but other extramedullary sites of the reticuloendothelial system remain active. Steroids can minimize hematologic sequelae temporarily, raising hemoglobin and platelet levels while decreasing spleen size.

3.12.29 Pycnodysostosis

Pycnodysostosis is a skeletal disorder of autosomal recessive inheritance characterized by short stature, generalized increased radiodensity of bones (osteosclerosis), persisting open fontanelles and cranial sutures, obliquity of the mandibular angle and hypoplastic mandible, and hypoplasia of the terminal phalanges of the fingers (Fig. 3.27) [415]. It is a lysosomal disorder caused by cathepsin K deficiency [416]. It was initially described in 1962 by Maroteaux and Lamy

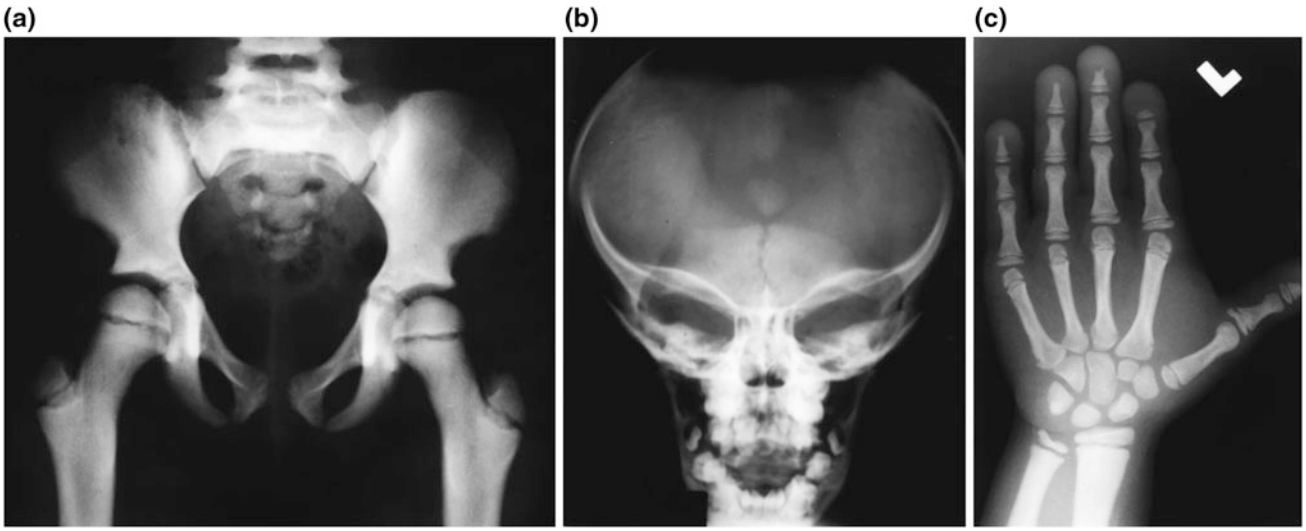


Fig. 3.27 Pycnodysostosis is a rare skeletal dysplasia characterized by increased bone density. Radiographic findings in pyknodysostosis usually allow it to be distinguished from osteopetrosis. The bone density is not as great. **a** Cortical thickening is seen but medullary demarcation is usually evident. **b** There are open cranial sutures, a diminished obliquity of the mandibular angle. **c** Defects of the terminal phalanges of the fingers are seen in which they are either absent, shortened, or tapered

[417, 418]. Multiple studies have now identified cathepsin K mutations in all patients although usually with different genotypes [419, 420]. Cathepsin K is a lysomal cytosine protease localized exclusively in osteoclasts and thus plays a major role in bone resorption. The bone density is not as great as in osteopetrosis demonstrating cortical thickening but also showing narrow intramedullary canal normal. Hematologic abnormalities do not occur, the patients are systemically well. Laboratory studies show serum electrolytes renal function and liver function indicators. The distal fingers are short and bulbous with dysplasic nails and terminal phalanges showing an absence of the distal 2/3rds or at least marked shortening and tapering. The distal part of the clavicle and the distal ulna are tapered and shortened. The major orthopaedic problem is frequent mid-diaphyseal long bone fracture with a tendency to either delayed union or non-union. The fracture line is often transverse, a sign of underlying pathologic bone. Eventual healing can occur with cast treatment but internal fixation and bone grafting may be needed. [415]. Nakase et al. in a study of surgical outcomes after treatment of 6 femoral and tibial fractures recommended intramedullary nailing rather than Ilizarov external fixation since external fixation had a tendency to be followed by re-fracture [421]. Histologic studies show dense lamellar cortical bone but one sample [415, 422] showed persisting woven bone surrounded by lamellar bone which is an index of limited bone remodeling due to osteoclast dysfunction. Two other patients studied with iliac crest biopsies showed thickened cortices and dense trabeculation of the marrow spaces [423]. Lamellar bone predominated but with highly irregular ("chaotic") organization. This presumably contributed to the tendency to fracture. Osteoclasts appeared able to resorb mineral but not the matrix.

3.12.30 Osteogenesis Imperfecta

3.12.30.1 Overview

Osteogenesis imperfecta (OI), one of the most common inherited connective tissue disorders, is characterized by increased bone fragility causing multiple fractures and often marked deformity. Molecular abnormalities in approximately 85 % of patients are present in the type I collagen molecule (COL1A1 and COL1A2) but a large number of different mutations along the collagen chains have been found which accounts for the wide variation in clinical severity [7, 424]. Over the past few years molecular abnormalities also have been found in patients with no primary structural mutations in type I collagen. These are primarily seen in lethal/severe OI and are still related to collagen since they are involved in the post-translational modification of types I, II, and V collagen via the prolyl 3-hydroxylation complex. These mutations are in the cartilage-associated protein (CRTAP) and LEPRE 1, encoding prolyl 3-hydroxylase 1 (P3H1) which form a complex that performs hydroxylation and brings the prolyl cis-trans isomerase cyclophilin-B to the unfolded collagen [425]. CRTAP, P3H1, and cyclophilin B are members of a protein complex that is required for the proper hydroxylation and positional rotation of a single proline residue (amino acid 986) in the alpha-1 and alpha-2 chains of type I collagen. Three additional causes of autosomal recessive OI have been detected [425]. These variants are generally severe clinically being found in autosomal recessive types II and III OI. They are not seen in the milder type I variant and are increasingly categorized as autosomal recessive types VII, VIII, and IX O.I.

The cartilage model of the developing embryonic bones is normal but the bone tissue is abnormal. In the more severe

variants however there is a true growth retardation leading to short stature. This diminished stature is a combination of (i) spine and limb shortening due to fracture and angular deformation, (ii) damage to physeal tissue by periphyseal fracturing, and (iii) systemic diminution of physeal stimulation (since shortening is not invariably associated with the first 2 factors). The clinical disease state is manifested in tissues in which the principal matrix protein is type I collagen mainly bone, dentin, sclerae, and ligaments. The phenotypic manifestations are variable in severity, ranging from perinatal lethal forms with crumpled bones and severe deformity to clinically silent forms with subtle osteopenia, normal stature and no deformity. In general, clinical subtypes represent a series of syndromes related to classes of molecular defects, each with a reasonably well-defined phenotypic pattern.

3.12.30.2 Classifications

The wide clinical variability in osteogenesis imperfecta has led to multiple attempts at classification. The current classifications are heavily weighted to the gene abnormalities and their proponents either don't mention the earlier systems at all or, if they do, consider them too simplistic to be of any use. This is unfortunate since, in a clinical-functional sense, they still have considerable value.

a. *Congenita-Tarda*: Looser, in 1906, classified OI into 2 types on the basis of when the first fractures occurred: congenita (fractures at birth) and tarda (fractures after the perinatal period) [426]. He noted that the prognosis in the congenita type was poor, with a high mortality rate. Seedorff, in 1949, further subclassified OI tarda into gravis (fracture occurs within the first year of life) and levis (fracture occurs after the first year of life), noting that tarda gravis was usually associated with the development of severe deformities and disability [427].
b. *Temporal-radiographic classification (Shapiro)*: The temporal-radiographic classification of OI combines the time of initial fracture and the radiographic appearance of the bones with the older congenita-tarda approach [122]. This approach provides a clinical index of severity with good and very early prognostic implications.
   The prognostic indicators assessed in the study were the age at initial fracture and the radiographic appearance of the long bones and ribs at birth or at the time of initial fracture if this occurred after birth. Those patients who had intrauterine fractures and/or fractures at birth were defined as having osteogenesis imperfecta congenita (OIC), with this group divided into A (OIC-A) and B (OIC-B) subgroups, based on the appearance of the long bones and ribs in newborn radiographs. Those who fractured initially after birth were defined as having osteogenesis imperfecta tarda (OIT), with this group divided into those who first fractured before walking, subgroup A (OIT-A), and those who first fractured after walking had begun, subgroup B (OIT-B). Consideration was not given as to whether a fracture was of the upper or lower extremity, and wormian bones of the skull were not considered as fractures.
   Osteogenesis imperfecta congenita A. There have been multiple intrauterine and birth fractures affecting virtually all bones. The extremities are shortened and deformed. The femurs in particular are markedly shortened, widened, and crumpled at birth, sometimes showing posterior bowing. Other radiologic findings include a small, bell-shaped rib cage with multiply fractured, short, and locally or extensively widened ribs; tibias that are wide and present with 45°–90° anterolateral bowing; a high likelihood of short, broad humeri; and a caput membranaceum with wormian skull bones.
   Osteogenesis imperfecta congenita B. Intrauterine and/or birth fractures occur, but at birth the long bones are of normal shape and length except where localized broadening is present in some in response to intrauterine fracture repair. Even those bones with extensive fracturing demonstrate regions of normal metaphyseal funnelization. The ribs are of normal length, narrow or normal in width, and show less extensive and often minimal fracturing. The rib cage assumes a normal conformation. There is a caput membranaceum with wormian skull bones.
   Osteogenesis imperfecta tarda A. These patients are born without fractures, but first fracture before or when beginning to walk. The long bones and ribs at the time of initial fracture are of normal shape and length but appear somewhat narrow and osteopenic. The rib cage is unremarkable.
   Osteogenesis imperfecta tarda B. These patients fracture first after walking has begun. The bones at the time of initial fracture are of normal shape, width, and length. In most, they are radiologically normal; in some, cortical thinning and minimal osteopenia are recognized. The rib cage is radiologically normal.
c. *Sillence classification*: A classification system was developed by Sillence in 1979 based on a comprehensive survey of patients in Australia [123, 428]. The Sillence classification divides OI patients into 4 types on the basis of clinical, genetic inheritance patterns, and radiologic features. Type I OI is the mildest and most common form. Inheritance is autosomal dominant, although new mutations are frequent. Type I is subclassified into the more common type A (without dentinogenesis imperfecta) and the less common type B (with dentinogenesis imperfecta). The sclerae are blue, and the first fractures usually occur in the preschool years, after walking has

begun. There is commonly absence of significant deformity; kyphoscoliosis is comparatively mild and uncommon; and stature is generally normal. Life expectancy is normal for patients with type IA OI and only marginally diminished for those with type IB.

Type II OI is the lethal perinatal form. Many fetuses are stillborn and survivors are often born prematurely. The disorder is usually lethal within the first few weeks of life, but some affected infants survive for several months and a few live for one or more years. Death is generally due to respiratory failure, intracranial hemorrhage, or brainstem compression. The sclerae tend to be light gray or grayish-blue. There are multiple intrauterine fractures, and the femurs, tibias, and ribs are short, broad, crumpled, and deformed. Inheritance was thought to be autosomal recessive; however most cases appear to result from new dominant mutations in a proband of unaffected parents. Occasionally unaffected parents have multiple affected children; this is thought to result from parental mosaicism or to be due to a rare autosomal recessive form.

Type III OI is the severe deforming form, with fractures generally present at birth. The sclerae are generally normal in color. Frequent fractures and deformity are common, stature is typically severely shortened, and the spine is often deformed. Respiratory complications and dentinogenesis imperfecta are common. Inheritance is thought to be autosomal recessive; however new dominant mutations are common, and a rare autosomal dominant variety exists. Life expectancy is decreased, but affected individuals live into adulthood. Early mortality is due to respiratory illness, injury with intracranial hemorrhage, and basilar invagination.

Type IV OI is a moderately severe form with great phenotypic variation, but is usually intermediate in severity between type III and type I. This variant is infrequent, accounting for approximately 5 % of cases. Sclerae are normal in color, short stature is variable, dentinogenesis imperfecta is common, and fractures and deformity are relatively common. Inheritance is autosomal dominant. Life expectancy can be decreased depending on disease severity; however, a large percentage of patients function independently well into adulthood.

d. *Radiological subclassifcation of OI type II*: A radiological classification subdividing OI II into A, B, and C categories has been proposed with short stature, lethality and multiple congenital long bone fractures present in all types [429]. It is unclear whether these relatively minor differences will be tied to specific gene abnormalities or, as seems more likely, they represent different responses to intra-and extra-uterine pressure.

e. *Additions to Sillence Classification*: Three additional types of OI were added to the Sillence classification by Glorieux and colleagues based on clinical, radiographic and some histological criteria [430–432].

Type V OI is characterized by hypertrophic callus post-fracture, calcification of the forearm interosseous membrane and dense metaphyseal bands. It is autosomal dominant without blue sclerae or dentinogenesis imperfect [430].

Type VI OI has frequent fractures, vetebral compression, long-bone deformity, normal sclerae and no dentinogenesis imperfecta with the presence of abundant unmineralized osteoid on histologic study [431].

Type VII OI is autosomal recessive with rhizomelic limb shortening and coxa vara [432] and has subsequently been found to be due to CRTAP mutations [433].

Type VIII OI was added by Cabral et al. for the LEPRE 1 mutation [434].

Type IX OI has a milder skeletal phenotype than types VII and VIII and was found to be due to a mutation in the peptidyl-prolyl isomerase B gene (PP1B) which results in a lack of cyclophilin B (CYPB) the third component of the collagen prolyl 3-hydroxylation complex [435].

f. *Revisions to modified Sillence Classification. Van Dijk et al*: In an effort to keep the current Sillence classification from expanding with each new gene mutation found, van Dijk et al. proposed revising the Sillence classification to type I, IIA, IIB, IIC, III and IV, with additional qualification based on the gene mutation identified [436]. This initially attractive approach was considerably blunted by also including types V and VI which are clinical descriptions without current gene identification, one of which appears as an isolated family with histologic description added even though histology is not otherwise included in current classification systems.

For maximum clinical usefulness, classification should include (i) simple to more complex parameters, (ii) indications of lethal versus non-lethal and non-ambulatory versus. ambulatory functional status, and (iii) multidisciplinary determinations-clinical, radiographic, and histologic, along with (iv) correlation with gene mutations. This implies the value of including known factors from multiple disciplines, adding new information from these disciplines as it becomes available, and correlating this with gene mutation findings as they too expand. Having one type defined on the basis of newborn lethality and another on histologic abnormalities is of limited value.

Initial categorization based on time of initial fracture and clinical/radiographic criteria has very good orientation value even though these approaches tend to be disregarded by many today. The congenital/tarda considerations remain valuable as inherent indices of severity. Congenita, tarda gravis and tarda levis are helpful along the lines of severe, moderate, mild categorizations. The

temporal-radiographic categorization provides a functional component using criteria by which every patient is assessed in the clinical setting. It asks the question: when was the first fracture and what was the radiographic appearance of the bones at that time? This information serves as an approximate, but reasonably accurate, indicator of the structural strength of the bones in any patient. These variables are known for each patient. To this baseline information, the gene mutation is added (when available) as a crucial qualifier. Daly et al. found very good correlation between the Sillence and Shapiro (temporal-radiographic) approaches [437]. In time, the actual mutation alone might be informative of the entire expected outcome, but experience with other gene disease makes this unlikely.

Classifications often raise controversy. Van Dijk et al. [436] backed their 2010 classification while Barnes et al. [435] supported the updated Sillence approach with nine categories, feeling that "separating recessive and dominant forms in osteogenesis imperfecta nosology has several advantages" in that it "provides distinctions that lead to clearer genetic counseling". The nosology group of the International Skeletal Dysplasia Society in their 2010 revision agreed to retain the Sillence classification as the universally (their words) accepted way to classify the degree of severity in OI but also to free (their words) the Sillence classification from any direct molecular reference. They then increased the Sillence types from 4 to 5 [referring to type 5 as Osteogenesis imperfecta with calcification of the interosseous membranes and/or hypertrophic callus] [6]. The temporal-radiographic classification remains helpful for projecting clinical severity early [437, 438].

Characteristic radiographic findings in the lethal perinatal form of OI are seen in Fig. 3.28a.

3.12.30.3 Clinical Characteristics

The musculoskeletal features of OI are variable in their extent and severity, depending on the clinical subtype and reflecting the underlying genotypic heterogeneity [122, 438–442]. Gross skeletal features can include short stature (with dwarfing in severe forms), kyphoscoliosis and pectus excavatum. The skull is often misshapen, with a broad forehead, flattened posterior cranium, overhanging occiput, bulging calvaria, and triangular facial shape. Depending on the severity of disease, there may be marked long-bone deformity with anterior bowing of the humerus, tibia, and fibula and antero-lateral bowing of the femur, radius, and ulna.

The hallmark of OI is bone fragility. As with the other phenotypic features of OI, the tendency to fracture is extremely variable, with manifestations ranging from innumerable fractures in utero and at birth to their virtual absence throughout life. The timing and number of fractures is included in some classification schemes. The more severe forms of OI are characterized by earlier and more numerous fractures. These fractures often occur after minor trauma. Fractures generally heal with abundant callus; however, the reparative bone is also abnormal, and fractures frequently lead to malunion and occasional pseudarthroses with resultant long-bone deformity. The incidence of fractures decreases after puberty and rises again in women after menopause and in men after 60 years of age.

The radiographic features of OI are also proportional to disease severity. The radiologic hallmark of OI is diffuse osteopenia associated with multiple fractures and deformities. Generalized osteopenia is seen in almost every case, and there is often equal involvement of the appendicular and axial skeletons.

The long bones of the lower extremities are usually more severely affected than those of the upper extremities. The long bones most often appear slender; however, they may show focal areas of thickened cortices secondary to callus buttressing or telescoping of fractures. The metaphyses of the long bones can be trumpet-shaped and cystic in appearance. In severe, cases, "popcorn" calcifications appear in childhood in the metaphyseal/epiphyseal regions as displaced, fragmented physeal cartilage undergoes endochondral ossification. These calcifications commonly resolve after skeletal maturity, when all cartilage is transformed to bone.

The vertebrae in OI often demonstrate flattening or are biconcave secondary to multiple microfractures. The overall incidence of spine deformity in OI is approximately 60 %, ranging from 90 % for congenita forms to 10–40 % for tarda forms. Thoracic scoliosis is the most common spinal deformity and is associated with osteoporosis, compression fractures, and ligamentous laxity. The spinal deformity is rarely isolated and overall thoracic deformity associated with multiple rib fractures, scoliosis, molding of the soft thorax and pectus excavatum or carinatum can be sufficiently severe to compromise respiratory function.

The skull is characterized by wormian bones but this finding is seen primarily in the more severe variants, congenita A and B types or Sillence II and III variants (Fig. 3.28b). The wormian bone appearance represents small, independent areas of primary ossification within membranous bones arranged in a mosaic pattern. The softened skull tends to develop a flattened occipital region as the affected child lies in the supine position; prominent frontal bossing and delayed closure of the fontanelles are also characteristic. Basilar invagination at the softened foramen magnum region can lead to cervicomedullary compression in the severe OIC A, B and Sillence II, III variants.

Hyperplastic callus formation is rare but can occur in patients with OI. It often presents as pain, an enlarging mass,

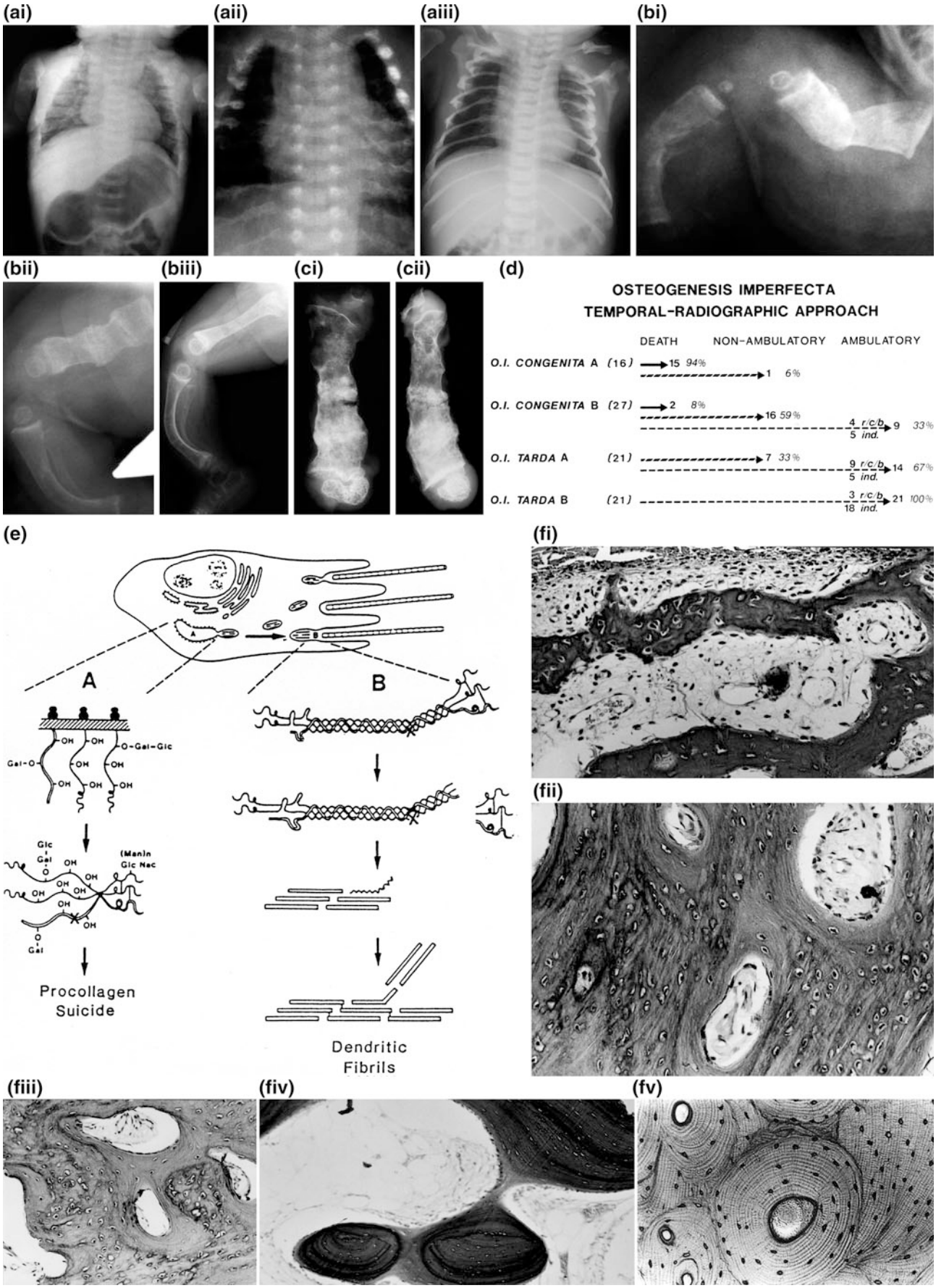
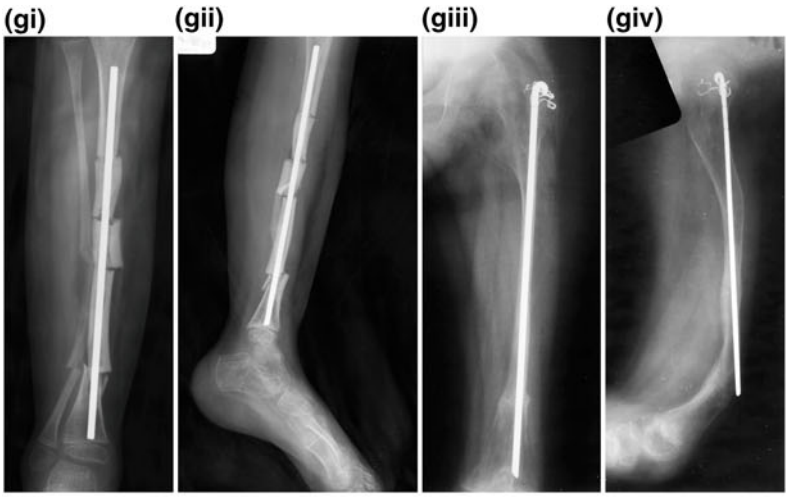


Fig. 3.28 (continued)



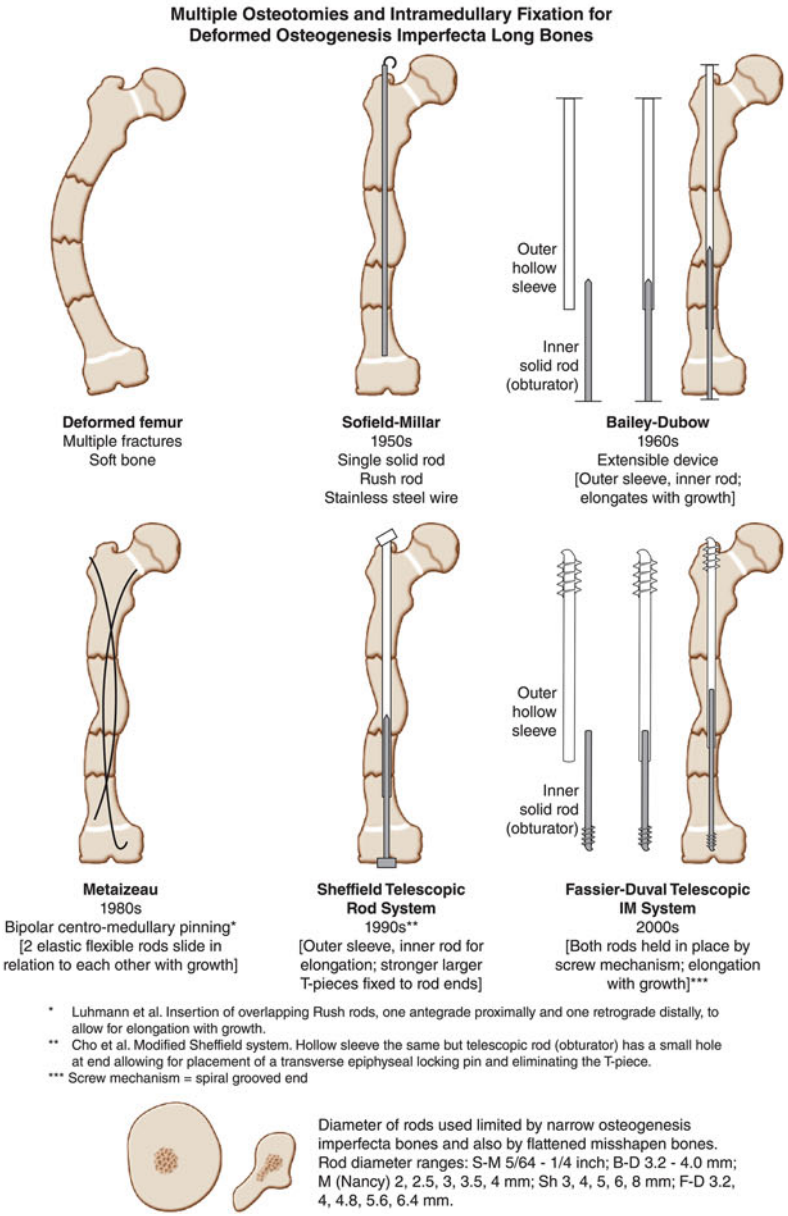


Fig. 3.28 (continued)

and erythema, and can be difficult to distinguish from osteosarcoma radiographically, clinically, and even histologically.

The articular cartilage appears normal. The physis often shows disorganization of the proliferative and hypertrophic zones with increased permeation of cartilage by metaphyseal blood vessels. The metaphysis is composed of a scanty, woven primary spongiosa. There is increased bone turnover as defined by tetracycline-labeling studies.

Dentinogenesis imperfecta is characterized by soft, translucent grayish colored teeth. The teeth are affected in a nonuniform manner with involvement usually greater in the primary teeth than in the secondary teeth. The enamel wears easily, and the teeth are carious, shortened, and susceptible to cracking. On X-ray films, the crowns are bulbous, and there is obliteration of pulp chambers. About 30 % of individuals with all types of OI have significant dental involvement. The Sillence classification scheme subclassifies type I and type IV OI on the basis of the presence or absence of dentinogenesis imperfecta. Dental treatment includes crowning, dentures, and intraosseous implants.

The blue sclerae in OI are the result of increased corneal translucency (secondary to abnormal collagen), which reveals the underlying uveal pigment and blood vessels. This color changes with age, becoming more grayish in adulthood. The pericorneal region of the sclera is often white and opaque, resulting in a "Saturn's ring" appearance and there may be opacities in the periphery of the cornea, giving an arcus juvenilis appearance. The classic blue sclerae are most characteristic of the more benign autosomal dominant type I variants. The more severe type III progressively deforming types often have white or slate gray sclerae rather than blue sclerae. Hypermetropia is common.

The skin in OI is often thin, translucent, and easily distensable owing to collagen insufficiency of the dermal layer. Surgical scars commonly heal with widening. Ligamentous laxity is a characteristic feature of OI. Pes planus is the principal clinical manifestation, but other disorders of hyperlaxity, such as subluxating patellae and dysplastic hips, are occasionally seen. There is often a secondary muscular hypotonia and underdevelopment related to tendon or ligament anomalies and reduced activity. There is increased vascular fragility, which presents with bruising owing to the weakened perivascular connective tissues. A small minority of patients demonstrate nonprogressive aortic root dilatation. Valvular disease, in particular mitral valve prolapse, is much less common than in Marfan syndrome, but has been reported.

The onset of hearing loss in OI, seen primarily in the type I benign autosomal dominant variant, begins in adolescence and becomes problematic for nearly 50 % of affected adults. Hearing loss can be conductive, sensorineural, or mixed. The extent of deafness is variable; however, loss in the high-frequency range is characteristic. Treatment usually involves prosthetic stapedial footplate replacement or stapedectomy. Other otologic findings include recurrent middle ear infections and sinusitis, tinnitus from stapedial fixation, vertigo from labyrinthine involvement and speech delay.

Low-pressure hydrocephalus is occasionally seen in patients with severe forms of OI. The anterior fontanel remains open, and there is general dilation of the ventricles with cortical atrophy. The process is usually self-limiting and does not require shunting. Basilar impression occurs predominantly in Sillence type III and type IV OI. There is brain stem and spinal cord compression at the foramen magnum, resulting in progressive cerebellar disturbance and lower cranial decompression, which has had variable results.

Abnormalities of thermal regulation. Patients with osteogenesis imperfecta often show a generalized disturbance of energy metabolism leading to a hypermetabolic state. Metabolic abnormalities, present to a variable extent in

◀ **Fig. 3.28** **a(i–iii)** Radiographic apearances of ribs in patients with lethal perinatal OI (Sillence II, OIC A) are shown. Rib cage at birth shows diminished lung fields and multiple rib fractures with either broadened or very narrow bone structure. **b(i–iii)** Radiographic appearances of femur and tibia in patients with lethal perinatal OI are shown. In **i** and **ii** short, broad and crumpled femurs are seen but structure closer to normal is also seen in congenital forms like iii that survive longer. Midshaft angulation of the tibia is also common. **c(i, ii)** Specimen radiographs are shown of femur in case of lethal perinatal OI in anteroposterior (**i**) and lateral (**ii**) projections. Note central fracture, marked demineralization, crumpling and absent cortical structure. **d** Patient outcome based on temporal-radiographic classification is shown. (Reprinted with permission from Shapiro F, Consequences of an osteogenesis imperfecta diagnosis for survival and ambulation. J Pediatr Orthop. 1985;5:456–462). **e** Structural alterations of collagen fibrils following a mutation are shown. **f(i–v)** Histopathology of OI bone provides valuable clues to the severity of the underlying disorder. In the most severe lethal perinatal variants woven bone only is seen (**i**) and even that is present in markedly diminished amounts. The bone tissue is usually described as hypercellular but that term is actually indicative of scanty matrix formation. In the most severe cases isolated spicules of bone are seen with no continuity between them. In disorders of moderate severity (**ii–iv**) woven bone persists but is generally surrounded by lamellae of more mature bone. The greater the amount of lamellar bone, the stronger the underlying tissue. In the mildest benign dominant cases, histologic structure is close to or may be indistinguishable from normal (**v**). **g(i–iv)** Multiple osteotomy with intramedullary rod fixation is resorted to in the presence of multiple fractures which have caused increasing bowing deformity. A post-operative example is seen (**i**, **ii**). In severe cases only Rush rods or Steinmann pins can be used for fixation (**iii**, **iv**). With growth, bone extends beyond the rod ends, predisposing the bone to further deformation and fracture and need for repeat surgery. On occasion however the bone remains straight and additional surgery is not needed. **h** An overview of the development of multiple osteotomies and intramedullary fixation techniques for deformed OI long bones is illustrated. Expanding rods or 2 rods inserted from opposite end of the bone are used increasingly to provide better protection of the bone with fewer surgical interventions during the growing years

patients with OI, are characterized by heat intolerance, elevated body temperature, increased sweating, and resting tachypnea and tachycardia. These findings are generally attributed to high metabolic activity and turnover of the connective tissue cells. Under anesthesia the body temperature often rises even further although in most instances these are not associated with true malignant hyperthermia with its muscle rigidity, arrhythmias and acidosis. A few true episodes of malignant hyperthermia have been described however in OI. Cor pulmonale is seen frequently in those with severe restrictive lung disease in particular with long-standing rigid kyphoscolioses.

3.12.30.4 Diagnosis

Post-natal diagnosis. The diagnosis of OI is based on clinical, radiographic, and molecular criteria. Fibroblast cell culture from skin biopsy specimens or DNA analysis can now be used to detect collagen molecular abnormalities (discussed in the "Molecular Basis" section) in approximately 85 % of patients with OI and an additional 5–7 % of children, usually with the more severe autosomal recessive variants, have abnormalities due to CRTAP, LEPRE 1, cyclophil B or other mutations which affect post-translational modifications of the collagen molecules [425, 443].

The differential diagnosis of OI in infancy is relatively limited. Diagnosis of mild variants in childhood and adolescence can be more difficult due to less severe involvement. Idiopathic juvenile osteoporosis is an extremely rare disorder with onset at puberty. It is characterized by generalized osteopenia and propensity to fracture. Spontaneous remission has been reported. It can be distinguished from OI by its onset in adolescence, the presence of normal sclerae and teeth, and a negative family history. Hypophosphatasia presents with multiple fractures, deformities, and osteopenia. Hypophosphatasia resembles OI with blue sclerae, bowing of legs, and osteopenia; it can be differentiated from OI by abnormal laboratory findings such as the urine excretion product phosphoethanolamine and markedly decreased serum alkaline phosphatase levels. The distinction between mild forms of OI and child abuse (non-accidental injury—NAI) can be difficult, but is crucial to consider. Both may present with a propensity to fracture without a clear history of definite trauma. Classically, abuse usually presents with multiple fractures in different stages of healing, posterior rib fractures, metaphyseal corner fractures, and skull fractures. Other signs of abuse include bruises, skin burns, and retinal hemorrhages. Marlowe et al. reviewed 262 patients where collagen testing in their laboratory was done in situations where NAI was suspected but collagen testing was done in an effort to detect OI unrecognized by clinical examination. Testing was done on cultured fibroblasts. Eleven of the samples had alterations in type I collagen consistent with the diagnosis of OI and in 11 others the diagnosis could not be excluded. The authors concluded that collagen testing could be valuable in detecting OI in a small group of patients not diagnoseable by clinical-radiographic criteria where NAI was being suspected [444].

Prenatal diagnosis. Prenatal diagnosis of OI can be made on the basis of structural characteristics noted on fetal ultrasound, collagen molecular studies of cultured chronic villus cells or genetic linkage studies with the use of collagen markers. Prenatal detection in pregnancies at risk for OI can provide valuable information for genetic counseling and obstetric management. Genetic counseling can provide information concerning the likely outcome of future pregnancies and the prognosis for individual affected children. In actuality, however, this is difficult because of the high incidence of spontaneous mutations and sporadic cases, the lack of diagnostic tests in the index case, and the lack of an accurate carrier test.

Ultrasonography can effectively screen fetuses for severe forms of OI, but it remains difficult to detect mild forms. Sillence type II OI (OIC A) can be recognized on ultrasound scans obtained at 16–20 weeks gestation by assessing femoral length adjusted for gestational age, extent of mineralization, evidence of fractures, skull echogenicity, and thoracic abnormalities. Mid-trimester ultrasonography is usually useful in detecting type III OI by depiction of intrauterine fractures and deformity. Advances in transvaginal ultrasound may provide a means of first-trimester prenatal diagnosis of severe forms of OI.

If a certain biochemical defect of collagen or a specific mutation has been identified in an affected parent or sibling, prenatal detection can be accomplished by screening fetal tissue for the presence of that defect. This is performed by culturing chorionic villus cells and examining the electrophoretic properties of the collagen they produce. Amniotic fluid cells are, in general, not useful because most cells synthesize a variant of type I procollagen. Linkage studies performed with the use of collagen markers are currently the diagnostic investigation of choice for families with autosomal dominant OI, allowing genotyping of the fetus.

3.12.30.5 Detailed Assessment of Consequences of Diagnosis

The temporal-radiographic classification provides an indication of eventual outcome or prognosis based on the time of initial fracture and the radiographic appearance of the bones at time of initial fracture [122].

Osteogenesis imperfecta congenita A. Fifteen of the 16 patients died (94 %) [122]. Two were stillborn, one died at 4 h, 6 between 1 and 6 weeks, 2 at 3 months, and the others at 4, 11, and 16 months and at 3 years 9 months of age. One patient survived to 14 years of age but never walked, and

was wheelchair bound following intramedullary fixation of all 4 major lower extremity long bones.

The patients who survived until 11 and 16 months of age had sequential radiographs that demonstrated progressive widening of the long bones and ribs. Radiographs in the 14-year survivor demonstrated the femurs to be short, wide, and crumpled at birth, whereas the tibias were broad and deformed with severe anterior angulation. The ribs were thin with only occasional local broadening due to repair; the rib cage demonstrated more normal size and shape. The long bones widened until 4 months of age, then began to diminish in width, and subsequently required intramedullary rods at 6 years.

A caput membranaceum with wormian bone formation was noted in all patients. All had a negative family history with clinically normal parents. Two of the children with OIC-A were brother and sister, born 3 years apart, who died at 3 weeks and 3 months, respectively. There were no instances of parents with children with OIC-A giving birth to less seriously affected children with osteogenesis imperfecta.

Osteogenesis imperfecta congenita B. Two patients (8 %) died of respiratory problems at 3 and 5 months. Sixteen (59 %) of the patients were wheelchair bound and 9 (33 %) were ambulatory in some fashion. Eight of the 16 wheelchair-bound patients had intramedullary rods placed in from 1 to 4 of the major lower extremity long bones. Five patients walked independently without requiring intramedullary rods or external assistive devices, although 3 required osteotomy or osteoclasis. Four patients walked using external assistive devices; 3 of these had stabilization with intramedullary rods.

A caput membranaceum with wormian skull bone formation was noted in all patients. Some developed a normal-appearing skull radiographically with time, whereas others persisted with delayed fontanelle closure and/or wormian bones several years after birth. Eighteen patients with early radiographs showing all bones each had evidence of healed or healing intrauterine fractures.

A negative family history was documented in 96 % (24 of 25 patients). The 1 individual with a positive family history had a father with osteogenesis imperfecta who walked with crutches after multiple surgical procedures, including femoral rod placement, and a brother who had an initial fracture at 2 weeks of age. This patient has had all 4 lower extremity long bones internally stabilized with rods but remains in a wheelchair at 10 years of age with long leg orthoses for protection.

Osteogenesis imperfecta tarda A. There were no deaths in this group. Seven patients (33 %) were ultimately wheelchair bound whereas 14 (67 %) were able to walk. Three of the 7 who were in wheelchairs had intramedullary rods. Five in the ambulatory group walked independently, whereas 9 used crutches or braces or had been stabilized with rods. In this latter group, 5 had rods placed in from 1 to 4 lower extremity long bones. Four of those with rods required other assistive devices to walk, and one walked without other assistance.

The age at initial fracture did not correlate with eventual ambulatory capability. In the 5 who eventually walked independently, the ages at initial fracture were 4 weeks, 5 weeks, 6 weeks, 6 months, and 12 months. In those who ultimately were wheelchair bound, the ages at initial fracture were 3, 4 (3 patients), 7, 9, and 10 months.

A negative family history was documented in 89 % (17 of 19). Of the 2 with a positive family history, one girl's father had OIC-B. The other patient's father had OIT-A. He had also fractured shortly after birth, and his family had a high incidence consistent with an autosomal dominant transmission.

Osteogenesis imperfecta tarda B. All patients were ambulatory. There were no deaths. Of the 21 patients, 18 were able to walk independently, and 3 were ambulatory with crutches. Of these 3, one had rods placed in all 4 lower extremity long bones. The age at initial fracture varied from 14 months to 9 years of age. Sixteen (76 %) patients had a positive family history of the autosomal dominant pattern. Of the 5 with a negative history, 3 of these were the only patients with OIT-B who did not walk independently.

3.12.30.6 Significance of Various Classification Schemes

The temporal-radiographic classification of osteogenesis imperfecta reflects the severity of involvement and allows the physician to provide early guidelines concerning survival and ambulation. In the OIC-A group, a virtually universal (94 %) death rate occurs. The appearance of the femurs, tibias, ribs, and rib cage is characteristic. Distinction from the patient with OIC-B is possible, however, on the basis of the newborn radiographs. Such a distinction is extremely important as there is a significantly better prognosis in the OIC-B group, with 92 % surviving. The 2 most important areas in differentiating infants with OIC-A from those with OIC-B are the rib cage and the femurs. Chest size and shape in the child with OIC-B are normal or at least close to normal as are the individual ribs, even if some fractures have occurred. Some OIC-B long bones at birth have healed intrauterine or fresh fractures but also show extensive normally shaped areas possessing normal metaphyseal funnelization. An infant with severe OIC-B is distinguished from a patient with OIC-A by these regions of normal metaphyseal funnelization. Figure 3.28c illustrates the progressively improved rates of survival and ambulatory capability as one moves from the OIC-A group to the OIT-B group.

A classification of congenita patients has been reported that documents a similar prognosis based on radiographs of long bones, ribs, skull, and vertebrae. The skull has not been included here because of the difficulty in quantifying wormian bones and the fact that caput membranaceum and

wormian bones were present in all patients with congenital disease. Thus the skull findings did not correlate with survival and ambulation. Retrospective classification into mild, moderate, and severe forms based on degree of bone deformity several years after birth has been reported as had subclassification of the tarda group into type I, with lower extremity bowing, and type II, without bowing. It thus appears premature to abandon totally the congenita-tarda approach, as has been suggested. Other studies have detailed the range of variation noted in the intrauterine period and with the congenita types [429, 445, 446].

The Sillence classification as originally described (4 types) in fact correlates well with the congenita/tarda temporal-radiographic classification. The congenita A group encompasses Sillence type II lethal perinatal patients; congenita B and tarda A are generally Sillence type III patients with progressive deformity; and tarda B represents the Sillence type I benign autosomal dominant patients.

It is difficult to categorize patients with osteogenesis imperfecta by this or any approach on purely clinical criteria. Classification by the Sillence approach is particularly difficult in the early phases of the disease, which is the time that parental anxiety re prognosis is highest. It frequently requires a few years to classify individuals appropriately with the Sillence approach, as tooth and scleral findings are either not apparent at birth or change with time. There is also lack of unanimity as to clinical genetic patterns. Although the Sillence approach attempts to take the heterogeneity into account, it is evident from recent biochemical findings on molecular abnormalities of collagen that heterogeneity is vastly more extensive than originally thought. It still appears practical to consider the age at the time of initial fracture and the radiographic appearance of the bones at initial fracture as providing important guidelines for counseling and management. This is particularly important as fractures represent the most debilitating feature of the disease. Our modification of the congenita-tarda approach is effectively an index of disease severity. It is not intended to, nor can it, provide a rigid disease classification, which can only come with molecular definition.

The term "congenita" is used to refer to fractures occurring in utero or at birth, whereas initial usage of the term by Looser applied congenita only to intrauterine cases with birth fractures defined under the tarda group [426]. Seedorff [427] and King and Bobechko [445] have also defined congenita this way, subdividing the tarda group into tarda gravis, with fractures occurring at birth or in the first year of life, and tarda levis, with fractures occurring initially after one year. The approach used here attempts to overcome the problem of having cases with fractures at birth referred to as tarda cases, which is semantically awkward. More important, when radiographs in such cases were carefully reviewed, 18 of 18 patients with total body radiographs showed old healed or healing intrauterine fractures. This led to the congenita designation, with all these patients as OIC-B.

The temporal-radiographic approach delineates well patients with a predominantly negative family history (OIC-A 100 %, OIC-B 96 % and OIT-A 89 %) from those with a predominantly positive history (OIT-B 76 %). Those with a negative history, already considered to be a heterogeneous group by clinical and collagen studies, would have both autosomal dominant new mutations and autosomal recessive patterns of inheritance. The positive history group comprises the more benign autosomal dominant condition.

OIC-B and OIT-A are not genetically distinct, as shown by 3 families in which one affected member was OIC-B and another OIT-A. This phenomenon was also noted by Seedorff. It is also noted that 3 of the 5 patients with OIT-B and a negative family history were the only 3 patients with OIT-B not walking independently, which might indicate a more severe genetic abnormality.

The radiographs at birth or at the time of initial fracture, if this occurs after birth, are used as the classification baseline for this approach. Bones that are originally narrow can widen with the onset of a fracture-repair-fracture-repair cycle. Thus, broadened bones in a 4-month-old child might be less ominous than in a newborn in a situation in which the newborn's radiograph demonstrated long bones to be normal in terms of length, width, and shape. When initial radiographs in a congenita form are not available and short, broad bones are demonstrated at 3–4 months of age, the significant prognostic factor is whether the bone width and shape are progressing toward normal with time or continuing to widen with time. If the latter situation is seen, the prognosis becomes progressively dimmer.

Ambulation in those having intramedullary rods progressively improved from OIC to OIT-B. Of the patients with OIC having rods, 9 remained wheelchair bound and 3 walked with assistance, whereas of the patients with OIT, 3 were wheelchair bound, 5 walked with assistance, and one walked unaided.

3.12.30.7 Molecular Biology of Collagen Defects

Studies examining the skin of patients with OI gave the first clear indication of collagen abnormalities. Subsequently, skin fibroblast cell culture studies have confirmed that the cells of affected individuals produce either decreased amounts of collagen or defective collagen. Detailed biochemical investigations have demonstrated heterogeneity of type I collagen defects. There has been increasing awareness of underlying collagen gene and molecular abnormalities in OI but little investigation of the ways in which these abnormalities translate into structural and functional defects of bone. From 85 to 90 % of all patients with OI have mutations in 1 of the 2 genes, COL1A1 and COL1A2, that

encode the chains of type I collagen but large numbers of different mutations have been found. In osteogenesis imperfecta there have now been over 800 molecular defects of type I collagen detected and more discoveries can be expected to saturate the mutation map. The clinical spectrum ranges from benign autosomal dominant variants (Sillence I) in which patients have few fractures to progressively deforming types (Sillence II and some Sillence IV) with multiple fractures and an often non-ambulatory status to lethal perinatal variants (Sillence II) where the paucity of bone formation is marked and individuals are stillborn or die within the first year of life [447].

Osteogenesis imperfecta is caused by mutations in the COL1A1 (18-kilobase [kb] size, located on the long arm of chromosome 17) and COL1A2 (38-kb size, located on the long arm of chromosome 7) genes that encode the 2 pro-α1 (I) and one pro-α2 (I) chains of the type I procollagen trimer respectively. These genes contain more than 50 exons to generate about 1,450 amino acids of each chain. The formation of the essential triple helical structure of procollagen I from these 3 pro-α (I) chains depends on the presence of glycine in every third position in the 1,014-residue triple helical domain and is stabilized by the presence of hydroxyproline. The triple helix is propagated from the carboxyl-terminal end toward the amino-terminal end of the molecule. The mature molecule is then secreted from the cell into the extra-cellular matrix, where the amino-terminal and carboxyl-terminal propeptides are removed enzymatically and type I collagen fibrillogenesis occurs by self-assembly.

Large numbers of mutations of the COL1A1 and COL1A2 genes, including single base-pair changes, deletions, insertions, premature stop codons, and splicing mutations have been described, causing forms of OI ranging in phenotype from mild to lethal. The most frequent mutation types are single base-pair substitutions in either of the two alleles that later encode for glycine in the triple helical domain of the chain.

The molecular basis of Sillence type I OI remains poorly understood. Cells from affected individuals largely demonstrate a quantitative defect of type I collagen; they synthesize and secrete about half the normal amount of type I procollagen. This is due to decreased synthesis of pro-α1 (I) chains; in general the pro-α2 (I) chain is normal. The mutation often occurs in one allele, resulting in about half the normal amount of the molecule, as type I procollagen must contain 2 pro-α1 (I) chains.

The vast majority of infants with type II OI appear to be heterozygous for mutations that result in substitutions for glycine residues within the triple helical domain of either the pro-α1 (I) or the pro-α2 (I) chain. In some instances, exon-skipping mutations in either gene can result in this phenotype. Type III and IV phenotypes can also result from heterozygosity for point mutations of glycine residues within the triple helical domains of either chain of type I procollagen or from exon-skipping mutations.

There are several basic concepts concerning the nature of mutations and their phenotypic consequences. Quantitative mutations that decrease expression and synthesis of normal type I procollagen molecules result in milder phenotypes, such as type I OI. Qualitative mutations that lead to structural aberrations and abnormal type I procollagen result in more severe phenotypes, such as types II and IIII. The severity of the phenotype reflects the location of the mutation within the chain, the nature of the mutation and the chain in which the mutation occurs. In general, with point mutations, the phenotype becomes milder as the mutation is shifted toward the amino-terminal end of the chain, because the essential triple helical structure is formed from the carboxyl-terminal end toward the amino-terminal end in a zipper-like helical-coiling manner. With glycine substitution mutations, amino acid replacements with bulkier side chains such as arginine, result in more severe phenotypes than those with smaller side chains such as serine and cystene. Mutations in the COL1A2 gene have milder consequences than similar mutations in the COL1A1 gene, as the type I procollagen molecule has 2 pro-α1 (I) chains and 1 pro-α2 (I) chain.

The expression of these mutations into the observed phenotypic patterns is still incompletely understood. On the molecular level, these mutations can decrease the rate of synthesis, decrease the thermal stability of the triple helical molecules, delay the rate of folding of the precursor procollagen molecule, increase the level of aberrant post translational modification of procollagen chains, and impair the rate of export of molecules from cell to matrix [448–450]. There is no simple relationship between the type and position of a mutation in the helix to phenotype [451]. Mutated chains are more slowly incorporated into fibrils than normal collagen molecules; demonstrate an abnormal configuration, with more branching, shortening or thickening; and impair mineralization by providing a mutated structural template for incorporation of hydroxyapatite crystals. Biophysical studies indicate that there are variations in the stability of different regions within the type I collagen molecule that fold and unfold cooperatively. This structural and dynamic heterogeneity plays an important role in self-assembly and function of collagen fibers. Regional variations in triple helix stability are increasingly being studied and understood and the existence of looser, less stable, and tighter, more stable, structural regions within the triple helix is accepted. Collagen stability is based on the specific amino acid sequences at any particular region [452]. Algorithms have been derived to relate the amino acid sequence of a collagen triple helix to its thermal stability based on the triple helical stabilization tendencies of individual amino acid residues and their intermolecular and

intramolecular interactions. This is studied by determining melting temperature values of a number of triple helical peptides of varying length and sequence. The collagen triple helix is composed of repetitive Gly-X-Y sequence, requiring Gly (glycine) as every third residue. As noted above, the collagen triple helix is not uniform in structure or stability. Studies if collagen peptides show that variation in amino acid content leads to small but significant variations in super-helix twist. In short, there is increasing ability to demonstrate molecular stability from amino acid and peptide sequence (prediction of stability from sequence) [453].

Since more than 80 % of lethal to moderately severe cases result from subluxations of the obligatory Gly residues the triple helix is disrupted leading to structural abnormality and consequent weakness [454]. In a study of collagen melting temperature done on 41 different Gly substitutions from 47 OI patients several conclusions were reached: (i) no significant overall correlations of collagen melting temperature with Gly substitution identity; (ii) no straightforward correlation of collagen melting temperature with the local helix stability at the substitution site [local defined as involving less than 5–10 adjacent gly-X-Y triplets]; and (iii) regular collagen melting temperature variations with the substitution location at a larger regional site of the triple helix [452].

Setting aside theoretical considerations, 14 of 15 cases of α1(1) Gly substitutions from Gly-691 through Gly-823 were found to be lethal [454]. Bodian et al. [455] developed a model for predicting clinical lethality resulting from glycine mutations in the α1 chain of type I collagen. The phenotype resulting from a glycine mutation in COL1A1 is considered to depend both on the mutation site along the triple helix and the amnio acid replacing glycine. A decision tree was established based on position and substituting residue to model the relationship between these findings and lethality. The model was tested using 208 distinct mutations comprising the non-redundant set of of COL1A1 mutations in 389 patients from the OI mutations consortium [454]. Both sets of information (position and substituting amino acid) are needed. Different substitutions at the same position can lead to different clinical outcomes. On the other hand, each substituting amino acid leads to different phenotypes depending on where the glycine being replaced is situated. The model predicts all Gly mutations with the 178 N-terminal residues of the triple helix to be non-lethal. (This is supported by other observations that substitutions in the first 200 residues are generally non-lethal). Mutations C-terminal to Gly 178 are classified by substituting amino acid. Ala and Ser substitutions are all predicted to be non-lethal and all Arg, Val. Glu, and Asp are lethal. Cys substitutions are lethal when they occur C-terminal to position 688. Mutations C-terminal to 178 have lethality based on the destabilization introduced by the substituting residue. It has been shown that Arg, Val, Glu, and Asp are more disruptive to the triple-helical structure than those predicted to be non-lethal with Cys intermediate [456]. Use of measured thermostability values of these peptides would produce the same decision tree.

Clinical Outcome Based on Information from OI Mutations Consortium.

The OI Mutations Consortium published an outline of clinical status in relation to mutation analysis from OI patients determined to have mutations in Type I collagen genes COL1A1 and COL1A2. Quantitative defects causing type I OI were not included. There were 832 independent mutations collected, 682 resulting in substitution for glycine residues in the triple helical domain and 150 altering splice sites (18 %). Phenotypic relationships emerged with differences for each chain. In COL1A1 one third of the mutations resulting in glycine substitution are lethal, especially when the substituting residues had a side chain or were changed. Substitutions in the first 200 residues are non-lethal. Two exclusively lethal regions (helix positions 691–823 and 910–964) align with major ligand binding regions leading to considerations of collagen binding with integrins, matrix metalloproteinases, fibronectin and COMP-cartilage oligomeric matrix protein]. Mutations in COL1A2: predominantly non-lethal (80 %) but lethal regions align with proteoglycan binding sites along the fibril in 8 regularly spaced clusters.

The end result of these molecular changes eventually translates into the microscopic and gross pathologic features characteristic of OI. Figure 3.28d demonstrates how collagen mutations lead to structural fibillar changes.

(ii) Mutations in the collagen prolyl 3-hydroxylation complex [CRTAP (cartilage associated protein), P3H1/LEPRE 1 (prolyl-3 hydroxylase 1/leucine-and proline-enriched proteoglycan 1), and PP1B/CyPB (peptidyl-prolyl isomerase B gene/cyclophilin B)]. Beginning in 2006 a series of studies in OI patients without mutations in type I collagen defined additional molecular mechanisms for the disease. Three types of mutation were found in each of the three components of the collagen prolyl-3 hydroxylation complex. Mutations in the cartilage-associated protein (CRTAP) or prolyl3-hydroxylase 1 (P3H1/LEPRE 1) lead to a lethal to severe autosomal recessive OI that overlaps with the lethal perinatal OI II and the progressively deforming OI III. P3H1 is also known as LEPRE 1 (leucine and proline-enriched proteoglycan 1) [438]. The CRTAP and P3H1/LEPRE 1 mutations cause OI with rhizomelic limb shortening and delayed collagen folding. Mutations in the third component of the prolyl 3-hydroxylation complex, a stop-codon mutation in the peptidyl-prolyl isomerase B gene (PP1B) results in a lack of cyclophilin B (CyPB). In the few patients with the latter disorder there was moderate OI without rhizomelia and normal modification of the collagen helix (i.e. normal collagen folding.)

Many now refer to type VII OI as being due to CRTAP mutations, type VIII OI to P3H1/LEPRE 1 mutations and type IX OI to CyPB mutations.

The newer variants are still collagen-related mutations. The collagen prolyl 3-hydroxylation complex consists of CRTAP, LEPRE 1, and CyPB which catalyzes a specific post-translational modification of type I, II and V collagen. CRTAP and LEPRE 1 are responsible for dysregulation of hydroxylation of a single proline residue of the collagen chain at position 986 of both the triple helical domains of type I collagen alpha (I) and type II collagen alpha (II) chains. CRTAP and LEPRE 1 form a complex that performs the hydroxylation and brings the prolyl cis-trans isomerase cyclophilin B (CyPB) to the unfolded collagen. Interestingly, mutations in CyPB have normal collagen chains during synthesis within the endoplasmic reticulum. In those cells with an absence of normal Pro986 hydroxylation folding of the collagen helix is delayed and there is over-modification of multiple proline and lysine residues by prolyl 4-hydroxylase (P4H) and lysysl hydroxylase (LH).

It is estimated that a deficiency of CRTAP or LEPRE 1 causes severe or lethal autosomal recessive OI which accounts for 5–7 % of all severe cases of OI.

Different gene mutations continue to be found in disorders defined as OI even beyond those listed above. At present however, COL1A1 and COL1A2 mutations still account for 90 % of cases and more than 1,000 heterozygous collagen type I mutations have been identified [457]. In 2014 van Dijk and Sillence summarized that 17 genetic causes of OI had been identified with more expected. In their review the upgraded Sillence classification of 5 syndromic groups (clinical, descriptive, numerical) was also accepted and re-defined. Titles of the groups were listed as: OI Type 1, Non-Deforming OI with Blue Sclerae; OI Type 2, Perinatally Lethal OI Syndromes; OI Type 3, Progressively Deforming OI; OI Type 4, Common Variable OI; and OI Type 5, OI with Calcification in Interosseous Membranes. Updated molecular mutation causes included: COL1A1, COL1A2; mutations in the collagen prolyl 3-hydroxylation complex (CRTAP, P3H1/LEPRE 1, and PP1B/CyPB); and (autosomal recessive) mutations in WNT 1, SP 7, BMP 1, FKBP 10, PLOD 2, SERPINF 1, SERPINH 1, and TMEM 38B [457].

3.12.30.8 Histopathology of Osteogenesis Imperfecta Bone

The histologic structure of the bone differs markedly in the various types, is essential to an appreciation of the functional capacity of the bone, and thus warrants independent study to allow for meaningful correlation with molecular, microstructural biomechanical and clinical radiographic abnormalities. The histopathologic features of OI vary depending on disease severity [458–461]. Overall, there is a generalized decrease in bone tissue, with the bone structure in most cases demonstrating a mixture of woven and lamellar patterns. The histologic appearance of bone in OI patients follows the normal developmental and structural pattern but rarely achieves the fully compacted lamellar state. The more severe the involvement, the more immature the structural pattern (Fig. 3.28e). In the most severe forms of OI, the bone appears histologically as a woven bone matrix devoid of any organized lamellar pattern [462] There are plump osteoblasts crowded along prominent osteoid seams, large oval osteocytes surrounded by small amounts of matrix, and morphologically normal osteoclasts. Histological sections from patients with less severe OI show a definite tendency to lamellar bone formation. The lamellation and osteon formation can be rudimentary, partially compacted, or full compacted in localized areas. Osteoid seams are prominent, and there is hypercellularity, with larger than normal osteocytes and osteoblasts in the areas of woven bone. There is a correlation between the degree of osteonal maturity and bone strength as indicated by ambulatory status. Efforts are being made to correlate molecular defects with histologic changes [463].

Bone in a biomechanical sense is a non-homogeneous composite structure with mineral and organic phases. It is structured in an intricate hierarchical array—molecules, macromolecules, microfibrils, fibrils, fibers and so on—with each level of structure serving as a template or scaffolding for the next larger level. Much is known about collagen deposition patterns in normal bone but detailed structural analyses have not been performed in relation to the pathogenesis of OI bone and in relation to its molecular abnormalities. Cortical bone formation is initiated with collagen deposition in a randomly oriented pattern referred to as woven or coarse fibered bone followed by its progressive replacement with a definitive lamellar structure until the matrix becomes well compacted in osteonal systems. Jaffe [464] has defined coarse-fibered primary bone and fine fibered lamellar bone; Weidenreich [465] defined woven-fibered bone, parallel fibered bone and lamellar bone; and Smith [466] defined woven-fibered bone, primary osteones, secondary osteones, surface bone and interstitial bone. More detailed study of the 3-dimensional patterning of collagen has been performed using polarization optics and both transmission and scanning electron microscopy. Giraud-Guille has defined a “twisted plywood” pattern of collagen deposition [467]. Neville has summarized the biology of fibre deposition patterns in many plant and animal tissues including bone with the lamellar bone containing both an orthogonal and helicoidal architecture [468]. Even the lacunar-canalicular system in bone, within which reside the osteocytes and osteocyte processes linking adjacent cells, is felt to have structural and biomechanical implications. Since the organization of collagen in OI bone is always imperfect with abnormal cortical bone development the

pathologic hallmark, knowledge of the mechanisms of matrix transformation is important.

3.12.30.9 Orthopedic Management

Overview. The overall goals of orthopaedic treatment of OI are to maximize comfort and function, minimize fracture and deformity, and allow the patient to achieve independence [440]. Care must be individualized, depending primarily on the severity of the disease and the age of the patient.

Sillence type I OI (OIT B), especially in its milder forms, has only a minimal impact on the patient and the role of the orthopedic surgeon is limited to conventional fracture care. Early death almost invariably occurs in type II OI (OIC A) before any orthopedic intervention is indicated while the fractures in those who survive longer are simply splinted for comfort. Type III and type IV OI present the greatest management challenges for the orthopedist in terms of fracture prevention, fracture management, limitation of deformity, and optimization of function. Most of the patients in the III-IV category of Sillence are OIC B or OIT A by the temporal-radiographic congenita-tarda approach. In the long term series from which the latter classification was derived approximately 1/3rd of OIC B patients walked, usually with treatments of rods, braces or crutches, while 2/3 of OIT A patients walked. The aim of therapy in these groups is to convert non-ambulatory patients to the ambulatory group while minimizing deformity and negative post-fracture sequelae.

The management of OI begins with early detection in utero for pregnancies at risk to guide obstetric management. Cesarean section is often recommended to minimize birth trauma. In the neonate with deforming OI (type III and some type IV), immediate life-threatening problems of respiratory insufficiency and intracranial hemorrhage are managed by neonatologists. In utero fractures have usually healed and recent fractures often do not require special treatment other than splinting. The parents are educated about handling of the infant and about the natural history of the disease.

In infancy and childhood, physical therapists can help to optimize normal development as the infant develops trunk control and limb use. The orthopedist is involved in helping to obtain the greatest degree of mobility possible and in the treatment of fractures, which can be frequent. When fractures occur, we use as little immobilization as possible to minimize disuse osteopenia and muscle atrophy. Well-padded fiberglass or plaster splints with Ace bandages are favored over complete circumferential casts. In moderate and severe OI, the multiplicity of fractures, the underlying osteoporotic bone, and the abnormal mechanical stresses on malaligned bones can lead to further fractures and deformity, interfering with the ability to stand and walk. After the first 2 or 3 years of age in those who are showing a considerable propensity to fracture and angulate external support from orthoses may be necessary to optimize function. Deformity that is impairing function can be addressed surgically by multiple osteotomies and intramedullary fixation. Both bracing and intramedullary rods are used however only when fully independent function is failing since both methods decrease weightbearing stresses on bone and can predispose to further osteopenia.

Fracture rates almost always decrease dramatically after puberty, in both males and females [469]. The value of keeping the limbs well aligned until this time is further heightened by this fact. The diminished rates of fracture are well documented. They are not specifically due to increased caution with age but appear to represent a relative biological strengthening of the bone presumably due to diminished bone turnover allowing the matrix synthesized to persist and be incorporated into structurally stronger units. There is no evidence of any change in collagen type synthesized with time. The fracture rate increases again in women after menopause and in men after age 60 years [470].

Nonoperative treatment is the mainstay of orthopedic management of OI. Depending on disease severity a comprehensive and progressive program of mobilization and bracing if needed is pursued for patients with ambulatory potential. The goal is to reach ultimate independent function. Lightweight bracing can be helpful for external structural support to promote stance and locomotion and for the prevention and treatment of fractures. Braces allow for earlier weight bearing post-fracture. A program of appropriate seating and wheelchair locomotion is pursued for nonambulatory patients.

Closed treatment methods are the initial approach to fracture management. Fractures generally heal often with exuberant callus but with the same abnormal bone quality. There is a subset of patients however who heal slowly with fracture sites that persist for years with fibro-osseous unions, which however can be stable. This appears to occur in less than 5 %. The difficulty in fracture management lies in prevention of angular and rotational deformity and of the vicious circle associated with immobilization—further osteoporosis and muscle atrophy—and repeat fracture. Lightweight splints and braces are most often used with the emphasis on early mobilization.

Operative intervention is indicated for recurrent fractures at the same site, deformity that impairs function and femoral fractures as early as 5 years of age to prevent long term immobilization with long leg or hip spica cast treatments. Surgical management must be individualized taking into account the severity of the patient's deformity, the diameter of the long bones, and the advantages and complications of each technique.

With femoral fractures intramedullary fixation, ± a small side plate and long leg casting ± a pelvic band with hip hinge can keep a child ambulatory during the healing phase.

General principles in the surgical management of OI include avoiding bone surgery in patients under age 2 years, avoiding plate-and-screw fixation in favor of intramedullary fixation, and use of gentle technique for muscle and periosteal preservation and minimization of soft-tissue bleeding. Bone-holding clamps and pneumatic tourniquets should be avoided, as they can crush fragile bone. Radiographic control is essential, as the deformities are often three-dimensionally complex necessitating different views. The optimal age for surgical intervention for deformity is controversial; some recommend early intervention as young as 2 years of age with intramedullary rods, but traditional management involves accepting deformity from closed treatment until the patient is about 5 years old and then proceeding to corrective osteotomies. An excellent clinical guideline is to consider surgical intervention when deformity or frequent fractures or both are preventing the child from continuing progress towards ambulation. If a plateau in function short of walking independently has been reached or if regression is occurring surgical intervention with intramedullary rods, and osteotomy if needed, is warranted, Those bones needing straightening or suffering fracturing are treated; there is no mandatory need to place intramedullary rods in both femurs and both tibias because one or two regions need intervention. Various techniques for deformity correction have been described including closed osteoclasis with casting or splinting, closed osteoclasis with percutaneous intramedullary nailing, multiple corrective osteotomies with an open intramedullary nailing with a solid non-elongating rod and currently use of elongating rod systems.

Fractures and deformity are much more common in the lower extremity than in the upper extremity in the OI III, progressively deforming variants. Bracing is much more common for the lower extremity and virtually all osteotomies in OI are for femoral and itbial deformation. Humeral, radial and ulnar rodding can also be used effectively for recurrent fractures or unacceptable deformity [471].

3.12.30.10 Specific Concerns in Surgical Management of O.I. Deformity

(a) *Intramedullary Rodding*: Cortical bone thinness and porosity plus the young age at which corrective surgery may need to occur have combined to favor the use of intramedullary rods rather than diaphyseal or metaphyseal plating. Intramedullary rods are either solid or elongating. This technique was developed and assessed in great detail by Sofield and Millar over a 10 year period with initial paper in 1959 [472]. The technique involved *fragmentation* of the deformed bone throughout the diaphysis and adjacent metaphyses into 3 or 4 straight fragments, *realignment* of the fragments to straighten the bone even if they needed to be rotated or even reversed in postion and then *stabilization by intramedullary rod fixation* to allow for healing and subsequent diminution of fracturing. They reported on use of the procedure most commonly in osteogenesis imperfecta (80 procedures on 22 patients with an age range from 10 months to 13 years with most done in the 2–8 years range. They used stainless steel rods ranging from 5/64ths of an inch to ¼ of an inch in diameter with the projecting end of the rod bent. Rush rods or Kuntscher rods were used where wider bone diameters allowed. Williams also showed favorable results [473]. Subsequent modifications sought to minimize bone exposure, preserve the periosteum to enhance healing, and minimize the number of osteotomies [474]. Ambulation is considered to be improved in most studies but some report diminished walking post-surgery with the lower limb Sofield approach [475].

(i) *Solid intramedullary rods*: Solid intramedullary rods can be used in OI children of all ages from 2 years or younger to skeletal maturity. In patients who are very small or young or with markedly narrow bones they are generally the only form of stabilization available. Patients are often so severely affected that Kirschner wires, Steinmann pins, Rush rods or analogous constructs are employed. While relatively easy to insert compared to elongating rods, bone growth leaves areas of metaphysis and diaphysis "unprotected" leading to fracture and deformity and the need for additional surgery to exchange for longer rods. In many instances however growth continues beyond the end of the rod without problems. If continued protection with intramedullary rods is needed, solid intramedullary rods can be placed at proximal and distal ends of a long bone with mid-diaphyseal overlap allowing for continued protection with growth.

(ii) *Elongating intramedullary rods*: Elongating intramedullary rods have a decreased replacement rate when compared with nonelongating rods; however, they are weaker, traverse the physis, are technically more demanding, as they require a larger medullary canal and central placement, and are associated with complications related to disassembly and nonelongation [476, 477]. The initial elongating rod was developed by Bailey and Dubow [477]. Shortly after the introduction and widespread acceptance of intramedullary rodding for young

children with OI [478] it was recognized that solid single rods would need fairly frequent replacement owing to growth. The concept of 2 interdigitating rods which would slide on one another with growth developed and 'elongating' rods soon became available. As early as 1962 Bailey and Dubow reported on their work with an outer sleeve within which a second or inner rod was placed. Since the rod was in one epiphysis (secondary center) they also performed investigations in puppies showing that centrally placed transepiphyseal rods did not affect growth (detailed report in 1981 [479]). In the femur the narrower inner rod was placed distal to proximal via knee joint arthrotomy with a small T-piece in the secondary center for stabilization. The second wider rod was placed proximal to distal from the intertrochanteric area with proximal stabilization by a washer and figure-of-eight suture. Both clinical measurements and histology showed no significant growth effects of the transphyseal rods (up to 7/64 inch diameter) across the distal femoral physis.

Favorable clinical results, although with some problems, were reported by Marafioti and Westin [478], Bailey [479] (in which he reported a case with 3 inches extension of one femur and 3½ inches of the other), Rodriguez and Bailey [480] (reporting on the modification having a T-piece at both ends to enhance stabilization), and Lang-Stevenson and Sharrard [481]. In 30 cases, mean lengthening was 3–4 cm [480]. In 10 patients, 7 of whom never walked pre-rods, 7 were able to walk and 2 others were walking prior to the need for revisions [481].

In a relatively large series comparing elongating rods (47) to non-elongating rods (106) the average time between replacement operation increased from a mean of 2.5 years (non-elongating) to 4.1 years (elongating rods). The re-operation rate was also appreciably lower for the elongating rods (21 %) compared to the non-elongating rods (73 %) [478]. Complications of the elongating rods (in all series) included migration of either segment, bending of the rods, fracture of the rods, non-elongation of the rods and infection. Specific reports of complications included 60–70 % for Bailey-Dubow rods aginst 55 % for non-elongating rods [476], 63.5 % for Bailey-Dubow rods in 107 roddings [482], and more complications in patients operated under 5 years of age and in the tibia [483]. These complications, once the technique of insertion was mastered, were basically dependent on the nature of the disorder and the mechanical limitations of the device.

Subsequent reports show a tendency to improved results with modifications of the elongating rods. Wilkinson et al. [484] developed what is now referred to as the Sheffield rod in the 1980s and noted improved mobilization post-rodding in 24 patients. It featured a larger and fixed T-piece for better stabilization at the epiphysis but did require arthrotomy at knee for femoral rod and ankle for tibial rod. They reported that walkers pre-rodding (Shapiro congenital types) were 2 of 17 (12 %) and after rodding 11 of 17 (65 %) were walkers—2 independently and 9 with aids. In the tarda group 14 % walked pre-rodding and 86 % post-surgery. Similar findings were seen when patients were categorized by Sillence criteria (27–82 % in type I; 0–72 % in type III; and 0–50 % in type IV). The Sheffield telescoping rods have diameters of 3, 4, 5, 6 and 8 mm and variable lengths from 50 to 300 mm. They are designed for femoral, tibial, and humeral insertions. The T-pieces are permanently fixed to the rod ends. A long-term follow-up was done at an average of 19 years post-original surgery [485]. There were 22 patients at a mean age of 24.7 years (18–36 years) of age who had a total of 66 rods (femur 40, tibia 23, and upper limb 3). There were 15/22 Sillence III or IV and 20/2 Shapiro congenital/tarda. Results were favorable especially regarding decrease of fractures, comfort and minimization of deformity. Few converted to independent walkers but many became mobile with walking aids. In the 66 long bones treated with elongating rods 33 (50 %) needed secondary operation. These included replacement of outgrown rods (10) which is not truly a complication. Problems included 4 fractures of bone with bent rod, 6 proximal rod migration in femur, 4 infections, 3 tibial rod migrations, 2 distal femoral rod migrations, 2 broken rods and one each of rod loosening and bone rotation needing correction. The patient satisfaction rate was high.

Revisions of existing elongating rods and development of new systems continued in efforts to improve results [486–494]. Ruck et al. reported on 60 children with OI who had 101 femoral Fassier-Duval (FD) rods while on bisphosphonates [493]. The mean age at initial rodding was 3 years 11 months (range 1.2–11.8 years). Types III and IV OI were present in 57/60 patients. The assessment focused on functional rather than technical outcomes. Benefits in ambulation, gross motor function, self-care and mobility were documented. The paper refers to a 35 % complication rate with the FD rod compared to a 55 % rate with the Bailey-Dubow rod. Also based on studies from multiple centers reported at meetings, the rate of re-operation was 14.3 % for the femur and 18 % for the tibia. Post-rodding fracture through the osteotomy sites was 20–25 %.

Another study by Birke et al. reviewed the first 24 FD rods (OI 15 cases) at a pediatric center [494]. In the small OI group there was a 40 % complications rate (6/15) including proximal rod migration, limited telescoping, and joint intrusion. The group felt that further use of the technique was worth pursuing.

Cho et al. modified the Sheffield rod so that the telescoping rod does not require arthotomy of the distal joint [486]. Their system dispenses with the distal T-piece with the distal obturator a simple rod with a hole and interlocking transverse epiphyseal screw. The cumulative survival rate of 32 rods (23 tibial, 9 femoral) 4 years postoperatively was 88.7 %.

A comparison of the Sheffield elongating rod versus non-elongatings rods also supported the value of elongating rods [487]. Both were valuable in decreasing fractures from 2.63 to 0.04 in elongating segments and 1.58–0.21 in non-elongating segments. However, the time period between primary operation and re-operation was 4.4 years (elongating) compared with 2.6 years (non-elongating) and between primary operation and re-rodding was 6.3 years (elongating) compared 2.9 years (non-elongating). Chockalingam and Bell [488] described an easier way to exchange the Sheffield rod.

An additional approach to the elongating rods, developed by Fassier and Duval, features no trans-articular entry points and proximal and distal epiphyseal threaded fixation [489]. The Fassier-Duval rods are passed anterograde from proximal to distal, not requiring arthrotomy of the distal joint. The male solid nail is screwed into the distal epiphysis while the female nail is screwed into the bone of the proximal epiphysis. The best technical description of the system and surgical methods is from the manufactuer's manual [490]. Early results were favorable [491] while longer term detailed studies are beginning to appear. In a 2010 meeting abstract Mickel reported on 38 Fassier-Duval extensible rods [492]. The unplanned replacement rate was 34 % (13/38). All unplanned replacements were in patients being treated with pamidronate. Problems included rod bending, associated fracture, rod migration through bone externally, loss of fixation, and failure to elongate.

When multiple osteotomies are performed, the individual fragments should be as long and straight as possible. Placement of osteotomies in diaphyseal regions enhances stability when combined with intramedullary rods (Fig. 3.28f). Some bone shortening may be necessary when there are severe deformities, as the taut soft-tissue structures on the concave side can be stretched excessively when deformity is corrected. Some patients with OI III requiring long bone osteotomy and intramedullary fixation have narrow bones which only allow for Rush rod or Steinmann pin fixation. Radiographs can be misleading concerning the medullary canal diameter since the diaphyses in those with severe involvement are often oval or flattened in one plane further decreasing the diameter of rod that can be inserted. Immobilization with casting or braces until bone union occurs is almost always necessary.

Non-elongating rods can be very effective in OI and are easier both to insert and to revise. With long bone growth the bone beyond the end of the rod is again prone to bending and fracture. Many remain asymptomatic with no need to revise, by adding a longer rod, since non-rodded cortical and trabecular bone may strengthen and remain straight even without an intramedullary rod. Rush rods and Kirschner wires can be used for IM stabilization. Metaizeau reported the use of 2 Rush rods inserted in opposite directions to provide complete intramedullary support without using a formal elongating rod system [495]. With growth the overlapping rods separate, sliding past one another within the intramedullary canal but allowing for several years of growth before a gap is formed between the two ends within the canal. This approach has been referred to as bipolar centromedullary pinning [495] or sliding central medullary nailing [496]. Luhmann et al. have used this technique as well [497]. Development of the multiple osteotomy-intramedullary rodding technique for osteogennesis imperfecta bones is outlined in Fig. 3.28g.

(b) *Correction of Varus Deformity of Proximal Femur*: A common deformity in moderate to severe OI in the early years of life is coxa vara. Deformation is often present either in the newborn or within the first year of life due to high proximal femoral fractures healing with the malunion position. This deformity is particularly troublesome since it predisposes to recurrent fractures and greatly delays or prevents the child from walking. Once it becomes evident that the deformity is delaying motor progression corrective surgery is both warranted and highly beneficial.

Fassier et al. [498] in a review of 18 cases of coxa vara having proximal femoral osteotomy in OI (plus 3 with fibrous dysplasia) found average age at surgery of 8.3 years (range 3.3–15.8) with good results using intertrochanteric osteotomy with IM rod and K-wires.

(c) *Spinal deformity*: Spinal deformity in patients with OI is difficult to manage [499]. Truncal shortening of thoracolumbar spinal segments can occur secondary to collapse of osteopenic vertebrae. If the patient is symptomatic, a well-padded spinal orthosis is helpful. Scoliotic and kyphoscoliotic curves are often superimposed and can progress rapidly. The soft, deformed rib cage and truncal shortening combine to render bracing relatively ineffective, but it can be helpful in mild to moderate variants of OI and as a sitting aid for the non-ambulatory child. In milder forms of OI, bracing can be utilized for curves of 20°–40° or kyphosis greater than 40°. Spinal fusion should be considered for scoliotic curves greater than 40° to halt progression. For patients with more severe involvement bracing is ineffective and can itself produce thoracic cage deformity. There is a higher incidence of complications and relatively lesser

correction from spinal fusion in OI since internal fixation is limited by poor bone quality. Autogenous iliac-crest bone graft is generally not available and patients have a tendency to increased bleeding. Good corrections and fusions are obtainable however. The segmental sublaminar wiring technique of Luque has produced good results as have posterior hook based systems.

Worsening motor function progressing even to quadriparesis can occur in severe OI III and II variants owing to cervicomedullary compression with basilar invagination, similar to what occurs in some skeletal dysplasias with occipito-cervical deformity [500].

(d) *Lower Extremity Length Discrepancies*: Asymmetric fracture and deformity patterns can leave patients with OI with significant lower extremity length discrepancies. Bone strength may be so porous that lengthening procedures are not generally warranted but successful lengthening in late adolescence or early adulthood has been reported.

(e) *Olecranon fractures*: Fractures of the olecranon are relatively common in Type I OI and may be bilateral. If displaced, open reduction and stabilization followed by casting leads to good results without growth sequelae [501].

3.12.30.11 Medical Management

At present there is no cure for OI. Multiple previous attempts to strengthen bones with more than 20 compounds including hormones, mineral compounds and vitamins were ineffective. Albright reviewed initial positive reports for the value of calcitonin, estrogen and vitamin D, none of which in retrospect had adequate controls or stood the test of time [502]. Once collagen was identified as the molecular site of disease medical efforts temporarily slowed. Three current forms of intervention hold possible promise for the future.

(i) *Bisphosphonates*: Glorieux et al. reported on the value of cyclic intravenous administration of pamidronate, a bisphosphonate, for diminishing the fracture rate (by 1.7 per year), diminishing chronic bone pain and increasing bone density in a study on 30 children 3–16 years of age with types III and IV OI [503]. Biphosphonates inhibit resorption of bone thus increasing bone matrix mass. Most early studies used pamidronate given by intravenous infusion for 3 consecutive days and repeated every 4 months. One value of this approach is the assured level of bisphosphonate and the controlled timing of treatment. Dose regimens vary from center to center. The availability of oral bisphosphonates, such as alendronate, led many clinics to adopt it for use in children but oral uptake is much more variable and assurance of intake much less reliable. The variability of types of bisphosphonates used, dosing, and frequency of treatments is much greater than for intravenous treatments. Good overviews of experience with bisphosphonates in OI are provided by Burnei et al. [438], Castillo et al. [504], Rauch and Glorieux [505, 506] and Phillipi et al. [507].

Early reports stressed marked and rapid decrease of chronic bone pain and a rapid rise in vertebral bone mineral mass. Histomorphometric studies of iliac bone biopsy showed increased cortical thickness [505, 508]. Histomorphometric studies using repeat iliac crest biopsies in 25 patients treated with intravenous pamidronate showed increases in bone parameters (bone mineral density mean cortical width and cancellous bone volume) in the first half of the observation period with much less change in the second half. The authors observed that gains appeared to be realized in the first 2–4 years of treatment. References were made to a decreased rate of fractures and improved ambulation in some but not all studies [438, 504, 507].

Forin et al. studied 29 patients (median age 8.7 years) although the median followup was only 16 months [509]. Those less than 2 years of age received 0.5 mg/kg/day and those greater than 2 years received 1.0 mg/kg/day in cyclic infusions of 3 days repeated every 2 months (younger group) or every 4 monhts (older group). Daily supplementation of calcium, vitamin D and physical therapy was also added. Pain decreased after the first infusion cycle. Fracture incidence decreased from 15 to 0.5 per year (younger group) and from 2 to 1 per year (older group). Bone mineral density increased in spine (median 55 %) and femoral neck (median 16 %).

The American Academy for Cerebral Palsy and Developmental Medicine treatment outcomes committee reviewed the literature on the effectiveness of bisphosphonates on bone fragility in [504]. Bisphosphonate treatment was first reported in OI by Devogelaer et al. in 1987 [510]. They used 3-amino-1-hydroxypropylidene-1, 1-bisphonate 250 mg orally daily for periods of 2 months alternating with 2 months of non-treatment for a year in a 12 year old girl. They reported "striking improvement" in clinical and radiographic criteria. Pamidronate, alendronate and risedronate are next generation aminobisphosphonates. These compounds inhibit farnesyl-pyrophosphate synthase, a key enzyme in the pathway required for isophenylation of intracellular proteins. This results in failure to attach lipids to proteins that are tethered to the cell membrane of osteoclasts impairing their biological function of bone resorption, thus favoring new bone formation.

A literature search to 2007 under the asupices of the Cochrane Collaborative [507] found 70 studies in children with OI less than 18 years of age at time of treatment that met inclusion criteria, although only 8 of these with a total of

101 patients had a sufficiently high level of internal validity to be truly informative. The studies in the entire review confirmed improvement in bone density (on DEXA scans). Most studies, but not all, showed a decrease in fracture rate in the 30–60 % range. Short-term side effects were minimal and consisted of fever and muscle aches with the first infusion. There have been variable reports of delays in bone healing of osteotomy sites after intramedullary rodding but not delayed healing of fractures [511]. Since the cellular mechanism for both is the same, it is unclear why this would be the case. Results on bone pain dimunition are also variable. Questions also remain about dosing regimens and length of treatment. Pamidronate is given by intravenous injection which limits its acceptability for some patients. Oral medications show slightly less favorable results and are still not approved for use in children and adolescents in most jurisdictions. Another concern is that bisphosophonates remain in the body for several years after cessation of treatment. Discontinuation of medication a few weeks or even months prior to bone surgery thus has no realistc expectation of ridding the body of exposure. Suggestions have been made to limit treatment after 2 years.

The value of alendronate was examined in randomized, double-blind, placebo-controlled 2-year study in 139 pediatric patients 4–18 years of age with severe OI [512]. One hundred and nine patients were randomized to 5 mg alendronate (weight < 40 kg) or 10 mg alendronate (weight > 40 kg) daily and 30 patients to placebo. Bone mineral density increased in the alendronate patients but remained essentially the same in placebo patients. Treatment with alendronate did not reduce the risk of fracture, lead to a reduction of bone pain, or increase cortical width. The incidence of delayed fracture healing was slightly greater in the alendronate group (16 % vs. 19 %).

Use of oral risedronate was studied in a randomized, double-blinded, placebo controlled fashion in a total of 26 children and adolescents with mild OI (type I) for 2 years. While there was slight increase in lumbar spine areal bone mineral density in the risedronate group no differences were noted between control and risedronate groups in terms of histomorphometry of iliac bone (cortical width and trabecular bone volume), vertebral morphometry, bone pain or number of new fractures [513]. The Cochrane database system review [507] found increases in bone mineral density with bisphosphonate in OI but no other statistically convincing evidence of a decrease in fractures.

The potential value of bisphosphonates in OI along with their relatively widespread use places an obligation on those treating patients with OI to develop a rational approach to their use and study. Approaches differ widely. We favor their use in children having severe or recurrent bone pain as the primary indication and strongly recommend it for this reason. Frequent fractures (a few per year) is also a strong indication. We do not strongly recommend it as prophylaxis or if there are relatively few serious fractures. Consideration must also be taken to limit its use to 2–3 years out of concern for high retained levels due to slow excretion. Marini [514] pointed out that intravenous pamidronate in children causes substantial increases in vertebral bone density and in cortical thickness. There was no change in trabecular thickness although trabecular number increased. She noted that many parameters plateaued after 2–3 years of infusions. The possibility was discussed that bones over time with prolonged treatment actually became more brittle. Reports of "rock hard" bones making surgery difficult were surfacing anecdotally. She recommended caution in long term use (greater than 3 years), lower doses or longer intervals, and careful assessments re bone quality which was not well defined by DEXA scans.

(ii) *Bone Marrow-Mesenchymal Stem Cell Transplants*: Another modality under investigation seeks to actually replace or bypass deficient collagen secreting bone cells by bone marrow transplant or marrow stromal cell-mesenchymal stem cell transplants [515, 516]. These cells are precursors of osteoblasts and could theoretically synthesize normal collagen thus eliminating or bypassing the deficient gene pool. These approaches remain investigational in relation to the relatively slow translation of stem cell therapy in general into humans, and especially for non-lethal disorders.

(iii) *Suppression of Mutant Genes*: Suppression of mutant genes seeks to decrease the expression of the mutant allele by introducing ribozymes into the cells to cleave the mutant gene product leaving the normal gene product intact and bringing about a milder phenotype with normal but quantitatively less collagen.

3.12.30.12 Pain in Osteogenesis Imperfecta

Pain is common in osteogenesis imperfecta due to several factors including fractures that are clinically and radiographically evident, subclinical cortical and trabecular micro-fractures due to the osteoporosis, and muscle and joint pain due to relative immobility. Many patients, particularly in the second decade of life and early adulthood, turn to analgesic agents for comfort and a few became dependent on addictive medications. It is essential to establish a clear plan with patients and families for pain management issues early on. Appropriate splinting for limb discomfort, surgery to stabilize fractures and minimize deformity, appropriate bracing and wheelchair modifications for non-ambulatory patients, treatments with bisphosphonates if recurrent pain is a problem, and involvement with physical theorapy to improve standing/walking, muscle strength and joint range of motion all play a role in maintaining comfort. When pain

medications are used, addictive medications should be strictly limited. Some physicians use narcotics in OI patients only in-hospital post-surgery for a few days and, even in these situations, muscle relaxants rather than narcotic analgesics play a major role in limiting post-surgical pain.

3.13 Anesthetic Implications in the Skeletal Dysplasias

Orthopedic and other surgical procedures are frequently indicated in patients with skeletal dysplasia. Although these can be performed safely in the vast majority of cases there are specific anatomic and physiologic abnormalities associated with the skeletal dysplasias which must be carefully considered by the anesthesia team.

3.13.1 Occipital and Cervical Structural Abnormalities in Skeletal Dysplasia Patients

Frequent problems can include: foramen magnum stenosis, occipitalization of C1, odontoid hypoplasia and cervical kyphosis and stenosis. Manipulation of the cervical region during intubation and anesthesia in patients with these disorders can produce abnormal cord pressure and pyramidal tract signs. Preoperative cervical spine radiographs are warranted in the skeletal dysplastic patient with further study involving CT scanning or MR imaging recommended in those where structural abnormalities are detected. Virtually all patients with achondroplasia have stenosis of the foramen magnum with 5–10 % showing some evidence of cervicomedullary compression. Patients with Morquio's disease all have abnormalities of the odontoid and most patients with SED congenita also have such irregularities. In such children positioning on the operating table is done with even greater care than normal, tracheal intubation is cautious with flexion-extension of the neck minimized and in many instances fibre-optic intubation is warranted. In many patients with spondyloepiphyseal dysplasias the neck is short which makes intubation more difficult and many of these patients also have a pectus carinatum which further augments the difficulty.

3.13.2 Airway Abnormalities

Upper airway obstruction can occur not only due to cervical-occipital anatomy but also with other disorders including a large tongue, large tonsils and adenoids, stiffened temporo-mandibular joints, tracheal narrowing owing to diminished transverse growth of the tracheal cartilage rings, and angular malposition of the maxilla and mandible owing to facial growth abnormality. Patients with the mucopolysaccharidoses have difficult airway intubation. Other abnormalities include: laryngomalacia, laryngotracheal stenosis, micrognathia, and cleft palate.

3.13.3 Pulmonary Abnormalities

Those with skeletal dysplasia can have respiratory dysfunction from such factors as thoracic cage malformation with rib hypoplasia and progressive kyphosis, scoliosis, and thoracic lordosis. Structural abnormalities leading to thickening and narrowing of the walls of the trachea and bronchi particularly in the mucopolysaccharidoses and in some disorders with cartilage hypoplasia can occur. Many of the thoraco-lumbar kyphoscoliotic conditions in the skeletal dysplasias tend to be more rigid than those seen in idiopathic disorders such that respiratory compromise is potentially greater during surgery. Diaphragmatic motion can be further aggravated in those with kyphoscoliosis and short stature by associated hepatosplenomegaly especially if it is massive.

3.13.4 Neurologic Abnormalities

Major neurologic abnormalities associated with skeletal dysplasias are hydrocephalus, cervico-medullary compression, and compressive spinal cord and nerve root syndromes. The latter 2 findings are associated with foramen magnum stenosis (invariable in achondroplasia), odontoid hypoplasia with cervical instability (seen in many disorders), generalized thoracolumbar spinal stenosis, lumbosacral spinal stenosis, and severe kyphosis or kyphoscoliosis usually at the thoracolumbar junction. Exostoses can lead to neurologic problems with intraspinal position or adjacent to peripheral nerves most commonly the peroneal nerve in relation to proximal fibular lesions.

Many patients with skeletal dysplasia have disproportionately large heads owing to the fact that skull and facial bone is minimally to nonaffected since it is preformed in membrane and not in cartilage. Macrocephaly alone is not of medical or anesthetic concern. In those situations where hydrocephaly is prominent signs of elevated intracranial pressure may necessitate decompressive ventriculoperitoneal shunting.

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Bone and Joint Deformity in Metabolic, Inflammatory, Neoplastic, Infectious, and Hematologic Disorders

4

4.1 Rickets

4.1.1 Terminology

Rickets is a disorder of childhood characterized by the persistence of variable amounts of undermineralized or nonmineralized endochondral cartilage and osteoid. There are many causes of undermineralization but the common final pathway during the growth years leads to a series of similar clinical, radiographic, and histopathologic sequelae. Skeletal deformities are due to mechanical stresses on the undermineralized weakened bones.

4.1.2 Pathogenesis of Rickets

Mineralization of cartilage in the hypertrophic zone region of the growth plate is an integral part of the endochondral ossification process. It is stimulated by the presence and concentration of certain molecular constituents of the cartilage and accomplished by normal concentrations of circulating calcium and phosphorus. Disturbances of endochondral mineralization lead to deformities, in particular in growing bones, since mineralization of the lower portion of the growth plate is an integral part of the endochondral sequence which underlies longitudinal bone growth. Poorly mineralized cartilage in the hypertrophic cell region of the growth plate prevents appropriate signaling to the advancing vascular and osteoprogenitor front from the metaphysis which then leads to the failure of appropriate bone deposition in the metaphyseal area. This in turn leads to stunting of growth and bowing of the long bones through the abnormally softened physeal and metaphyseal regions. Jaffe defined a triad of changes in the endochondral bone sequence with rickets involving: (1) deficient calcification of the matrix of the proliferating cartilage; (2) an abnormal accumulation of cartilage (thickened growth plates); and (3) deposition of unmineralized osteoid [1]. The longitudinal arrangement of the physeal cartilage cells is lost, vascular invasion is limited and poorly oriented and the undermineralized chondroid and osteoid tissues mingle in disorganized fashion at the physeal–metaphyseal junction.

4.1.3 Experimental Models of Rickets

Once the biochemical defects in rickets became known, experimental models were produced to study the structural changes in growth plate cartilage and cortical and trabecular bone and to note the effects of varying biochemical and hormonal permutations on the disease process.

4.1.3.1 Dodds and Cameron

Dodds and Cameron demonstrated that the structure of the proximal tibial growth plate in rats was made rachitic by dietary changes primarily involving a diet low in Vitamin D [2]. They noted the high degree of similarity between the histologic changes in rickets in human and rat bone. Normal epiphyseal cartilage is composed of 5 zones: zone of reserve cells; zone of flattened cells and cell multiplication; zone of cell growth where mitosis or cell proliferation has stopped but the cells themselves increase in size; zone of fully grown cells comprising the end of the rows where the cells have attained their full size (the term hypertrophic cell was not used to describe this zone which was also referred to as the zone of calcification owing to "the deposition of calcium salts in the longitudinal walls between columns of cells but not in the transverse walls between cells within the columns"); and zone of cartilage removal in which marrow advancement, resorption of cartilage matrix, and deposition of bone on calcified cartilage cores occurs. They recognized that "narrow tongues of marrow advance along the rows of cartilage cells, removing the uncalcified transverse wall and liberating the cells from their lacunae." The calcified portions of the matrix served a double purpose guiding the advancing marrow and forming a base upon which the bone was deposited. In the zone of calcification, calcification advances steadily into the lower regions of the growth plate, keeping 3 or 4 cells ahead of the advancing marrow which removed the cartilage.°

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In normal physeal cartilage, there are 5 processes which maintain a constant relation to each other, these being cell multiplication, cell growth, calcification of the matrix, cartilage removal, and deposition of bone. The physeal cartilage maintains a constant thickness during growth and the zones within it maintain nearly the same relative proportions. In rickets, one of the major changes is the thickening of the physeal cartilage which can be noted both radiologically and histologically. When histologic samples of rachitic rats are examined, the increased thickness does not occur uniformly throughout all 5 levels, but it is concentrated in zones 4 and 5. The zones of reserve cells, flattened cells and cell multiplication, and the zone of cell growth are normal. Major alterations, however, occur in zones 4 and 5 which are the zones of fully grown cells (the hypertrophic cell zone) and the zone of cartilage removal. Histology shows marked thickening of the zone of fully grown cells which in some instances is as much as 12 times its normal thickness. This is the region which normally would have been calcified, and owing to the failure of calcification, cell and matrix resorption patterns are altered markedly. Cell multiplication and growth continue above. The thickening of the cartilage therefore is due not to accelerated proliferation but to its retarded transformation and removal. There is a thickening of the zone of enlarged cells (zone of cell hypertrophy), which consists of uncalcified or poorly calcified cartilage. When a certain degree of thickening of the hypertrophic zone occurs, mechanical effects crush or flatten the cell columns followed by angulation or lateral deflection of the cartilage cell and matrix columns. This occurs adjacent to the metaphyseal bone and is often so marked that the usual linear alignment of the physeal tissues is positioned at right angles to the longitudinal axis of the bone. This disordered structure further confuses the orderly vascular invasion from below.

The cupping or concave characteristic of the metaphyses at the ends of the bones in human rickets is also demonstrated in the rat model. In the normal bone, the ends of the metaphyses are usually linear or slightly convex. Rather than being exclusively mechanical, as is widely suspected, the cupping deformity is due to the fact that physeal growth and calcification at the periphery is less affected than it is centrally leading to the alteration of physeal shape. In other words, "cupping is produced by a greater retardation of calcification near the axis of the cartilage than near its margin." Eventually, the noncalcified cartilage is removed, but in a slow and irregular fashion. There is more removal at the periphery than centrally leading to an irregularity in thickness of the plate and in bone deposition patterns. The cartilage of the physis is not only irregularly thickened but also irregularly invaded and resorbed. It is observed that "the absence of calcification thoroughly disorganizes the process of cartilage removal. The marrow no longer advances directly along the rows of cells, but instead advances by broad tongues as wide as two, three or more rows of cells." The process is disorganized leaving isolated masses of cartilage with irregular formation of osteoid upon them. The rachitic type of cartilage removal does not result in normal trabecular bone, but rather, a mass of isolated pieces of uncalcified cartilage embedded in osteoid and marrow. The general outlines of the structural changes in rickets are shown in Fig. 4.1.

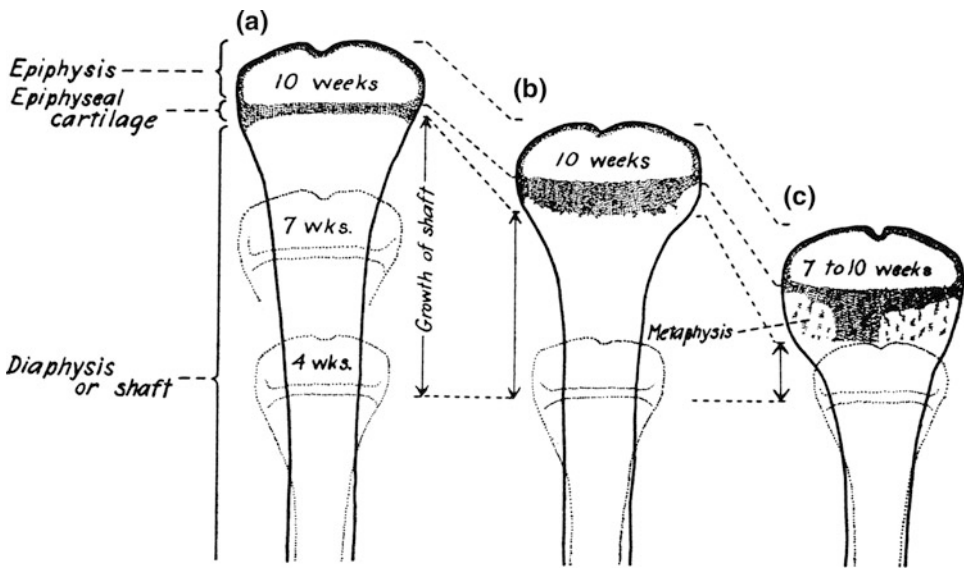

Fig. 4.1 The general outlines of the structural changes in rickets are illustrated (2). Note the physeal widening concentrated in the middle part of the physis in severe rickets with less involvement at the periphery. This translates radiographically into cupping of the metaphyseal regions. (Reprinted with permission from Dodds and Cameron, Studies on experimental rickets in rats. Am J Anat. 1934;55:135–165. Copyright 1934 Lippincott Williams and Wilkins). **a** Normal. **b** Mild Rickets. **c** Severe Rickets

4.1.3.2 Shohl and Wolbach

Shohl and Wolbach induced rickets in rats by altering their dietary intake of calcium and phosphorous [3]. Histologic studies showed evolution of the condition at various deprivation levels. The important histologic criteria of rickets result from disturbances in endochondral bone formation and from failure of bone matrix or osteoid to calcify in all locations. The earliest manifestation of developing rickets is a moderate increase in the thickness of the physeal cartilage with an irregular border on the metaphyseal side and in particular absence of ingrowth of capillaries. There is continued activity of the proliferative zone of the physis but the normal differentiation into the hypertrophic zone does not occur. The initial abnormality is a combination both of failure of formation of this hypertrophic cell layer and the absence of ingrowth of capillaries. Calcification of the cartilage matrix within the hypertrophic zone ceases and osteoid accumulates around the capillaries of the metaphysis adjacent to the cartilage but does not undergo mineralization. In more advanced cases, the noncalcified cartilage at the metaphyseal end of the physis becomes transversely rather than longitudinally oriented owing to the mechanical effects of weight bearing on the weakened tissue. The osteoid increases in amount with time and since it is noncalcified it is also molded in a transverse direction by the pressure of weight bearing. With continuation of the rickets, the cancellous bone of the metaphysis actually disappears, and there is in addition resorption of the adjacent cortical bone.

Mild rickets is characterized by diminished penetration of the physeal cartilage by capillaries, marked irregular thickening of the physeal cartilage presenting an irregular border on the metaphyseal side, persistence of cartilage cells in the metaphyseal bone, and abnormal stratification of the lower regions of the physeal cartilage. Moderate rickets is characterized by almost complete absence of penetration of cartilage cells by capillaries, increased thickening of the physeal cartilage because of the continued activity of the proliferative zone and the survival of cells on the metaphyseal side, incorporation of cartilage cell groups into bone trabeculae which themselves are nonmineralized osteoid, and further disorganization of physeal cartilage. In the most severe variants, there is complete absence of penetration of cartilage cells by capillaries, further thickening of the physeal cartilage, incorporation of cartilage cells into metaphyseal tissue (rather than its resorption) and large amounts of osteoid at the periphery of the metaphysis. There is failure of physeal cartilage cells to complete their cycle of growth, maturation, degeneration (by which is meant hypertrophic change), and failure of cartilage and osteoid matrix to calcify. The proliferative activities of the cartilage cells, capillaries, and osteoblasts are not inhibited but the smooth sequence of changes is markedly disturbed owing to failure of cartilage and osteoid mineralization.

4.1.4 Pathology of Human Nutritional Vitamin D Deficiency Rickets

Park reviewed the pathology of rickets in a classic monograph [4]. In the growing child, the findings in the physeal cartilage are most sensitive but abnormalities of both the endochondral and intramembranous bone sequences are seen. The first demonstrably pathological changes occur in the hypertrophic regions of the growth plate with a failure of normal calcium deposition but newly forming bone of the cortices and trabeculae is also affected. The primary histopathologic finding of the bone tissue is an increase in the thickness of the osteoid layer both within the cortex and surrounding the trabeculae of the marrow. In adults, where the disorder is referred to as osteomalacia, the presence of increased osteoid seams is the major histopathologic finding since the physes have closed. In those children who are older and grow at a relatively slower rate than the younger child the intramembranous bone osteoid is also a prominent finding. Most observers feel that bone resorption also occurs due to the secondary hyperparathyroidism although the tendency is not just to remove the mineral but also the matrix as well. Park commented on the irregularity of the distribution of osteoid throughout an individual bone and indeed throughout the entire skeleton due to the local mechanical conditions governing bone synthesis and resorption.

The more evident changes in rickets in the young child are those at the physeal–metaphyseal junction. These are more marked the younger the child, the more severe the rickets, and at those physes which experience most extensive growth. The earliest changes seen involve decreased mineralization of the longitudinal cartilage trabeculae within the hypertrophic zone. With increased severity of this occurrence, the adjacent bone formation which normally occurs on the calcified cores is also diminished since the osteoid cannot be mineralized and collapse of the weakened matrix leads to isolated and horizontally positioned cartilage–bone trabeculae of the physeal–metaphyseal region. The associated vascular invasion of the area then becomes disturbed and orderly invasion stops. Growth of the cartilage within the proliferating zone continues leading to thickening of the physis. The irregular vascular invasion leads to further disturbances in the normal endochondral sequence.

Wolbach stated that "the first histological evidence of rickets is the absence in whole or in part of the layer of clear (hypertrophic) cells and the consequent absence of ingrowth of capillaries" [3]. Park noted that in the human, there is generally patchy irregularity of calcification in the physis rather than abnormalities in a uniform fashion along a common front. The next series of histopathologic changes in rickets involve compression of the softened cartilage trabeculae and the adjacent cartilage/bone trabeculae that

occurs with continued weight bearing. In the most severe degrees of compression, the lower physeal and metaphyseal matrix lies horizontally rather than parallel to the long axis of the bone. Focal areas of abnormality are seen initially. Both in rat models of rickets and in human samples, flattening and compression of the trabeculae tend to occur centrally but not at the periphery. At the extreme, periphery compression is unusual. Collapse at the physeal–metaphyseal (or cartilage-shaft) junction is not universal but is dependent on the combination of rapidity of growth, severity of the rachitic process, and local pressure. It is seen chiefly at the faster growing ends of the long bones in young children. The compressed cells and matrices are limited to the lowermost parts of the physis and adjacent metaphysis, and offer a formidable barrier to vascular invasion. The crushed tissues centrally prevent vascular invasion and enable the physeal cartilage to remain intact.

Radiographically it is the increased height of the physis along the longitudinal axis of the bone which first characterizes the disorder. Histopathologic studies show that this is due partially to failure of mineralization of the hypertrophic zone but later to increase in the proliferating zone height since it continues its growth but does not transform to a calcified region. Increased radiolucency is also due to deposition in the adjacent metaphysis of osteoid which does not become fully mineralized. The proliferative cartilage increases in amount not due to more rapid growth but due to the fact that it accumulates passively. It is not transformed into an effective hypertrophic zone layer owing to the abnormality of mineralization and, centrally, to prevention of vascular invasion by the crushed and abnormally oriented cartilage–bone tissue interface. The findings are similar in many animal models and in the human.

Vascular invasion of the lower margins of the physeal cartilage is deranged in terms of its normal pattern because of the failure of calcification of the cartilage matrix columns. The reason is twofold: one relates to the fact that vascularization appears to be triggered at least partially by mineralization of the matrix, while the other difficulty relates to the collapse of the cartilage matrix trabeculae such that the vascularization is made more difficult mechanically by the oblique and horizontal position of the cartilage and osteoid seams. The periphery of the physeal cartilage appears to be somewhat protected continuing a relatively normal growth without a tendency to collapse at the lower levels. These descriptions explain the histologic and radiologic cupping of the metaphyseal region which is only partially a response to mechanical influences. The physis centrally is thicker such that the adjacent metaphyseal bone is concave in shape, more depressed centrally and rising in a circumferential fashion toward the periphery. Tension thus becomes important causing the lower part of the thickened physis centrally to give way such that the lateral part is pulled around and upwards toward the outer surface of the shaft leading to the cupping phenomenon. In rickets, the normal vascular invasion from below into the hypertrophic zone is altered. For some time, the physis thickens with little to no vascular invasion occurring. In severe rickets, however, vascular invasion of a highly pathologic and damaging type eventually breaks through. Rather than having a vessel delve into a single column of hypertrophic chondrocytes, there is a tendency for a relatively wide invasive track to be found involving 3 or 4 groupings of cartilage cells. In severe rickets, there is often an arc of dilated capillaries from the metaphyseal marrow attacking simultaneously dozens of cartilage columns. Park clearly points out the irregularity of vascular invasion of the proliferating cartilage in rickets. Compressed cartilage furnishes considerable obstruction to vascular penetration. Even slight rearrangements of the cartilage structure, in particular the linearity of chondrocyte and matrix orientation, make vascular invasion from below more difficult. If the vessels cannot advance in a linear fashion they tend to disperse laterally leading to a sinusoidal pattern of entrance in an irregular fashion.

Vascular invasion of thickened abnormally structured physeal cartilage in severe rickets, once established, comes from 3 sites. The first is from the adjacent metaphyseal bone. A variable number of bush-like vascular formations protrude into the cartilage. Some are thick and progress to the reserve zone. Some are thin and enter only the lower compressed layer. The buds have single individual stems. Branching occurs within the cartilage but adjacent vessels do not anastomose. With increased advancement into the cartilage the vessel systems become long and thin, a late occurring invasion referred to as “en masse” invasion. Cartilage cells and adjacent matrices are both attacked and no osteoid or bone formation occurs. A tissue destructive effect occurs with the extreme often sinusoidal dilatation of the invasive vascular tufts. The second site of vascular invasion is from the cartilage canals of the epiphysis and the third is from the perichondrial vessels. The methods of invasion are exactly the same regardless of site of origin. Histologic specimens of thickened rickets physes in the severe chronic stage show the cartilage to be riddled with vessels.

Tissue responses with healing. When treatment begins, calcium is deposited both in the hypertrophic layer of cartilage and in the osteoid of the bone trabeculi. The repair sequence with new calcification tends to occur in the most recently synthesized hypertrophic zone while the deeper area which has collapsed tends to repair later. The areas where vessels are quite wide do not appear to be associated with early remineralization. Table 4.1 outlines the progressive histopathologic changes in rickets.

Table 4.1 Sequence of histopathologic changes in nutritional vitamin D deficient rickets

1. Deficient calcification
• of cartilage in longitudinal septae of hypertrophic zone
• of osteoid in zone of provisional calcification
• of cortical and trabecular osteoid
2. Physeal thickening
• initially of hypertrophic zone
• also of proliferating zone (not converted to hypertrophic zone)
• diminished to absent vascular invasion from metaphysis
3. Compression of central lower physeal tissues
• physeal thickening concentrated in central 4/5th of physis
• compression of lower physeal zone chondrocytes and matrix (mechanical)
• oblique/horizontal orientation of cartilage/osteoid matrices
• vascular invasion further diminished due to compressed, malaligned matrices
4. Cupping of metaphyseal ends of bones
• physis thicker centrally than peripherally (bone formation more prominent at—periphery leading to concave appearance)
5. Slowed growth
6. Pathologic vascular invasion of markedly thickened physes
• from vascular tufts from metaphyseal marrow
• from cartilage canals of epiphyses
• from perichondrial tissues
[pathologic invasion via long nonanastomosing vascular tufts; wider than normal; invading and destroying in sinusoidal pattern; not synthesizing bone or osteoid; transphyseal; riddling thickened cartilage with sinusoidal channels]
Repair with vitamin D therapy, calcium, and phosphorus availability from stages 2 → 6, depending on time of diagnosis and treatment. Calcification begins initially in most normal, most recently synthesized part of physis and then spreads to older, more damaged regions

4.1.4.1 Vitamin D Levels in Blood

Vitamin D levels in blood have recently been established in large scale studies. Gordon et al. prospectively studied 307 healthy primary care patients 11–18 years of age at a large pediatric clinic in Boston MA, USA, from 2001–2003 [5]. Vitamin D insufficiency was defined as existing with levels 20 ng/ml or less, vitamin D deficiency as 15 ng/ml or less, and severe vitamin deficiency as 8 ng/ml or less. By these criteria, 74 patients (24 %) were considered to be vitamin D deficient and 14 (4.6 %) were severely deficient. If the level of D deficiency was considered to be ≤20 ng/ml then 129 (42 %) could be considered deficient. The prevalence of deficiency was highest in African American teenagers and during winter.

A followup study was done in 365 healthy infants and toddlers 8–24 months of age from the same primary care clinic from 2005 to 2007 using slightly different parameters [6]. Vitamin D deficiency considered as ≤20 ng/ml was 12 % (44/365) and 40 % (146/365) were below an optimal threshold of 30 ng/ml. In the vitamin D deficient group 3, (7.5 %) had rachitic changes on plain X-rays, while 13 (32.5 %) had demineralization.

The general consensus of opinion is that levels of vitamin D ≤20 ng/ml indicate D deficiency; >20 to <30 ng/ml represent suboptimal (or D insufficiency) levels; and ≥30 ng/ml are the optimal/normal level.

4.1.5 Classification of Types of Rickets

The process of mineralization is mainly guided by the serum concentrations of calcium and phosphate. Most forms of rickets can be classified into one of two types, those primarily associated with decreased serum levels of calcium (calciopenic rickets) and those primarily associated with decreased phosphate levels (phosphopenic rickets). The lack of calcium availability results either from a deficiency of calcium intake, which is rare, and more commonly from low intake of vitamin D or disorders of vitamin D metabolism or action. Lack of phosphate availability results either from excess phosphate loss or inadequate phosphate intake. Those disorders with diminished calcium generally respond well to vitamin D therapy, while effective treatment of phosphopenia requires phosphate replacement as part of the management program. Table 4.2 outlines the forms of rickets in these two broad categorizations. Subsequent discussion will concentrate on the 3 disorders most commonly seen in an orthopedic setting because of the associated bone deformities: nutritional vitamin D deficient rickets, X-linked hypophosphatemic

Table 4.2 Outline of causes of rickets

I. Hypocalcemic–Calcipenic rickets
1. Inadequate calcium intake
2. Vitamin D deficiency
(i) Nutritional vitamin D deficiency
(ii) Malabsorption of vitamin D (intestinal, pancreatic or hepatic disease)
(iii) Absence of exposure to sunlight
3. Impaired 25-hydroxylation of vitamin D resulting from hepatic disease (biliary atresia, cirrhosis)
4. Impaired 1-hydroxylation of 25-hydroxy vitamin D
(i) 2º to renal disease
(ii) Due to autosomal recessive vitamin D-dependent rickets, type I (inherited inability to 1-hydroxylate 25-OH vitamin D with otherwise normal renal function)
5. Impaired target organ response to 1, 25 diOH vitamin D
(i) Vitamin D-dependent rickets, type II (inherited failure of target organ response due to structural variations of receptors)
(ii) Response impaired by anticonvulsants phenobarbital and Dilantin
6. Increased turnover/losses of vitamin D
(i) Nephrotic syndrome (loss of vitamin D)
(ii) Anticonvulsants (Dilantin and phenobarbital) stimulate hepatic clearance of vitamin D metabolites
II. Hypophosphatemic–Phosphopenic rickets
1. Inadequate phosphate intake
2. Deficient renal tubular reabsorption of phosphate
(i) X-linked hypophosphatemic rickets
(ii) Autosomal dominant and autosomal recessive hypophosphatemic rickets
(iii) Hypophosphatemic rickets with hypocalciuria
3. Generalized disorders of renal tubular transport inducing hypophosphatemia
(i) Renal tubular acidosis
(ii) Fanconi syndrome (multiple disorders characterized by phosphaturia, glycosuria, and aminoaciduria)
4. Tumor-induced hypophosphatemia
Soft tissue and fibrous tumors produce factors inhibiting
Renal tubular reabsorption of phosphate
[Failure to control renal phosphate excretion also underlies renal osteodystrophy]

rickets, and renal osteodystrophy, previously referred to as renal rickets.

Detailed reviews on calcium, phosphorous, vitamin D, and parathyroid hormone interactions include those of Chesney et al. [7], Cole et al. [8], and Reichel et al. [9]. Investigational study of vitamin D continues along with increasing recognition worldwide of the recurrence/persistence of the problem of nutritional vitamin D deficiency [10–16].

4.1.5.1 Nutritional Rickets

(a) *Pathophysiology*: Nutritional rickets due to a deficiency of vitamin D intake while still infrequent is being seen more often in North America and Europe in association with breast feeding and special dietary practices including macrobiotic, vegetarian, and strict vegan diets. Allgove has extensively reviewed the medical literature showing the current status of increasing frequency of rickets in relation to dietary habits and environmental conditions throughout the world [14]. Children raised on unsupplemented breast milk in association with a strict vegetarian diet are particularly prone to a rickets disorder. The vitamin D content of maternal milk is very low and the content in an infant diet in general is also very low. Minimal exposure to sunlight especially in densely populated northern urban environments during winter also worsens vitamin D levels. Many patients are of black or Asian origin [15]. Ladhani et al. reviewed 65 children from London and England, who presented with vitamin D deficiency from 1996 to 2001 [15]. They presented either with hypocalcemia or rickets. Children with plasma 25-hydroxy vitamin D levels <25 nmol/l (10 ng/ml) were considered to have vitamin D deficiency. Of the

65, 29 had hypocalcemic symptoms and 17 of these had no radiologic evidence of rickets. The remaining 48 had radiologic signs of rickets (with or without clinical signs). All cases normalized with vitamin D supplementation. The symptoms of hypocalcemia in 29 patients were convulsions (16), neuromuscular irritability (9), apnoea (3), and stridor (1). The hypocalcemia cases with symptoms occurred under 3 and over 10 years of age. In the 36 without hypocalcemia, there were no clinical signs with diagnosis made on a screening blood test in 13 but signs included bow legs in 10, bone pain in 4, swollen joints 3, bone abnormality 2, motor delay 2, and short stature 2. The ultraviolet rays of the sun lead to endogenous synthesis of vitamin D and children with darkly pigmented skin living in northern environments are particularly prone to develop rickets. Darker skinned individuals are fully capable of synthesizing vitamin D but require greater exposure to ultraviolet light to do so. The diagnosis of nutritional rickets is usually made in the later winter or early spring. Jacobsen et al. reported on 8 patients with nutritional rickets, all of whom were black, who had been breastfed until 6–12 months of age and then were placed on a vegetarian diet [16]. The situation can be worsened by other dietary deficiencies in particular of calcium or phosphorus.

The supplementary use of vitamin D following its discovery in the 1920s dramatically diminished the occurrence of rickets. The prevalence of nutritional rickets was extremely high prior to the discovery of vitamin D, with the prominent German pathologist Schmorl reporting an 80 % rate of some degree of rickets on autopsy findings of German children [17]. The clinical onset of vitamin D deficient rickets is gradual and generally evolves between 4–18 months of age, during the time of greatest growth velocity. Congenital rickets can occur due to maternal vitamin D deficiency and premature infants are more susceptible to vitamin D deficiency rickets. Vitamin D deficiency leads to reduced calcium absorption from the intestine and decreased circulating calcium levels. This in turn stimulates a secondary hyperparathyroidism. The serum calcium levels can be variable in vitamin D deficient rickets, primarily because of variable compensatory responses. Hypocalcemia is the most important biochemical abnormality but is seen in only approximately ½ of patients at time of diagnosis. In the others, the serum calcium levels are normal or only slightly diminished. Serum phosphate (P) levels tend to be low owing to diminished tubular phosphate reabsorption and low-urinary calcium excretion. There invariably is a markedly increased serum alkaline phosphatase level owing to osteoblast activation in the calcium deficient environment. Serum parathyroid hormone levels also tend to increase with increasing severity of the rickets. Vitamin D levels tend to be below normal or in the low normal range. The biochemical consequences of a vitamin D deficient rickets are illustrated in Fig. 4.2.

Studies over the past few years have shown that suboptimal Vitamin D status is common among otherwise healthy young children. In the study of healthy toddlers and infants, the prevalence of vitamin D deficiency (<20 mg/mL) was 12.1 and 40 % had levels below the accepted optimal threshold (<30 mg/dL). The prevalence did not vary by skin pigmentation but breastfeeding without supplementation (infants) and lower milk intake (toddlers) were significant predictors of vitamin D deficiency [6]. In these vitamin D deficient, children 3 (7.5 %) had rachitic changes on wrist and knee films and 13 (32.5 %) had demineralization. In November 2008, the American Academy of Pediatrics increased the daily recommended intake of vitamin D for infants and children to 400 IU/day [12, 18]. In a study 2 years later, Perrine et al. found very few children consuming "adequate" amounts of vitamin D. This was true for both breastfed or formula fed infants and they recommended oral vitamin D supplements for breastfed infants and those consuming <1 L/day of infant formula [18].

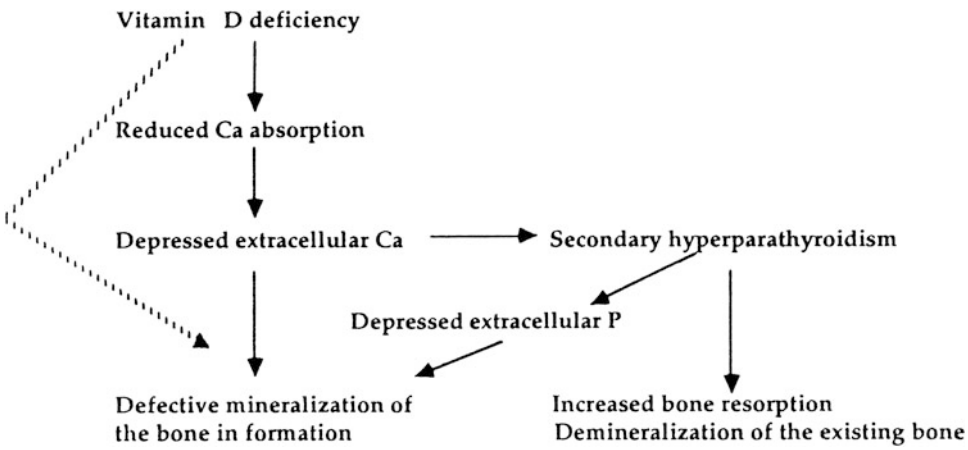

Fig. 4.2 The biochemical consequences of vitamin D deficiency rickets are shown [28]

(b) *Pathogenesis of skeletal abnormalities*: Decreased circulating and extracellular calcium leads to defective mineralization of newly forming bone and the secondary hyperparathyroidism worsens the situation as it elevates the serum calcium by increasing bone resorption which leads to further demineralization of existing bone. Owing to the importance of mineralization in the normal development of the physis, major histopathologic changes evolve in the epiphyseal, physeal, and metaphyseal regions with this disorder (Table 4.1) [1]. There is an absence or diminution of mineralization in the cartilage matrix of the hypertrophic region, thickening of physeal cartilage which continues to proliferate but is unable to proceed to a normal hypertrophic sequence in the absence of mineral, and cupping of the metaphyses with the concavity towards the epiphyseal side as the epiphysis is displaced and is essentially embraced peripherally by the undermineralized and poorly developed metaphyseal areas. Rickets therefore induces marked changes at the physeal–metaphyseal region with considerable disorganization of the endochondral sequence noted. There is an accumulation of physeal cartilage which loses its orderly columnation. Marrow vessels tend not to penetrate the hypertrophic cartilage since what would appear to be one of their major signals, mineralization of the cartilage matrix, has not occurred. Where metaphyseal vessels do penetrate they do so at various angles and to various levels rather than being parallel to the long axis of the bone and well controlled at the lower levels of mineralization. Irregular accumulation of cartilage persists in the metaphyses. The marrow tends to be fibrous rather than vascular. The increased width of the physeal–metaphyseal region is particularly evident clinically at those regions of the developing skeleton, which are subcutaneous including the costochondral junctions and the distal radial and ulnar epiphyses. The secondary centers of ossification are undermineralized and their appearance may be delayed. The skull is soft and misshapen owing to the tendency of the child to lie on and flatten the posterior occipital region (rachitic craniotabes). The sutures are wider than normal and there is delayed closure of the fontanelles. There is increased protrusion of the sternum, localized prominence or beading of the chest wall along the lines of the costochondral junctions and grooving of the ribs along the line of attachment of the diaphragm referred to as Harrison's grooves. Demineralization and increased resorption also lead to unmineralized osteoid, referred to as osteomalacia, which preferentially weakens the metaphyseal regions in particular since they have the thinnest cortices, and contribute to the bowing deformation of the long bones.

(c) *Radiographic changes*: Radiographically the appearance of a thickened growth plate with metaphyseal cupping or concavity is highly suggestive of rickets. The metaphyseal bone is also less sharply delineated at its physeal margin being described as irregular, fuzzy, or frayed. The secondary ossification centers are less dense and may be delayed in appearance. This is particularly seen at the distal radius and ulna where growth is more extensive than at the proximal ends of these bones and where the physes are normally horizontal. With institution of medical treatment, repair shortly becomes evident radiographically. The poorly mineralized and thickened cartilage of the hypertrophic zone rapidly absorbs the calcium, and linear areas of radiodensity at the physeal–metaphyseal region are seen within weeks. Mineralization of the osteoid deposited by the periosteum then becomes apparent on x-ray, and the tendency of the bone is to return to normal density.

(d) *Deformities of Growth*: Bowing and angular deformities of the long bones of the lower extremities are common with upper extremity bones much less affected. At the knees both bow leg (genu varum) and knock knee (genu valgum), deformities can occur depending on the age at which the metabolic condition is present. A coxa vara deformity of the proximal femur is quite common and can be sufficiently severe that the neck of the femur forms a right angle with the long axis of the diaphysis. Owing to the thickness and relative poor mineralization of this region, deformities develop which further worsen the normal relationship between the epiphyseal and the metaphyseal–diaphyseal regions. Bowing occurs within the metaphyseal and diaphyseal regions which are thinner than normal and more osteopenic (histologic osteomalacia) owing to the presence of unmineralized osteoid and failure of deep compaction of the Haversian systems.

(e) *Fractures*:

(i) Fractures in very low birth weight infants with rickets. Fractures and rickets often occur together in very low birth weight (VLBW) infants (<1500 g) who are ill [19]. In the first year of life in 78 VLBW infants, there were 25 with the combined syndrome of fractures and rickets. All bones healed with remodeling of deformities after weight gain was induced with improved uptake and nutritional status. No specific orthopedic management was needed.

(ii) Fractures in rickets are simulating child abuse. Fractures in children with extremely low levels of vitamin D and rickets can be mistaken for child abuse. Diagnostic workup for either disorder must take this possibility into consideration and include

assessment of vitamin D, calcium, and alkaline phosphatase levels.

Paterson described a case of vitamin D deficiency rickets in a two and half-year old with failure to thrive, several fractures of the extremities, widening of the skull sutures, and even pseudofractures which was diagnosed as child abuse [20]. The case is significant in that classic radiographic findings of rickets were present. Subsequently the relative frequency of lower than normal range vitamin D levels (considered as insufficiency or deficiency) has become widely appreciated and checked by the pediatric and medical communities, although the large majority of these children do not have either the symptoms of clinical rickets or even the radiographic findings of rickets as previously documented in the developing skeleton. Increased concern for child abuse by physicians, hospitals, and child protection agencies has led to (often) zealous investigation of many childhood fractures for concerns of nonaccidental causation. As in the case of osteogenesis imperfecta, legal teams on both sides of the situation are addressing the (very common) "sub-normal or normal range" vitamin D levels in trying to determine their contribution to bone fragility. A paper by Keller and Barnes in 2008 raised the concern about undetected rickets and child abuse [21]. At a minimum, this has stimulated much discussion and some important studies. A 2013 commentary by Strouse seems the most balanced and accurate commentary [22]. He reviews several papers and indicates that the classic patterns of child abuse, especially regarding the radiography of fractures, continue to represent the strongest evidence for cases of child abuse. Schilling et al. examined vitamin D levels in children <2 years of age with (i) suspected abusive and accidental fractures, (ii) single and multiple fractures, and (iii) fracture patterns highly associated with inflicted trauma [23]. They studied 118 subjects. Deficient vitamin D levels (<20 ng/ml) were found in 8 %, insufficient levels (≥ 20 < 30 ng/ml) were found in 31 %, and sufficient levels (≥30 ng/ml) were found in 61 %. The majority of children (60 %) sustained accidental fractures, 31 % were nonaccidental, and 9 % were indeterminate. They found no association between vitamin D levels and child abuse diagnosis, multiple fractures, rib fractures or metaphyseal fractures. They concluded that vitamin D insufficiency was common in young children with fractures but not more common than in previously studied young children. Vitamin D insufficiency was not associated with multiple fractures or diagnosis of child abuse, and they felt that nonaccidental trauma remained the most common cause of multiple fractures in young children. They concluded that a low vitamin D level should not eliminate consideration of child abuse when a child presented with unexplained fractures [23].

Perez-Rossello et al. studied 40 children with vitamin D deficiency ≤20 ng/ml aged 8–24 months [24]. Detailed-computed radiographs of knees and wrists were assessed along with serum levels of calcium, phosphorus, alkaline phosphatase, and parathyroid hormone. Rachitic changes were seen in only 2 patients (5 %) and demineralization in 2 (5 %). There were no fractures. The study concluded that in infants with vitamin D deficiency, rachitic changes and definite demineralization were uncommon and fracture risk was low. Paterson continues to publish cases originally considered to represent child abuse that he considers to be due to unappreciated vitamin D deficiency [25].

(iii) Forearm fractures in African American children with vitamin D insufficiency. Evidence of forearm fractures in African American children 5–9 years of age with vitamin D insufficiency (serum 25-hydroxy vitamin D level <20 ng/ml) with decreased bone mineral density has been presented [26]. 17 cases the mean level was 20.1 (±7.3) ng/ml with a range of 10–38. Ten cases (59 %) were vitamin D insufficient. The authors concluded that a significant proportion of African American children with fractures in their study had vitamin D insufficiency.

(f) *Responses to Medical Therapy*: If treatment is begun within the first 2 years of life, the metabolic abnormality is readily corrected and any bowing of the long bones will almost always remodel without need for orthopedic intervention. Oral supplementation with 3000 units vitamin D daily for infants under 6 months of age and 6000 units vitamin D for older children has been recommended [27]. David has outlined that the temporal aspects of repair once therapy is begun with vitamin D and, if necessary, calcium supplements [28]. The earliest clinical sign of effectiveness is rapid motor improvement with the mild myopathy responding to the appropriate levels of calcium and phosphorus. Plasma Ca, P, PTH levels normalize within days or weeks but the levels of 1, 25 dihydroxy vitamin D and alkaline phosphatase tend to remain elevated for months until final healing of rickets has been achieved. The first

radiologic signs of healing rickets occur 2–4 weeks after initiating vitamin D therapy with the presence of linear dense deposits within the previously unmineralized cartilage at the lower end of the growth plate. These dense metaphyseal zones of calcification corresponding to the newly calcified cartilage may persist for 2–3 years until there is complete remodeling. Bowing of the long bones may take 4–5 years to disappear but should occur as long as there is no recurrence of the rickets condition. If compliance to daily therapy is a concern, stosstherapy, a single large dose of vitamin D (300,000–600,000 units) given either orally or parenterally, can be used [29]. If hypocalcemia is the presenting symptom initial treatment with calcium supplementation might be needed and oral calcium longer term might need to be taken along with vitamin D.

4.1.5.2 Familial Hypophosphatemic Rickets (X-Linked Hypophosphatemic Rickets [XLH])

(a) *Pathophysiology*: This is now the most common type of rickets seen in growing children. It is an X-linked dominant disorder associated with a renal tubular defect in phosphate transport and subsequent bone deformities. It was recognized as a distinct disorder by Albright et al. in 1937 and defined as rickets resistant to vitamin D therapy (vitamin D-resistant rickets) [30]. They noted 6 cases where much more vitamin D was required for cure than was ordinarily needed for management of nutritional rickets. The patient with rickets resistant to vitamin D therapy had clinical and histologic evidence of a true rickets and hypophosphatemia that appeared due to a secondary hyperparathyroidism. The disorder of metabolism was corrected and the healing of rickets took place only with massive doses of vitamin D, and they concluded that the disturbance was not a deficiently disease like ordinary rickets but rather a form of rickets due to an intrinsic resistance to the antirachitic action of vitamin D. Shortly afterward Christensen defined the familial occurrence [31]. Winters and associates recognized the X-linked dominant inheritance pattern and reviewed the first 65 cases described to provide an overview of the disorder [32]. It was then evident that vitamin D-resistant rickets was a specific disorder characterized by a clinical, radiological, and biochemical picture similar to that seen in vitamin D deficiency rickets but progressing in spite of adequate antirachitic prophylaxis and healing only in response to very large doses of vitamin D [33]. The level of serum inorganic phosphorous is the most sensitive index of the abnormality. Both sexes are affected: females tend to have mild deformities or none at all while males are far more seriously affected with moderate to severe deformities. It is most commonly transmitted as a sex-linked dominant but rarer modes of transmission such as autosomal dominant, sporadic new X-linked mutations, and autosomal recessive forms have been reported. Glorieux has pointed out that, as is characteristic for a sex-linked dominant condition, it is fully expressed in male hemizygotes and variably expressed in female heterozygotes [34]. The phenotype of XLH is caused by a dual abnormality: a renal defect combining phosphate wasting and altered calcitriol synthesis and an osteoblast–osteocyte defect which decreases the ability of these cells to control mineral deposition in the matrix. Undermineralization of physeal cartilage and of osteoid is dependent ultimately on the decreased retention of phosphate by the kidneys owing to a failure of its reabsorption in the distal tubular system. The hypophosphatemia also fails to stimulate the 1-hydroxylation of 25-hydroxy vitamin D so that 1, 25 dihydroxy vitamin D levels are lower than normal. The renal phosphate leak diagnosed by increased urinary phosphate excretion and the loss of normal compensatory mechanism of 1, 25 dihydroxy vitamin D formation combine to produce very low serum phosphate levels. The persistent hypophosphatemia is the best way to recognize affected individuals in combination with elevated serum alkaline phosphatase activity and normal serum calcium. Bicarbonate and PTH levels are generally normal. There is no aminoaciduria. There is decreased calcium absorption from the gastrointestinal tract but also low-urinary calcium excretion.

An autosomal dominant hypophosphatemic rickets (ADHR) has also been identified. It has been shown to be due to missense mutations in a gene encoding a member of the fibroblast growth factor family, FGF 23 [35]. ADHR is characterized by low serum phosphorous, rickets, osteomalacia, lower extremity deformities, short stature, bone pain, and dental abscesses.

(b) *Gene abnormality*: Progress has been made in discovering the genetic abnormality in XLH. Linkage of the hypophosphatemic HYP locus to DNA markers on chromosomal band Xp 22.1 was established [36]. Subsequently, the candidate gene was identified that exhibits homology to a family of endopeptidase genes, members of which are involved in the degradation or activation of several peptide hormones [37]. The XLH gene, referred to formerly as PEX but now more commonly as PHEX (phosphate regulating gene with homologies to endopeptidases on the X chromosome), is composed of multiple exons. PHEX is a cell surface

zinc metallopeptidase with phosphate regulating functions. It is involved in the regulation of FGF23 and is mutated in XLH rickets. Intragenic separate deletions from 4 different families and 3 mutations were detected. Holm et al. found mutations in PEX in 9 of 22 unrelated HYP patients [38]. Continuing study involved analysis of 99 HYP families for PEX gene mutations [39]. Deletions, insertions, nonsense mutations, stop codons, and splice mutations occurred in 83 % of families screened in all 22 exons and 51 % of a separate set of families screened in 17 PEX gene exons. The wide range of mutations that align with regions required for protease activity suggests that PEX functions as a protease and may act by processing factors involved in bone mineral metabolism. This extensive mutation analysis revealed a range of defects in the PEX gene. A mouse model (hyp) was identified in 1976 and has provided a valuable tool to study the disease at cell and molecular levels [40]. The hyp mouse has rickets, osteomalacia, hypophosphatemia, and defective renal tubular reabsorption of inorganic phosphorus. Mouse pex is homologous to human PEX. PEX mRNA is expressed predominantly in human fetal and adult mouse calvaria and long bone [41]. They concluded that pex/PEX is a low-abundance transcript that is expressed predominantly in bone of mice and humans and that a large deletion in the 3^1 region of the pex gene is present in the murine hyp homologue of X-linked hypophosphatemia. Strom et al. also noted that the mouse homolog of pex was highly conserved between man and mouse [42]. The 3^1 end of the gene was found to be deleted in hyp mice. They concluded that the hyp mouse was not only a phenotypic model for X-linked hypophosphatemia in the human but also had similar genetic abnormalities. Another mouse model for the disorder is referred to as the Gy mouse which is a mutation found among offspring of an irradiated female mouse [43]. The Gy mice in addition to hypophosphatemia and other findings similar to X-linked hypophosphatemic rickets also show inner ear abnormalities. PEX gene deletions were also found in the Gy mouse variants.

It has more recently been noted that PHEX regulates FGF23 both of which are expressed in osteocytes. Osteocytes also secrete dentin matrix protein 1 (DMP1) and matrix extracellular phosphoglycoprotein (MEPE) that regulate bone mineralization. XLH is caused by inactivating mutations of PHEX which also results in increased expression of FGF23 in osteocytes. High circulating levels of FGF23 are characterized by hypophosphatemia, phosphaturia, decreased production of 1, 25 dihyrodroxyvitamin D, and rickets/osteomalacia [44, 45]. FGF23 is now known as the phosphaturic hormone. The bone-kidney axis plays a role in bone mineralization, vitamin D metabolism, renal phosphate handling, and parathyroid function.

(c) *Cell and matrix abnormalities in XLH Bone*: Studies by Engfeldt et al. on bone and cartilage from 4 patients with primary vitamin D-resistant rickets showed important abnormalities [46]. Histologic sections of the physis from the costochondral junction showed the characteristic pattern of rickets with thickening of the physeal cartilage, irregularity and persistence of the proliferating zone, and a disorganized and thickened hypertrophic zone. Vascular invasion from the metaphyseal region was highly irregular with widened blood vessels passing from the marrow cavity into the proliferative cartilage but in a random fashion and not associated with new bone formation. Adjacent metaphyseal osteoid was extensive. Much of their work concentrated on the appearance of the bone tissue before and after vitamin D therapy. They concluded that, although increased mineralization of the bone could occur, there was no change in the abnormal pattern of the collagen. Both the patterns of bone deposition and the extent of its mineralization were abnormal. While lamellar bone was seen by light and polarization microscopy, the collagen pattern of the sections was unusual and irregular and consisted of short bundles running in different directions. On occasion the collagen fibers were organized into the normal Haversian systems but the tendency was either for disorganized lamellar bone to be present and on occasion woven bone. The appearance resembled that seen in Paget's disease. The osteocyte spaces or lacunae were often wide and irregular and poorly defined. Pericellular mineralization was often minimal. Even within trabeculae there were widely varying areas of mineralization. Both the highly mineralized trabeculae and those showing a low mineral content displayed an apatite pattern with the same dimensions as that of normal bone. Numerous resorption cavities were present along with the variation in mineral content, the enlarged osteocyte lacunae, and the abnormal pattern of collagen deposition. Despite almost normal mineralization following massive doses of vitamin D, a distinct lack of normal compact bone formation was noted both histologically and by microradiography. This was also characterized by an enormous variability of the calcium content in different areas. The pattern was characteristic of a high-turnover pattern with extensive remodeling of the bone tissue with intense resorption and new deposition noted. They concluded that, although the high-dose vitamin D increased mineralization of the physis, it was unable to convert the structural abnormality of the bone tissue itself to a normal pattern.

An actual osteoblast defect in X-linked hypophosphatemia has been implicated based on detailed studies in the hyp mouse [47, 48]. To test the hypothesis of an abnormal osteoblast function in XLH periosteal osteoblasts isolated from normal and hyp mice were transplanted into normal and mutant mice. Impaired mineralization was seen in transplants of hyp cells into hyp mice as defined by excessively thick osteoid seams compared with transplants of normal cells into normal mice. When normal cells were transplanted into mutant mice osteoid thickness was again markedly increased indicating that the extracellular host environment was critical for bone formation. Further studies demonstrated an inability for hyp osteoblasts to produce normal bone when placed in a normal environment leading to the interpretation of an intrinsic cellular abnormality of the osteoblast as an important target for hyp mutations. There appear to be primary abnormalities in osteoblasts. Phosphate and vitamin D supplementation healed the mineralization defect at the epiphyseal plate region but not at the endosteal bone surfaces, suggesting that a bone resistant form of vitamin D is present. Lesions around the osteocyte lacunae never disappeared completely indicating a direct abnormality of the osteocyte itself.

(d) *Hypothetical model of disease*: Carpenter has utilized investigational findings in relation to XLH to produce a hypothetical model of the disorder [49]. He feels that both human and murine studies suggest that a humoral factor mediates the defect in renal phosphate transport. The disorder which is evident clinically in affecting the bones is independent of disease expression at the kidney, which is shown by the increased circulating phosphate levels although the organ itself otherwise functions normally. He feels that the mineralized tissues may reflect a gene dose effect not present in the kidney. The hypophosphatemia is not associated with appropriate production of 1, 25-dihydroxy vitamin D. The abnormal gene in XLH appears to encode endopeptidase but the human form is different from the murine form as it is under expressed in hyp mice. He feels that renal intracellular phosphate is probably normal which may mask the hypophosphatemic stimulus to renal 1, 25 dihydroxy vitamin D production. The important factors relating to phosphate movement across renal cell membranes are the existence of inorganic phosphate (Pi) regulating substances which preserve the intracellular levels of the proximal renal tubular cell. When Pi is insufficient a decrease in the factor would decrease the intracellular Pi thereby mediating an increase in membrane transport of Pi and 1 alpha hydroxylation of vitamin D. Unregulated persistence of such a factor during brief Pi depravation would disrupt appropriate renal Pi conservation and generation of 1, 25 dihydroxy vitamin D, which is the precise renal defect seen in XLH/hyp. Carpenter goes on to suggest that "the synthesis, processing or secretion of this putative humoral factor is rendered abnormal in XLH by mutations in the PEX gene such that normal regulation of the Pi homeostatic system is disrupted."

(e) *Clinical and radiographic characteristics*: The disorder has some meaningful clinical variations from nutritional rickets. The children are systemically well, there is no proximal muscle weakness, tetany does not occur, there is no bone pain, and the condition does not usually present clinically until 2–3 years of age or older. There is no involvement of the spine. The condition presents with hypophosphatemia, lower limb bowing deformities, and a slower rate of growth [49]. Characteristic radiographs are shown in Fig. 4.3.

Bowing deformities. The gradually developing deformity of the lower limbs involves proximal femoral bowing of a coxa vara type, anterolateral diaphyseal–metaphyseal femoral bowing, genu varum or valgum with proximal tibial bowing, and internal tibial torsion. Coxa vara deformity of the proximal end of the femur is a characteristic feature of severe XLH rickets in particular in those instances where growth and development have occurred over a few year period before diagnosis or where medical treatment is ineffective after diagnosis has been made. The bowing is associated with widening of the growth plate, thinning of trabecular bone owing to the failure of appropriate mineralized osteoid deposition, and also thinning of the adjacent cortices. The physeal–metaphyseal radiologic changes are the same as those described for nutritional rickets. There is thickening of physeal height, an irregular or frayed metaphyseal border, and cupping of the metaphyses. Physeal thickening may be asymmetric with one side of the physis (for example, the medial half) thicker than the other. The bending is not caused by a slip of the proximal femoral epiphysis or by a fracture through the neck but rather is characterized by continuity of tissue with a tendency for it to bend at physeal cartilage, metaphyseal bone, and diaphyseal bone regions owing to inadequate mineralization. Swelling of the wrist, ankle, and costochondral junctions is the same as that seen in the vitamin D deficient forms. Males are more severely affected than females with the sex-linked dominant inheritance. Dental abscesses are frequently seen due to abnormal tooth structure.

Short stature. Short stature is seen frequently in those affected and is almost always accompanied by the characteristic rachitic deformities. Normal stature is considered to range between 2 standard deviations

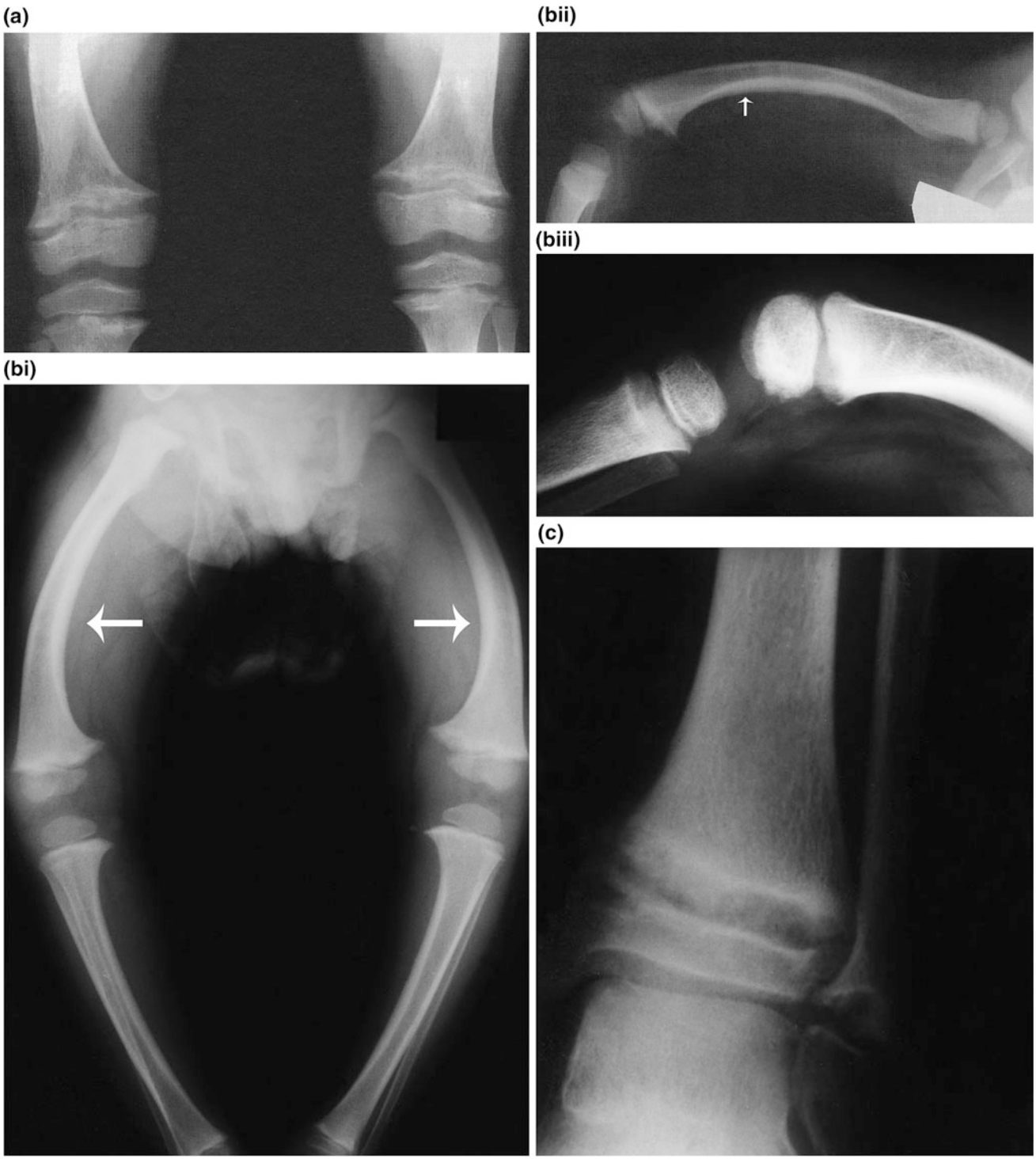

Fig. 4.3 Characteristic radiographs in familial hypophosphatemic rickets are shown. **a** Anteroposterior knee radiographs show widened distal femoral and proximal tibial physes. **b** Anteroposterior (i) and lateral (ii) radiographs show characteristic lateral and anterior femoral bowing (*arrows*) with (iii) flexed deformity of distal femoral metaphysis—epiphysis. **c** Widened physes of the distal tibias are seen

above and below the mean. Most patients with this disorder are below the second standard deviation below the mean but some are in the low normal range. The shortened stature is based entirely on the shortened lower extremities and is not solely or even primarily due to the bowing deformities. No form of medical treatment has affected overall height even where it improves the rickets metabolically and radiographically.

In several families studied by Burnett et al. no affected individual was taller than 65 in. [50]. Seven affected males had a mean height of 58.6 in. compared to 19 nonaffected male family members with a mean height of 68.7 in. In females, 19 affected had a mean height of 56.8 in. and 26 nonaffected had a mean height of 62.2 in. Similar findings were noted by Tapia et al. in a smaller series [51]. The final mean height in 4 males was 58.9 in. (range from 52 to 63.5) and in 7 females 56.5 in. (range from 52 to 58.5). Similar height ranges were listed by Pedersen and McCarroll with most adult patients between 51 and 59 in. and the tallest 65 in. [52]. Balsan and Tieder studied linear growth in a large group of XLH patients and noted no acceleration of growth with vitamin D or calcitriol regimens but saw "catch-up growth" in 10 of 16 on 1-hydroxy vitamin D3 [53]. Stickler and Morganstern studied the heights of 52 patients aged at least 18 years with X-linked hypophosphatemic rickets [54]. They concluded that there was no evidence that any form of treatment (vitamin D in high doses, vitamin D plus phosphate supplements, or calcitriol plus phosphate) had any effect on adult height. The complications of treatment, such as renal failure owing to vitamin D intoxication, led to the question as to whether or not medical treatment had any benefit at all. They even considered the possibility of recommending no treatment for the primary disorder. Their criteria for diagnosis involved hypophosphatemia, a high alkaline phosphatase level, radiological evidence of rickets primarily in the legs, and no response to vitamin D in physiological doses. They compared the treated patients to 8 other patients with the disorder, 4 of whom received no treatment and 4 of whom had been treated for 2 years or less. Regardless of the medical regimen used the final height was not affected by treatment; in addition neither the age at which treatment was started nor the duration of treatment had any affect on adult height. The 8 patients who had reached adulthood without any treatment or <2 years treatment had a mean standard deviation of 3.06 below the mean compared with 2.88 below the mean for 20 patients treated continuously for at least 8 years. There was also no correlation between treatment and the number of osteotomies the patients had undergone.

(f) *Medical treatment*: The medical treatment of XLH has continued to undergo changes since no fully curative regimen has been defined. While some studies have suggested that medical therapy is futile, most investigators at present continue to favor it while recognizing that it is neither curative nor totally benign. Research discoveries in relation to the disorder have better defined the underlying pathophysiology. The initial approach to therapy was the use of massive doses of vitamin D (>50,000 IU per day) which improved the rickets but also led to hyper-calcemia and renal damage in many instances as well as little if any improvement of the slow growth rate [30, 49, 54, 56]. Stamp et al. noted that they were unable to prevent recurrence of deformity or eliminate short stature in their patients [57]. Pierce et al. showed poor control with high-dose vitamin D and a tendency to hypervitaminosis D toxicity and renal damage when therapy continued [58]. The early evolution of therapy has been well summarized by Glorieux et al. [55]. They developed a treatment regimen which used 1, 25 dihydroxy vitamin D rather than vitamin D itself along with phosphate supplements to minimize phosphate induced hyperparathyroidism (Fig. 4.4). They noted improvement in the growth rate which they felt was primarily the result of the phosphate supplement. The overall growth period was not shortened and the adolescent growth spurt was of normal magnitude and duration. Metabolic control of the disorder was defined by a normal growth rate, normalization of the serum alkaline phosphatase, and radiologic healing of rickets. These parameters are also important determinants of the timing for orthopedic intervention. The medical regimen involves calcitriol twice daily and phosphate salts at 5 separate times over a 24-h period. The viewpoint of Stickler and Morgenstern was supported to a considerable extent by Verge et al. in a long-term study of 24 patients [54, 56]. A detailed assessment of the effects of medical therapy in XLH commented both on its effects on growth and on the negative occurrence of nephrocalcinosis. With the calcitriol and phosphate treatment, there was a slight statistically significant increase in growth with the mean height SD score minus 1.08 as compared with minus 2.05 in untreated historical controls. In 13 patients treated for at least 2 years, the increase in the mean height score was 0.33 from a −1.58 to a −1.25 range. This too was statistically significant. Actual height

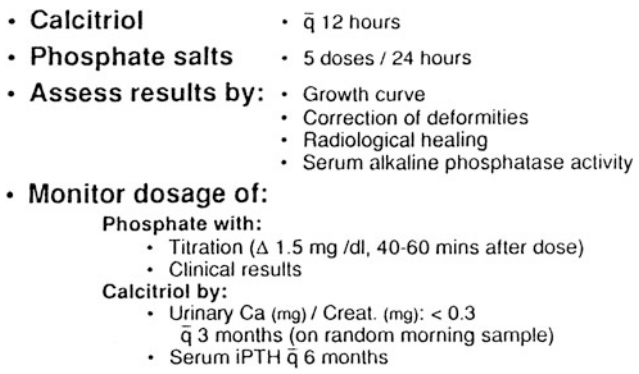

Fig. 4.4 Treatment profile for hypophosphatemic rickets is illustrated

measurements were not provided. In each group not all patients increased the rate of growth and some actually declined. The overall mean values, however, were indicative of slightly increased growth. There was much clearer evidence of the negative sequelae in terms of the nephrocalcinosis detected on renal ultrasonography. Nineteen of 24 patients (79 %) had nephrocalcinosis with the grade correlating significantly with the mean phosphate dose but not with the dose of vitamin D or the duration of therapy. The calcitriol and phosphate therapy helped minimize lower limb deformity since few patients required surgical intervention in terms of osteotomy, whereas before the introduction of the combination therapy the majority of such patients required correction. The childhood therapy or a continuation of such therapy past skeletal maturity was of no benefit to the adult patient. With regard to height, the combination therapy had a slight beneficial effect but some previous studies had failed to demonstrate any beneficial effect. The absence of nephrocalcinosis in untreated adult relatives within the patient population supported the belief that nephrocalcinosis was a sequela of therapy rather than part of the natural history of the disorder. The radiographic response to medical treatment showing increased density of the lower extremity physes and adjacent metaphyses is similar to that observed following treatment for nutritional rickets.

A study assessing the effectiveness of medical therapy showed that early treatment with oral phosphates and 1,25-dihydroxy vitamin D3, starting at <1 year of age, was significantly better than treatment started after 1 year of age in terms of growth, lesser levels of serum alkaline phosphatase, and radiographic signs of rickets [59].

Since the XLH disorder is benign with a full life expectancy any negative implications of therapy on renal function are of serious concern. The value in terms of bone strengthening and diminution of deformity is real but close assessment for evolving renal problems is essential. Glorieux strongly supports the need for treating patients with X-linked hypophosphatemic rickets [34]. A combination of phosphate and calcitriol therapy was considered best with patient compliance and close monitoring of renal and metabolic features essential. Diminution in the need for osteotomy was a major benefit with the other matters being controllable with close observation. Carpenter stresses that early treatment is likely to result in better outcomes [49]. Children from affected families should be screened for abnormal serum and urine phosphorous levels and serum alkaline phosphatase activity within the first month of life and then again at 3 and 6 months. If subsequent radiographic examination is suggestive of the XLH diagnosis therapy is started with calcitriol and phosphate. The dosage range is quite wide depending on the severity of the rickets, the response to therapy, and the complications encountered. The 3 major complications of therapy for XLH are hypervitaminosis D, hyperparathyroidism, and soft tissue calcification particularly in the kidney.

(g) *Orthopedic Management*: Virtually all operative treatment in XLH rickets is for femoral and tibial deformity. Upper extremity deformity necessitating surgical treatment is rarely seen. Evans et al. defined three levels of expectation in relation to deformities in XLH rickets [60]. In those patients in whom the diagnosis is made within the first year of life medical treatment will almost always cure or at least control the rickets such that deformities do not develop during the growing years. In those patients seen with mild deformities between 1 and 5 years of age, the institution of appropriate medical therapy should be sufficient to prevent the deformities from worsening to levels of clinical significance and to allow for spontaneous correction with growth as would be the case, for example, with instances of physiologic bowing of the lower extremities in this age group. In those patients >5 years of age at the time of diagnosis, medical treatment is often not sufficient to allow for correction of the deformities which have progressed to a considerable degree in many instances and osteotomy must generally be used. Rubinovitch et al. also indicated that children under 6 years of age with milder deformities frequently corrected with growth and good metabolic control, while those above 6 years of age with severe deformity generally needed osteotomy [61]. Pierce et al. expressed concern about the ability to correct deformity during the growing years and advocated brace management with osteotomy deferred until skeletal maturity [58]. Tapia et al. noted that the maintenance of correction gained by osteotomy in all 13 cases under adequate vitamin D therapy with recurrence of deformity in 50 % (9 of 18) of cases where it was inadequate [51]. More recently hemiepiphyseodesis has been used to prevent worsening deformity and, if timing is appropriate, to correct deformity without need for osteotomy [62]. Although asymmetric stapling of epiphyses has been used for over 60 years, it is now used more often, generally with application of an extraperiosteal 2 hole plate and screw [63]. It can be used in those <10 years of age with removal after correction of mechanical axis alignment with expectation for continuing growth. A subsequent paper on the "guided growth" method showed similar results with far fewer hardware complications using the 8-plate" (Orthofix, Verona, Italy) [64].

Medical therapy is increasingly difficult to use in older children as the level of cooperation for the rigorous medical regimens tends to diminish in all but the most committed of families and patients. Medication must often be given 4–6 times a day and involves pills or liquid intake which are both unpleasant to taste and in fairly large volumes. In addition, the medical therapy in many instances is not sufficiently refined to lead to full correction of the abnormality even if faithfully adhered to. Another problem relates to the nature of the deformity. In the femur, the bowing tends to involve the entire bone with an anterolateral bowing deformity seen. At the proximal end, there is a coxa vara; in the diaphysis, there is actual bowing owing to the weakened state of the cortices as well as the fact that during earlier time periods the metaphyseal regions were also bowed; and at the distal end metaphyseal and epiphyseal bowing is prominent owing to the extensive stresses at the knee region and the fact that 70 % of the growth of the femur occurs distally. Bowing of the tibia is not as marked generally but may also involve the entire bone. The proximal tibial bowing can be either genu varum or genu valgum depending on the time during the growth period that the rickets is most pronounced and on the weight of child. These multiplanar/multidirectional deformities may not be easily or fully correctable by a one-site intervention.

There are two important considerations in attempting surgical correction of limb deformities in growing children with rickets.

1. Medical therapy must be well established prior to the performance of corrective osteotomy. In severe nutritional rickets, which is unusual today, the disorder should be cured metabolically prior to surgical intervention; vitamin D therapy restores the serum phosphorus and alkaline phosphatase levels to normal. In those with familial hypophosphatemic rickets or other variants, the optimal form of medical management should be achieved prior to surgery. If there are several years of growth remaining correction of the deformity in the presence of continuing rickets will almost certainly have to be repeated as the subsequent growth in the presence of widened growth plates and weakened metaphyses will lead to recurrence of deformity. There is a marked tendency to delayed bone union, approaching nonunion on occasion, following osteotomy if the rickets is poorly controlled. In several papers over the past few decades, however, the osteotomies have been shown to unite regardless of the method of medical management. The impression is still gained; however, that healing can be delayed especially where medical control is suboptimal.
2. Close consideration must be given to the site of bowing, the alignment of both femurs and tibias, the timing of surgical interventions, and the method of immobilization post-osteotomy. Three surgical approaches are considered for bone deformities: (i) single-level wedge osteotomy for focal angulation, (ii) multilevel (2 or more) osteotomy for bowing which is multiplanar and involves the entire bone from proximal end to distal end (physeal, metaphyseal, diaphyseal, metaphyseal, and physeal bowing), and (iii) asymmetric physeal stapling for focal deformity which has caused physeal–metaphyseal angulation. Single-level closing wedge or opening wedge osteotomies are performed where deformity is reasonably localized with stabilization usually provided by rigid AO plate instrumentation although those expert in the use of external fixators have reported good results [65]. Song et al. used a combination following osteotomy of Ilizarov external fixation, sometimes adding distraction, rigid intramedullary nailing, and flexible intramedullary rods to correct childhood and adult deformities in 55 segmental deformities (20 femurs and 35 tibias) in 20 patients (9 children and 11 adults) [65]. All osteotomies eventually healed although there were 18 major and 13 minor complications running the gamut from refracture and recurrent deformity to nail-related problems (loosening, migration, and deep infection). The proximal femur is particularly difficult to correct in cases of moderate to advanced rickets but must be addressed or else reasonably good alignment achieved distal to it can be compromised by a persistent waddling gait. Even though the limbs appear straight clinically, mechanics of gait are not fully corrected if there is a persisting uncorrected proximal coxa vara deformity. For these reasons, approaches to the femur may require 2 or more levels of osteotomy followed by insertion of an intramedullary rod. The intramedullary rod is particularly effective in allowing for correction of the bowing of the proximal femur which has led to the coxa vara deformity. Biplanar or multiplanar angular deformity is often present throughout the entire extent of both the femur and tibia such that single-level osteotomy may not fully correct limb malalignment. Angular deformity if focal can also be corrected using asymmetric stapling. Great care must be taken to maintain the normal horizontal articular surface planes of distal femur and proximal tibia.

Osteotomies to correct femoral and tibial bowing have been studied in relation to the level of correction. In many instances, multiple osteotomies have been needed to gain full correction. Ferris et al. felt that diaphyseal osteotomies followed by intramedullary nailing for stabilization could be performed effectively at any age [66]. The deformities were multiplanar, involving flexion, lateral deviation, and rotational components. Wedge osteotomies of the diaphyseal

segment at one level rarely led to full correction. Intramedullary nailing had many advantages allowing for improved correction at 2 or more sites. Much of the deformity is concentrated in the metaphyseal region because of the closeness of the physis and the fact that undermineralized metaphyseal bone bows more readily because of the thinness of the cortices. It is often essential to perform correction at the metaphyseal level, although fixation is a problem. The recommendation was to perform the metaphyseal correction close to skeletal maturity since the likelihood of recurrence is greater at this region the earlier the deformity is corrected. They favored intramedullary rodding with interlocking nails for rotational stability even where a single-midshaft osteotomy was performed. They had experienced considerable difficulties with nonunion and delayed union, and recurrent deformity in osteotomies and asymmetric stapling in immature patients. Kanel and Price have shown the value of treating the multiplanar deformities with transverse osteotomies and use of unilateral external fixation [67]. This approach allows for multiple osteotomies and correction through the metaphyseal regions. The patient remains ambulatory with crutches with no need for cast immobilization. They reported on 29 osteotomies in only 9 patients, a reflection of the fact that most patients require bilateral femoral and tibial osteotomies. All osteotomies healed. The external fixators remained on for an average of 90 days. In milder deformities, asymmetric stapling toward the end of skeletal growth can be effective at distal femur or proximal and distal tibial physes. Fucentese et al. also report good results with axial corrective osteotomies and bone lengthening [68]. Kocaoglu et al. showed the value of osteotomies with attention to multiplanar correction in late adolescence once the contributing factors of growth were no longer involved. They reviewed 17 patients with hypophosphatemic rickets and 2 with renal osteodystrophy treated at a mean age of 26 years (range 14–57) [69]. Femoral (27) and tibial (16) osteotomies were done with deformity corrected using a monolateral external fixator with further stabilization provided by a locked intramedullary nail to prevent recurrence of deformity or refracture. Windswept deformity at the knees (one side varus the other side valgus) can occur with hypophosphatemic rickets. Al Kaissi et al. collected 7 patients from their department with hypophosphatemic rickets to assess orthopedic management [70]. All patients were male average age 12 years and had a mutation identified in the PHEX gene sequence (Xp. 22). The average age at diagnosis was 2 years 9 months. Serum phosphate levels were always low with normal calcium parathyroid hormone and 25-hydroxy vitamin D levels. The average valgus deformity was 35° and the average varus 22° at time of surgical intervention. Repeated interventions during the growing years are expected, to keep the patient comfortably ambulatory, although treatments at skeletal maturity generally are longstanding. Methods of management were age dependent: ages 5–7 years, osteotomy with K-wire fixation or hemiepiphysiodesis (guided growth); 8 years to skeletal maturity, osteotomy with external fixation using Taylor spatial frame; and after skeletal maturity, osteotomy with intramedullary locking nails. The clinic had previously reviewed their experience in X-linked hypophosphatemic rickets correcting femoral and tibial deformities with 37 operations (10 children) with multiple segments corrected using external fixation (Kirschner wires 18, Dyna Fix 3, Taylor Spatial Frame 13, and Ilizarov device 19) and internal fixation (intramedullary nailing 12) [71]. Examples of surgical corrective procedures for lower extremity deformity are shown in Fig. 4.5.

4.1.5.3 Renal Osteodystrophy, Renal Rickets

(a) *Pathophysiology*: Renal osteodystrophy refers to the secondary effects of progressive chronic renal failure on developing bone in children [72–75]. In the earlier literature, it was referred to as renal rickets. Lucas recognized the correlation between renal and bone disease in 1883 characterized by bending of the bones in adolescence seemingly due to epiphyseal displacement, although he did not refer to true epiphyseal slippage [76]. None of the deformities described were in the hips but knock knees (genu valgum) and flat feet (valgus ankles) were reported. The commonest causes of the renal failure are renal dysplasia, obstructive uropathy, and reflux nephropathy in the congenital group and chronic glomerulonephritis and focal glomerular sclerosis in the acquired group [77, 78]. The skeletal disorder is characterized by osteitis fibrosa, frank rickets, or osteomalacia and a series of typical clinical and radiographic abnormalities. These are due ultimately to a secondary hyperparathyroidism and include myopathy, growth slowdown, bone deformity, slipped epiphyses, and occasionally avascular necrosis. The kidney is responsible for synthesis of 1, 25-dihydroxy vitamin D3 (calcitriol), the most active metabolite of vitamin D. With renal disease, the decreased ability of the kidney to synthesize calcitriol leads subsequently to the development of secondary hyperparathyroidism. Renal osteodystrophy inhibits 25-hydroxy vitamin D-1 alpha hydroxylase leading to the impairment of calcitriol synthesis. The chronic renal failure syndrome is characterized metabolically by hyperphosphatemia, hypocalcemia, impaired renal calcitriol synthesis, and skeletal resistance to the calcemic action of parathyroid hormone. Radiologically this manifests as extensive skeletal demineralization and lytic destructive bone lesions resulting from the

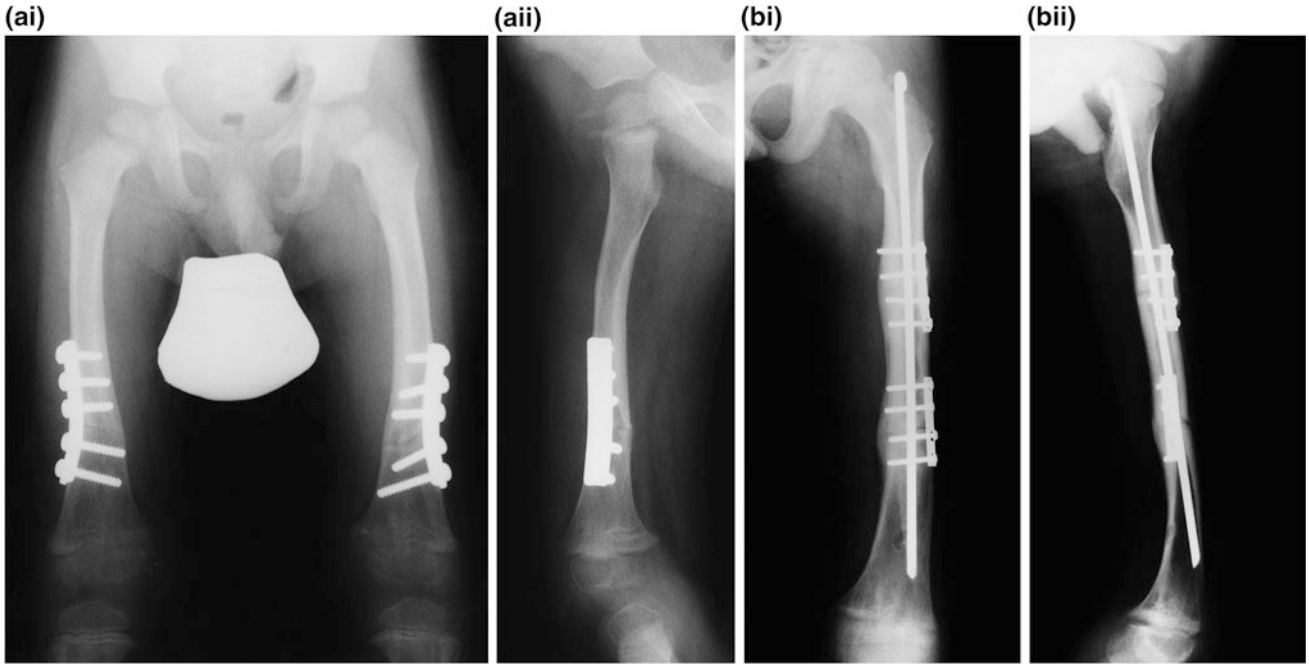

Fig. 4.5 Examples of surgical corrective procedures for lower extremity deformities in familial hypophosphatemic rickets are shown. **a** In the young patient (5–6 years of age) distal femoral valgus, extension osteotomies allow for good correction in anteroposterior (i) and lateral (ii) projections. **b** By 10–12 years of age multilevel osteotomies are often needed for correction; (i) anteroposterior and (ii) lateral projections

hyperparathyroidism. One of the characteristic findings of the disorder is a widening of the growth plates owing to failure of hypertrophic cartilage and metaphyseal bone calcification and the occurrence of slipped epiphyses throughout the skeleton (Fig. 4.6a).

(b) *Updated terminology of renal osteodystrophy*: A consensus group, Kidney Disease: Improving Global Outcomes (KDIGO), recently updated definitions for renal osteodystrophy [79]. They derived the term Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) to describe the broader clinical syndrome that develops as a systemic disorder of mineral and bone metabolism due to CKD with abnormalities in bone and mineral metabolism and/or extraskeletal calcification. The term *renal osteodystrophy* refers to alterations in bone morphology associated with CKD as assessed by histomorphometry including parameters of turnover, mineralization, and volume. It is important to recognize that this consensus group is primarily concerned with adult kidney dysfunction and with the use of bone biopsy subjected to a strict formulaic histomorphometry assessment, although some relevance to the pediatric age group is still present. Strictly speaking, renal osteodystrophy now requires a bone biopsy for definitive diagnosis and classification, including standard nomenclature and use of 3 key histologic descriptors—bone turnover, mineralization, and volume (TMV system) [80].

(c) *High-turnover and low-turnover bone lesions in renal osteodystrophy*: The use of bone biopsy techniques in assessing bone structure in particular in relation to renal osteodystrophy has allowed for the distinction of 2 patterns of bone abnormality [74, 81].

(i) Histomorphometry and the assessment of high- and low-turnover disorders.

High-turnover bone lesions. Bone abnormalities are defined as high turnover when the response to high serum levels of parathyroid hormone is characterized by the simultaneous occurrence of active bone resorption and increased osteoblastic activity. The combined increase in osteoblastic synthesis and osteoclastic remodeling activity leads to the high turnover. Increased osteoclastic activity leads to bone resorption with an increase in the number and size of osteoclasts and diminished matrix. Fibrous tissue then accumulates adjacent to the bone trabeculae and within the marrow with complete fibrous replacement of individual trabeculae in severe cases. Although osteoblastic activity is increased, there is inability to mineralize the matrix leading to persistence of disordered osteoid and accumulations of fibrous tissue. These histologic findings are incorporated under the term osteitis fibrosa.

Low-turnover bone lesions. The histologic hallmark of low-turnover bone disease is osteomalacia. This refers simply to the presence of excess unmineralized osteoid

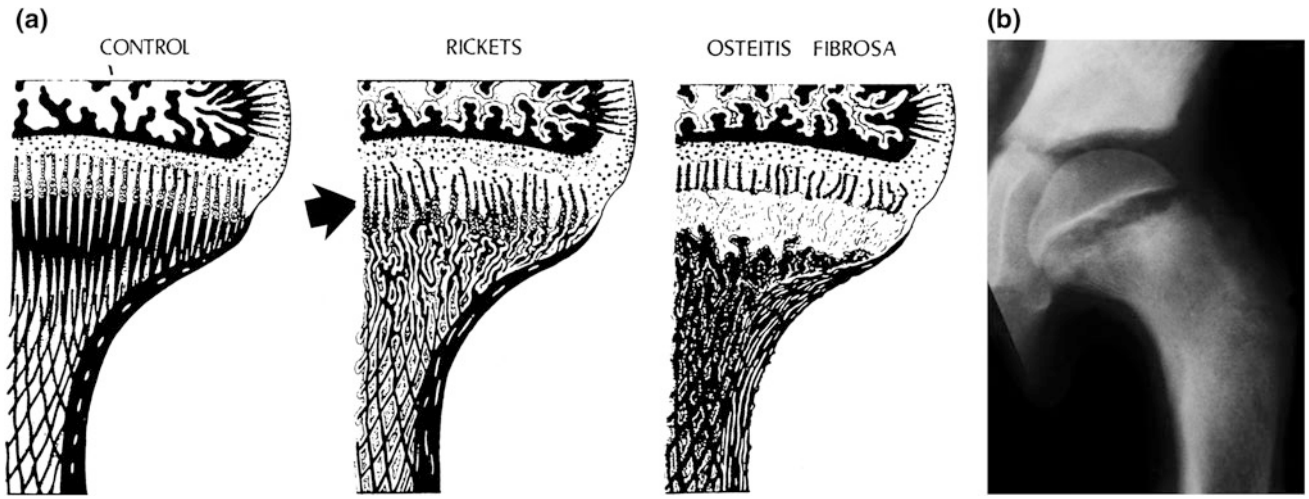

Fig. 4.6 **a** Illustrations from the work of Mehls et al. [87] show the physeal and metaphyseal changes in a child with rickets due to vitamin D deficiency (*central*) and renal osteodystrophy (*right*). The proliferating and hypertrophic regions of the physis are widened in vitamin D deficient rickets (*straight arrow*) while the additional characteristic histologic finding in renal osteodystrophy is resorption of the lower regions of the physeal cartilage and their replacement with fibrous tissue and poorly organized and mineralized woven bone. (Reprinted with permission from Mehls et al. Renal osteodystrophy in uremic children. Clin Endocrin Metab. 1980:9:151–176. Copyright 1980 Elsevier). **b** Characteristic radiograph shows bone changes in renal osteodystrophy with widened physis of proximal femur

which accumulates in bone owing to defective mineralization. The osteoid seams on trabecular bone within the marrow and cortex are thickened. When osteomalacia predominates, osteoblastic activity is markedly reduced. With continuation of a low-turnover state there are normal or reduced amounts of osteoid synthesized, no tissue fibrosis, diminished numbers of both osteoblasts and osteoclasts and little to no evidence of bone formation.

The TMV classification system for bone histomorphometry categorizes bone turnover (T) as low, normal, or high; mineralization (M) as normal or abnormal; and volume (V) as low, normal, or high. Assessments are done on iliac crest core bone biopsy samples processed by light microscopy. Double-tetracycline labeling is performed prebiopsy to assess bone formation rates. Mineralization is determined by the extent of osteoid volume and mineralization lag time and osteoid maturation time. Volume refers to the amount of bone per unit volume of tissue. It is determined by histomorphometry by measuring the amount of cancellous bone per unit area. The data can be represented well graphically by plotting three axes for the three descriptors and locating bars at appropriate sites.

(ii) Biomarkers for assessing mineral abnormalities in renal osteodystrophy (or chronic kidney disease). Serum PTH (parathyroid hormone) levels remain the best clinical indicator of bone turnover. Assays measuring 1–84 PTH peptide should become the standard. Ionized calcium is preferred in evaluating serum calcium. Serum total alkaline phosphatase is helpful in assessing bone turnover. Serum biomarkers such as osteocalcin and procollagen type 1 amino-terminal extension peptides are valuable markers of bone turnover in general but they have kidney-dependent elimination which, with kidney disease, makes interpretation difficult.

(d) *Bone Deformities in Childhood Renal Osteodystrophy: Angular Deformity, Slipped Epiphyses, Osteonecrosis*: Three major groups of orthopedic problems occur in the childhood end-stage group with renal failure: characteristic angular deformities, slipped epiphyses, and osteonecrosis. The most common bone deformities involve a genu valgum or genu varum which are due primarily to metaphyseal deformity either in the distal femur or the proximal tibia or both. Angular metaphyseal deformities about the knee predominate, the direction of which appears dependent on the age at which the renal abnormality occurs. In those under two and half years of age where physiologic bowing normally predominates metaphyseal distal femoral and proximal tibial varus worsen, whereas with disease worsening after this time the normal valgus increases to a pathologic range. Salusky has estimated that even with intensive vitamin D management of renal osteodystrophy, 20–25 % of pediatric patients undergoing long-term dialysis require orthopedic procedures for deformities [74].

Mehls has indicated that the majority of children who present with chronic renal failure are above 10 years of

age [73]. The most common deformity is genu valgum. In a study by Davids et al. 11 of 12 patients with apparent genu valgum had tibiofemoral angles >15° [82]. As well as assessing the tibiofemoral diaphyseal angle, they established measurements for a femoral alignment angle and a tibial alignment angle. In patients with chronic renal failure and renal osteodystrophy, the nature of the lower extremity angular deformity is related to the age at onset of renal failure. Those <3 years of age would tend to worsen the physiologic varus alignment while those occurring after that age would worsen the valgus position. In their series, all patients with genu valgum were >4 years of age at the onset of chronic renal failure. Oppenheim et al. identified 8 patients with significant valgus angulation of the proximal tibia which they felt was physeal in origin [83]. They likened the radiographic changes to those seen in tibia vara with Blount's disease. Eleven of their 27 patients with renal osteodystrophy were treated for genu valgum.

Apel et al. studied a pediatric renal transplant population in terms of skeletal abnormalities [77]. They analyzed 130 patients who had undergone renal transplantation and thus had end-stage renal failure or renal osteodystrophy. Osteonecrosis was seen in femoral head (6), lateral femoral condyle (1), and talus (3). All cases occurred after transplantation. Slipped epiphyses were seen at the proximal humeral epiphysis, distal radial epiphysis, proximal femoral capital epiphysis, and distal femoral epiphysis. The most common deformities were genu valgum, with other deformities being ankle valgus, coxa vara, genu varum, and ankle varus [77]. Scoliosis was seen in 5 patients. The distal radial epiphyses slipped at an average age of 6.6 years, proximal humeral at 9 years, proximal femoral at 10 years, and distal femoral at 11.75 years. The coxa vara deformities were noted at an average age of 3.1 years, genu varum at 4 years, genu valgum at 11.6 years, ankle varus at 1.75 years, and ankle valgus at 8.2 years.

Barrett and Papadimitriou reviewed skeletal disorders in children with renal failure all of whom had biochemical and radiologic evidence of renal osteodystrophy [78]. They reported on 16 patients out of 124 children with renal failure referred for management of skeletal problems. The nature and distribution of problems were similar to other reports. The most common deformity was genu valgum occurring in 11 of 16 children. Slipped capital femoral epiphysis was seen in 6 with all cases bilateral and all associated with genu valgum. Ankle valgus was seen in 4. The genu valgum was due to instability at the physis and bending of the metaphyseal regions. Other isolated deformities involved osteonecrosis of the distal femoral lateral condyle, osteochondritis dissecans, and progressive bowing of the femurs and tibias. Characteristic bone changes in renal osteodystrophy are illustrated in Fig. 4.6b.

(e) *Pathogenesis of bone deformities in renal osteodystrophy*:

Slipped Epiphyses: Epiphyseal slipping is the commonest and most severe of the orthopedic sequelae of a childhood renal osteodystrophy. Brailsford described the influence of renal rickets on the slipping of the proximal epiphysis of the femur in 1933 [84]. He described in detail two cases showing that the deformity was due to slipping of the epiphysis of the head of the femur rather than due to bowing of the proximal end of the femur. This correlation was substantiated by Mehls et al. who noted slipped epiphysis in 11 out of 112 children with renal osteodystrophy [85]. Their histologic studies, along with those of Krempien et al. [86], showed that epiphyseal displacement was not due to traumatic physeal or metaphyseal fractures. The mechanism appears to be somewhat different than that which occurs in idiopathic slipped capital femoral epiphysis. The slipped epiphyses in children with renal failure are a consequence of the general metabolic bone disease. Work by Mehls and colleagues has demonstrated that the slippage is secondary to physeal thickening and to associated osteitis fibrosa of the adjacent metaphysis [87]. In children with uremia, the normal transformation of calcified cartilage at the lower margins of the endochondral sequence into metaphyseal bone is irregular. There is undermineralization of the hypertrophic cartilage and thus a thickening of a cartilage layer of the growth plate. The metaphyseal bone too is abnormal since the undifferentiated and newly differentiated osteoblast and its osteoid matrix suffer from a defect of mineralization. There is a tendency for dense fibrous tissue to be interposed between the growth cartilage and the adjacent metaphysis. This is structurally weaker than the normal tissues and provides a plane of cleavage for slipping of epiphyses. The vast majority of slipped epiphyses in renal osteodystrophy are not associated with trauma, have little pain, and appear to be transphyseal entities and not metaphyseal fractures. Nixon and Douglas described two cases of bilateral slipping of the upper femoral epiphysis in end-stage renal failure [88]. Severe secondary hyperparathyroidism was present. Internal fixation was performed along with medical therapy with a good response. Shea and Mankin in 1966 reviewed 8 cases of slipped capital femoral epiphysis in renal rickets from the literature and described 3 of their own [89].

Each of their 3 cases was symptomatic, bilateral, and in females at 10, 12, and 13 years of age. Surgical stabilization was not done at that time but they noted no progression with conservative partial or nonweight bearing orthopedic treatment while medical/surgical renal treatment proceeded. Floman et al. reported bilateral slipped upper femoral epiphysis in an 18-year-old male with renal osteodystrophy [90]. Successful bone fusion occurred without additional slippage without orthopedic intervention following treatment with subtotal parathyroidectomy, chronic hemodialysis, and renal transplantation. Hartjen and Koman successfully treated a 3-year-old with severe bilateral slipped proximal femoral capital epiphysis using traction followed by stabilization with a specially fabricated screw without threads to minimize physeal damage [91].

Many epiphyses can be the site of slipping in renal osteodystrophy. The slipping which is virtually pain free occurs commonly at the proximal femur and renal osteodystrophy must be included in the differential diagnosis of slipped capital femoral epiphysis in particular where the patient is <10 years of age. Of importance, however, is the fact that other epiphyses may also slip in renal osteodystrophy, for example, those of the proximal humerus, distal femur, proximal tibia, and distal tibia [92]. When nontraumatic slipping occurs at any epiphysis other than the proximal femur, the finding is essentially pathognomonic for renal osteodystrophy. Other than an isolated report of slipped bilateral distal femoral epiphyses in scurvy, no other disorder has been implicated. The sites of epiphyseal slipping are age related. Before the age of 5 or 6 years, slipping can be seen in both the upper and lower femoral epiphyses and in the distal tibial epiphyses. In older children, the upper femoral epiphyses and the distal epiphyses of the radius and ulna are involved primarily. During and after puberty, slipping is seen frequently in the distal forearm bone epiphyses. Where there is extremely severe osteitis fibrosa epiphyseal slipping can occur irrespective of age in nearly all epiphyses. The slippage which occurs at the distal radial and ulnar epiphyses tends to be in a dorsolateral direction.

Great caution must be exercised deciding whether or not to perform surgical correction of slipped epiphyses. Extremely poor results have been noted when surgical correction has been undertaken before the metabolic bone disease has been cured or at least controlled. Although early intervention might be required on occasion for proximal femoral slippages even here the extreme youth of the children and the marked osteopenia of the bone may preclude effective pinning. It is essential that appropriate treatment of the metabolic bone disease occur prior to any orthopedic correction in particular where osteotomy is projected. Immobilization also should be minimized because of the worsening of any osteoporosis. Swierstra et al. noted good results in 3 distal femoral slippages in young children using long leg casts followed by orthoses in conjunction with medical management [93].

Metaphyseal Fractures: Osteomalacia with poorly oriented metaphyseal trabeculae leads to considerable weakening of the metaphyseal regions of the long bones. If the condition persists and the child remains active, there can be gradual deformity mediated through the metaphyseal bone region. In other instances, fracture can occur in these metaphyseal areas. It is extremely important to identify whether deformity in the region of the end of the long bone in renal osteodystrophy is due to slippage of the epiphyses or to acute or chronic bending through the adjacent metaphyseal region.

Osteitis Fibrosa: Mehls and colleagues have reviewed the specific differences in the physeal and periphyseal regions in renal osteodystrophy as compared with nutritional and vitamin D-resistant hypophosphatemic rickets [73, 87]. In early and middle stages of renal osteodystrophy, the zone of growth cartilage tends not to be increased in height but rather normal or even decreased. The early provisional calcification of the cartilage matrix is not defective. The abnormality is in the transition zone between the growth cartilage and the metaphysis which is highly abnormal in the sense that vascular invasion is virtually absent. There is a tendency for the chondro-osteoid trabecular regions to be resorbed by increased chondroclastic and osteoclastic activity. Growth cartilage is physically separated from the metaphyseal bone by a zone of fibrous tissue in advanced stages and often woven bone forms within this tissue rather than forming on calcified cartilage trabeculae. Radiographically it may be difficult if not impossible to distinguish rachitic changes with thickened growth plate cartilage and osteitis fibrosa of the growth zones as both would be radiolucent. Woven bone rather than lamellar bone characterizes the osteitis fibrosa condition. Endosteal fibrosis is also seen. In high-turnover states, the histologic response is fibro-osteoclastic while in low-turnover states osteoporosis/osteomalacia predominates.

Growth Retardation: Renal osteodystrophy is also associated with severe growth retardation. Bone age is noted to lag behind chronologic age relatively early in the course of progressive renal disease. Linear growth unfortunately remains impaired even with renal replacement therapies involving either hemodialysis or peritoneal dialysis.

There are significant relationships between growth hormone and bone and mineral metabolism with effects occurring on both the endochondral and intramembranous bone formation mechanisms. Mehls has noted specific changes in growth plate cartilage due to severe secondary

hyperparathyroidism in children with chronic renal failure [73]. Growth plate involvement in patients with osteitis fibrosa can lead to slipped epiphysis, bone deformities, and impaired linear growth. The expression of the receptor for PTH and PTH-related peptide (PTHrP) and the production of PTHrP itself plays a critical role in normal endochondral bone development. Deletion of the PTHrP gene in mice leads to early death and marked abnormalities of skeletal development. The growth plates are shortened and calcification of epiphyseal cartilage occurs prematurely. In addition, there is generalized overmineralization of the skeleton. Although serum growth hormone tends to be normal in chronic renal disease tissue response to growth hormone is often diminished. These appear to relate to changes in receptor expression and in postreceptor events. Growth hormone actions are mediated through insulin-like growth factor 1 (IGF-1). Various IGF binding proteins provide an additional mechanism by which tissue specific actions of GH can be altered. Growth hormone acts directly on bone and on growth plate cartilage and is thus critical for postnatal skeletal growth and the induction of the endochondral ossification sequence. A proliferative response to growth hormone has been documented in chondrogenic cells from epiphyseal growth plate, and growth hormone is considered a major regulator of cartilage growth. One mechanism of its action is the stimulation of the synthesis of IGF-1 locally within the growth plate cartilage. The differentiation of prechondrocytes to chondrocytes is stimulated by both GH and IGF-1. In the epiphyseal cartilage, IGF-1 acts primarily in a paracrine manner to enhance chondrocyte proliferation.

Osteonecrosis: Avascular necrosis is most common in renal osteodystrophy following renal transplantation but it can occur in the absence of transplantation. The femoral heads are the most common site in children but the distal femoral condyles also have frequent involvement. Mehls et al. reported on osteonecrosis of the femoral head in 3 patients in chronic renal failure in the absence of steroid therapy or transplantation [94]. The AVN was unilateral in each case and was noted at 4, 8, and 9.5 years of age. Other studies documented osteonecrosis after renal transplantation in children. Stern and Watts noted osteonecrosis in 9 of 36 (25 %) of children following renal transplantation [95]. Each case occurred in patients with skeletal age >10 years. There were no cases younger than this. Many patients had more than one site involved. AVN in 9 patients was in the femoral condyle (all bilateral), in 5 patients it involved the femoral head (bilateral in 4), in 4 patients it occurred in the talus (bilateral in 3), in 2 in the humeral head (bilateral in 1), and in 1 in both patellae. There was no correlation between the total dose of steroid and the development of osteonecrosis. On the other hand, the number of rejection phenomena correlated well with the development of osteonecrosis in that all patients in whom it occurred had at least one rejection episode while in 9 patients who had no rejection episodes there were no instances of osteonecrosis. There were, however, 15 patients with one or more rejection episodes who did not develop the osteonecrosis. Uittenbogaart et al. also noted avascular necrosis in 11 of 171 (6 %) recipients of renal allografts [96]. They also noted no statistically significant difference in the total steroid dose received during the first posttransplant year between patients where necrosis developed and those in whom it did not. The sites involved were similar to other studies with frequent multiple bone involvement. The main sites of involvement were the femoral heads, the distal femoral condyles, and the talus.

(f) *Orthopedic Treatment*: Control of the metabolic defect, by which is meant secondary hyperparathyroidism, should be optimal prior to any operative orthopedic treatment [74, 97]. Crucial to a good result following any orthopedic intervention is appropriate assessment and control of the metabolic status in the perioperative period. Surgical complications can often be found to be due to metabolic instability. Assessment can include bone biopsy as well as radiographic and biochemical studies. The aim of therapy is to control the secondary hyperparathyroidism with effective vitamin D management, restrict dietary phosphate, and minimize accumulation of toxic substances such as aluminum. Stabilization of the patient's metabolic profile can include dialysis, phosphate treatments, vitamin D replacement, correction of secondary hyperparathyroidism and chelation therapy for aluminum intoxication.

Oppenheim et al. indicated that when the secondary hyperparathyroidism was well controlled orthopedic surgical procedures became much more feasible in renal osteodystrophy [97]. A review of 24 patients with renal osteodystrophy who had undergone 41 orthopedic operations over a 6-year period indicated good results. There were no significant postoperative wound infections and all osteotomies healed within an appropriate time. Surgical procedures included pinning for slipped capital femoral epiphysis. Genu valgum or other angular deformities did not resolve once the secondary hyperparathyroidism had been controlled. None of nine patients demonstrated spontaneous improvement at the distal femur or proximal tibia although no details of age, severity of uremic involvement or degree of deformity were given. Osteotomy was performed at either distal femur or proximal tibia with good healing. Total joint arthroplasty has often been needed early in adult life for the sequelae of proximal and distal femoral osteonecrosis.

4.2 Inflammatory Disorders

4.2.1 Juvenile Rheumatoid Arthritis

4.2.1.1 Disease Profile

Juvenile rheumatoid arthritis (JRA) is an inflammatory disorder characterized by synovitis which can involve either one joint alone or two or more joints simultaneously or at different times [98, 99, 100–102]. Still defined the syndrome in children initially in an article in 1897 describing 22 patients, 19 under his own personal observation. The article "On a form of chronic joint disease in children" concluded that the disorder "occurring in children, and beginning before the second dentition, is characterized clinically by elastic fusiform enlargement of joints without bony change, and also by enlargement of glands and spleen" [103]. Since arthritis in children is both relatively common and clinically obvious, there were many references to it throughout the final decades of the nineteenth century in European centers [104, 105]. Cornil (a French pathologist) described well in 1864 chronic childhood arthritis in a 29-year old whose disease began at age 12 years [106]. The most severe variant is referred to as Still's disease, a multijoint synovitis associated with systemic symptoms involving pericarditis, lymphadenopathy, splenomegaly, and transient rash [98, 99, 102]. The most commonly affected joints in the child differ from the adult and involve knee, subtalar joint of the foot, and hip. The etiology of childhood rheumatoid arthritis remains obscure. Many of the better known rheumatoid inflammatory indices also remain normal in children for several months to years, even in the face of acute synovial involvement. The erythrocyte sedimentation rate is invariably elevated but other indices such as the rheumatoid factor, the C-reactive protein, and the ASLO titers can be normal. Swann has indicated that rheumatoid factor positive (seropositive) patients tend to show continuing synovitis while periarticular contracture is greater in seronegative patients [107]. Approximately 50 % of patients undergoing surgical intervention for JRA during the growth years were seropositive. The disorder would appear to include several distinct processes. Recognizable subgroups include: (1) systemic onset disease (20 %); (2) rheumatoid factor negative polyarthritis (25 %); (3) rheumatoid factor positive polyarthritis (5 %); (4) pauciarthritis associated with antinuclear antibodies and chronic iridocyclitis (30–35 %); and (5) pauciarthritis associated with sacroiliitis and HLA-B27 (10–15 %) [102]. Monoarticular arthritis refers to involvement of one joint only, pauciarticular to <5 joints, and polyarticular to 5 or more joints. Some refer to pauciarticular disease as oligoarthritis. Monoarticular onset occurs in approximately one-third of patients with most subsequently developing additional joint involvement a few months to years later. The monoarticular incidence in separate studies was 31, 32, and 39 % [101, 108, 109]. The American Rheumatologic Association defines objective arthritis in one or more joints for 6 consecutive weeks plus exclusion of other inflammatory disorders as diagnostic for JRA.

4.2.1.2 Classifications of Childhood Arthritis

Classification has been difficult although there is recognition that chronic childhood arthritis includes a heterogenous group of diseases. Classifications have been developed by several groups. The descriptive terms include: juvenile rheumatoid arthritis (JRA), commonly used in North America with criteria defined by the American College of Rheumatology (ACR); juvenile chronic arthritis (JCA), used by the European League Against Rheumatism (EULAR); and juvenile idiopathic arthritis (JIA) based on work of the International League of Associations for Rheumatology (ILAR). These have been well reviewed and summarized by Cassidy and Petty [100]. The important matters for the practitioner are not so much to classify as to make certain that (i) each joint is assessed, (ii) other systems of the body are examined for involvement, and (iii) appropriate laboratory tests are done. For the most part the diagnostic, criteria are similar across all classifications. Since the underlying etiology is not known and would appear to be variable (several causes) classification has come to rely upon patterns of joint and other system involvements.

For the diagnosis to be made the following criteria are needed. 1. Age of onset <16 years. 2. Duration of disease 6 weeks or longer (3 months for EULAR group). 3. Arthritis in 1 or more joints with joint involvement comprising swelling or effusion and two or more of: limitation of range of motion, tenderness or pain on motion, and increased heat on palpation. 4. Onset pattern type defined as systemic (with fever), oligoarthritis/pauciarticular disease (with fewer than 5 inflamed joints), or polyarthritis (with 5 or more inflamed joints). 5. Extended pattern type also includes: polyarthritis (rheumatoid factor +) or polyarthritis (rheumatoid factor −) (EULAR, ILAR); juvenile psoriatic arthritis (EULAR, ILAR); juvenile ankylosing spondylitis (EULAR, ILAR); inflammatory bowel disease (EULAR, ILAR); and enthesis-related arthritis (ILAR). [Entheses are sites of ligament and tendon attachments to bone and enthesitis is inflammation at these sites.] 6. Exclusion of any juvenile arthritis disorder for which the primary etiology is known [110].

In cases of suspected or diagnosed JRA, the following need to be particularly assessed: fever for at least 2 weeks, generalized lymphadenopathy, hepatomegaly or splenomegaly, serositis, skin findings of either evanescent, nonfixed erythematous rash or psoriasis (either in patient or strong family history), uveitis, spondylarthropathy, sacroliac joint tenderness, inflammatory bowel disease, dactylitis

(inflammation of fingers or toes), and nail abnormalities. Important laboratory tests include rheumatoid factor (either +, seropositive or −, seronegative), antinuclear antibody (ANA) (+ significant), and presence of HLAB27.

4.2.1.3 Pathobiology of Rheumatoid Arthritis

The disorder begins with a synovitis which is usually associated with an increase in joint fluid (synovial effusion) [111]. The swelling and discomfort associated with this generally lead to flexion contractures, muscle atrophy, and with time, increased periarticular fibrosis. Tendons around the joints can be involved with adhesions. Synovial involvement when long lasting can be followed by synovial fibrosis. The epiphyses themselves are affected secondarily. If the inflammatory process lasts for several weeks or more and is not responsive to treatment, the first plain radiologic change is an osteopenia of the secondary ossification center and adjacent metaphyseal regions. With time, there is a creepage of synovial tissue across the articular surface which leads to a subsequent degeneration of the articular cartilage. The characteristic fibrovascular material originating from the synovium and passing onto the cartilage surface is referred to as the pannus. With time, there is degeneration of the underlying articular cartilage and narrowing of the joint space. The osteopenia of the bone can be associated with small subchondral cysts. There are no other specific radiographic findings of a juvenile rheumatoid arthritis.

Major joint problems occur with continuing effusion and synovial proliferation which in itself can be uncomfortable and can lead to contractures and muscle weakness. Treatment is designed first to quiet the inflammatory process and second to rehabilitate the joint in terms of range of motion and associated muscle strength. One of the major orthopedic sequelae of a monoarticular juvenile rheumatoid arthritis in the growing child is the effect on the epiphyseal growth rate. The characteristic responses of the joint in juvenile rheumatoid arthritis have been assessed in studies on lower extremity length discrepancies. The increased vascularity associated with the inflammatory process leads to a stimulation of growth in the affected region and increased length on that side. This is particularly marked in those who have the inflammatory disorder prior to 10 years of age. In those who are affected initially after 10 years of age, the periphyseal vascular stimulation leads to premature cessation of growth and thus shortening of the involved limb. The increased vascularity of the joint region may lead to premature appearance of the secondary ossification centers in the involved epiphyses.

The age of onset of juvenile rheumatoid arthritis is between 1.5 and 8 years age with a second group showing a peak incidence between 11 and 14 years of age. In childhood, rheumatoid arthritis eye examinations are mandatory to assess for iridocyclitis or uveitis. A classic series of criteria defined by Ansell and Bywaters for definitive diagnosis required that the child have a polyarthritis affecting more than 4 joints for a minimum period of 3 months [98, 99]. Synovial biopsy will demonstrate hyperplasia of the synovial membrane, increased vascularization, and focal collections of lymphocytes and plasma cells. There is a high frequency of knee involvement. Other joints involved but less frequently are the wrist, hand, elbow, shoulder, and cervical spine. In the severe variants of Still's disease, the cervical vertebrae may be affected showing limitation in motion and apophyseal joints that may become ankylosed.

There is a fairly high incidence of recovery in juvenile rheumatoid arthritis which differs from the adult disorder. In one large series of cases, nearly one-half of the affected children showed no residual lesions of the involved joints 5 year later. Other studies also report 50 % of patients with a complete recovery, 25 % with a mild residual disability, and 25 % with worsening. The articular lesions of JRA are basically the same as those of rheumatoid arthritis in the adult.

It became evident decades ago that a series of growth disorders could be associated with juvenile rheumatoid arthritis. These involved: (1) a generalized lack of body growth; (2) a persistence of infantile proportions; and (3) asymmetry of growth. A common problem is the occurrence of lower extremity length discrepancies due either to overgrowth in the first decade of life owing to a chronic synovitis in particular around the knee or to premature physeal closure also at the knee in the early part of the second decade [112, 113]. Both occurrences are due presumably to increased periphyseal vascularity.

Bywaters reported on the pathologic aspects of juvenile chronic polyarthritis [111]. In the child, the much thicker hyaline cartilage protected the subchondral bone from erosion. Bone overgrowth of the secondary ossification center was common. In later childhood, Harris arrest lines were seen. An excellent study of abnormal ossification patterns in the distal femoral and proximal tibial epiphyses of children with longstanding JRA was performed by Sundberg and Bratstrom [114]. They assessed 63 cases ranging in age of onset from 6 months to 13 years. The most common time of onset was in the second year of life and the 3 highest years involved the ages from 2–5 years. With unilateral arthritis, they invariably found that the femoral epiphysis on the arthritic side was larger than that of the healthy side. They concluded that the difference in size of the femoral epiphyses usually appears within 1 year of the onset of the disease in some groups and within the second year in others. The enlarged size of the secondary ossification centers often amounts to 10–20 % and in isolated instances it can rise to 30 %. Differences in length were also seen. These growth

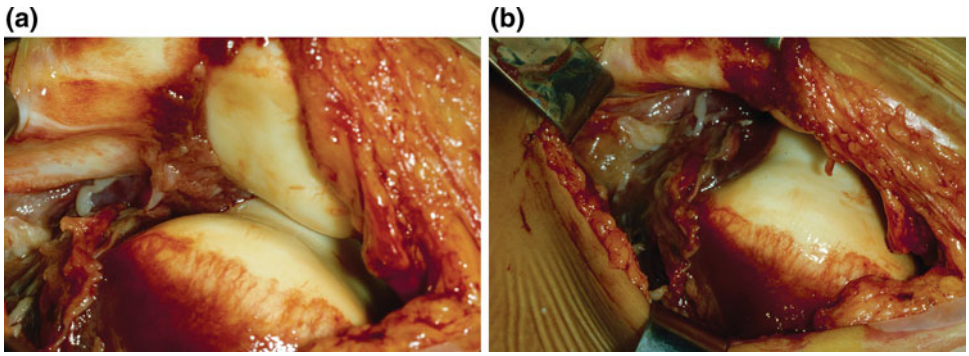

Fig. 4.7 Poorly controlled juvenile rheumatoid arthritis (JRA) can benefit from synovectomy. **a** At open operation, the distal femoral articular surface is partially seen below, the patella above and the markedly hypertrophic synovium (completely covering the tibial articular surface) at left. Note the pannus, the vascularized granulation/inflammatory tissue, passing onto the periphery of the femoral articular surface. **b** Another view of the knee at arthrotomy immediately prior to starting the synovectomy shows the distal femoral articular surface and peripheral pannus

abnormalities are magnified by the fact that the knee is the most commonly involved joint in JRA whether it be pauciarticular, monoarticular, or systemic. After the knee, the wrist is the next most commonly involved joint in JRA. It is particularly vulnerable to involvement with systemic and polyarticular onset disorders. Growth defects in this region occur in the ulna and in the fourth and fifth metacarpal bones as a result of premature epiphyseal fusion and ankylosis. The radiographic findings tend to be more marked than the clinical and only 6 % of patients in a large series showed clinical growth abnormalities. The shortened ulna can lead to ulnar deviation at the wrist, ulnar migration of the carpal bones, and subluxation. Brachydactyly can occur in the hand or foot. Bony overgrowth at the interphalangeal joints can occur. Hip growth abnormalities are the consequence of a chronic synovitis which itself can lead to diminished walking and progressive hip flexion contractures. Often the proximal femoral epiphysis becomes enlarged (coxa magna) and decreased activity is associated with a coxa valga. Only rarely does premature fusion of the proximal femoral capital epiphysis lead to a coxa vara deformity.

Initial Description of Pathoanatomy of Severe Chronic Childhood Arthritis. Cornil 1864. Cornil described a postmortem assessment of the right knee from a 29-year-old female whose symptoms began at 12 years of age and involved recurrent pain, swelling, redness, and heat leading to eventual ankylosis. She had a systemic disease and died of cardiac hypertrophy with fibrinous pericarditis [106]. The description (from JAMA, 1970) follows: the right knee was firmly ankylosed. The patella was attached to the femoral condyles by thick, fibrous tissue. The epiphysis was rarified, friable, and consisted of a thin layer of bone and an oily yellow marrow. The articular surface of the left knee showed velvet-like abnormal tissue; the swollen and fissured cartilage simulated the surface of a sponge; the cartilage had almost disappeared from the femoral condyle and was replaced with an uneven and a partially eroded bony surface. The phalangeal articulations showed less dramatic changes although the bone was denuded of cartilage, and deformations similar to those of rheumatic arthritis were present; the synovial membranes were inflamed and rough. The changes were typical of chronic articular rheumatism; pericarditis, pleurisy, and Bright's disease. It is clear that renal involvement and pericarditis were caused by the same chronic rheumatic process.

Regeneration Postsynovectomy in Animal Models. Synovectomy for various orthopedic disorders, including chronic childhood arthritis was used in the early decades of the twentieth century and detailed experimental studies in young rabbits clarified the principles of regeneration [115–117]. The intraarticular appearance of the knee in an adolescent girl undergoing open synovectomy is shown in Fig. 4.7.

4.2.1.4 Radiographic Findings

Plain radiographs remain the basic imaging tool to assess involved joints and adjacent bone. Ultrasonography can be used to assess intraarticular fluid or ganglion formation especially in the very young or around the wrist. MR imaging is best to assess intraarticular fluid, synovial inflammation, or articular cartilage degeneration.

Joint effusion and periarticular tendon sheath swelling can be seen to a certain extent on plain radiographs. Osteoporosis can be evident especially in juxtaarticular bone along with metaphyseal growth arrest lines. Persistent synovitis toward the end of skeletal growth can lead to premature growth plate fusion with actual minimization or previous long bone overgrowth. Other radiographic findings, usually with moderate to severe longstanding synovial hyperactivity, are: peripheral joint erosions of bone due to hyperemic synovium invading subchondral regions; joint space narrowing due to articular cartilage degeneration;

periosteal elevation and new bone formation along the midshafts of phalanges and metacarpals/metatarsals (dactylitis); small joint ankylosis (hands/feet); joint subluxation; cervical spine arthritis (facet joints) and atlantoaxial subluxation; lumbar spine facet joint narrowing with osteophytes; sacroiliac joint narrowing; and pathologic metaphyseal fractures and vertebral compression fractures (due to osteoporosis).

4.2.1.5 Medical Treatment and Prognosis

Aggressive medical treatment in JRA is essential with the following understandings. There is currently no cure for the disease and spontaneous remissions and exacerbations occur. The goals of treatment are to relieve pain, diminish the synovitis, maintain joint range of motion, maintain muscle strength and ambulatory status, control systemic and nonarticular components of the disorder, minimize the toxicity from medical treatments, and correct deformities due to sustained synovitis and asymmetric growth.

Medications. The first line of treatment to control synovitis is the use of nonsteroidal antiinflammatory (NSAIDs) agents. These are effective in approximately 75 % of cases. They include such agents as ibuprofen or naproxen. Other antiflammatory medications are aspirin (acetylsalicylic acid) and cox-2 inhibitors (celecoxib). Owing to the chronicity of the disorder, it is essential not to use potentially addictive analgesic medications from the opioid group which have no antiinflammatory actions.

The second line of treatment if symptoms persist is methotrexate, which works fairly well although its mechanism of action is unclear. This is sometimes referred to in the rheumatology literature as being in a DMARD group-disease-modifying antirheumatic drug.

The third line medications are glucocorticoids either orally with prednisone or intraarticular for large target joints not responding well to the previous medications.

The next approaches, relatively commonly used and under active investigation, are biologics (genetically engineered medications to control the immune response). Most commonly used are agents that inhibit tumor necrosis factor (TNF blockers). TNF is made by white blood cells and promotes inflammation associated with joint damage. The 3 main agents in this category are etanercept (Enbrel), adalimumab (Humira), and infliximab (Remicade). These agents must be used cautiously since in the process of limiting inflammation they increase susceptibility to infection.

If even these are not effective increasingly wide arrays of newer and older medications are used such as intravenous immunoglobulins (IVIG), various immunosuppressive drugs such as rituximab (Rituxin), other agents from the above-mentioned groups or combinations of drugs.

Prognosis. An outline of prognosis is developing based on a large number of long-term studies although it is not possible to be certain of outcome for any particular patient especially in the early months of the disorder. It appears that 60 % of patients have a satisfactory outcome without serious disability reaching adulthood with nonactive synovitis or functional limitation. Approximately 10–25 % enter adulthood with moderate to severe functional difficulties while 5 % or more develop recurrence as adults.

More accurate prognosis of outcome can be determined from the pattern of involvement and some of the laboratory indices. The poorest outcomes are seen with polyarthritis patients who are RF seropositive (especially older females with wrist and hand involvement); oligoarthritis patients also RF seropositive; and systemic patients with polyarthritis. Good outcomes are seen with polyarthritis patients who are seronegative whether or not they are ANA-positive, and oligoarthritis patients who are HLAB27 postive (older males) or who have systemic disease. Excellent outcomes are generally to be expected in those with oligoarthritis who are RF seronegative and those who are ANA seropositive (female, young).

Packham and Hall have written an excellent detailed study of 246 adults with juvenile idiopathic arthritis followed into adulthood [118]. Their paper reviews 15 previous long-term studies from 1966, 1976, and most from the 1981–2000 time period. Long-term studies following patients into adulthood show that 30–56 % patients have severe functional limitation. This refers to patients with 10–15+ years followup. When the same cohort of aggressively treated patients (in childhood/adolescense) are followed function initially improves but then deteriorated between 10 and 20 years. Another study found 12 % of patients in the poorer functional classes at 3–7 years from onset but 48 % so graded at more than 16 years followup. Social functioning, continuing pain, and depression are also increased in the adult years. Zak and Pederson reviewed 65 patients with an average 26 years of disease. Active disease remained in 37, 11 % had severe disability, and 22 % had already had major joint surgery [119]. The study by Packham and Hall had a very large cohort of patients (246) which represented 95 % participation. The mean age at disease onset was 7.1 years (0.8–15.9); mean age at long-term assessment 35.4 years (19–78); and mean disease duration was 28.3 years (8–73). Patients in the oligoarticular subset were younger at disease onset as were the polyarticular (rheumatoid factor negative) with age greater in polyarticular (rheumatoid factor positive) enthesopathy-related and psoriatic JIA subsets. The mean male and female heights were shorter than those of the general population. Use of oral steroids was associated with lower range heights. Micrognathia and long-term temporomandibular (TMJ) joint damage was seen in 40 %. Oligoarticular and enthesitis-related JIA had relatively few functional problems. Systemic JIA and seronegative polyarticular JIA were related to poor functional outcome.

Eye problems. Uveitis had affected 22 % at some time in disease course with higher levels in oligoarticular groups and lower levels in systemic and rheumatoid factor positive polyarticular groups. Glaucoma was relatively uncommon (only 4 %) and only occurred in those with uveitis. Cataracts (most requiring surgery) were seen in 10 %. Amyloidosis was seen in 8.9 %, primarily in those with systemic disease. An association with chlorambucil treatment was found.

Treatment medicines. All had used NSAIDs at some stage of their illness and 72 % were still using it in the long-term assessments. Of the patients 74 % had at some time received disease-modifying antirheumatic drugs (DMARDs), and 36 % were still taking them. These included methotrexate, gold, penicillamine, chloroquine, and sulfasalazine (amongst others). With oral steroids, 59 % had taken them with 24 % still taking them.

Orthopedic surgery. One major prosthetic joint replacement had already been done in 51 %. Total hip and total knee replacements accounted for almost all the procedures with shoulder 5 %, elbow 3 %, wrist, and ankle done infrequently. Patients in oligoarticular status needed joint replacement much less frequently. The subgroups with the worse prognosis regarding function were systemic and rheumatoid factor positive polyarthritis. Progression to polyarticular disease occurred in 80 % of oligoarticular patients.

In most, the synovitis appears not to "burn out" in adulthood; continuing disease activity is 50 % + in adults with JIA/JRA. The authors concluded that "adults with JIA often have significant levels of disability, usually related to severe continuing active disease over a prolonged period. There is a clear requirement for good transition from pediatric/adolescent to adult rheumatology and high-quality ongoing care."

4.2.1.6 Surgery in Juvenile Rheumatoid Arthritis

Surgery has been used in an effort to control the synovitis where medical treatment has failed, to correct angular deformities and to equalize limb-length discrepancies. In a rough estimate provided by a large rheumatology unit in Great Britain, approximately 10 % of their JRA patients had open surgical procedures [107]. Surgical rehabilitation in these patients is difficult because of the intraarticular synovitis, periarticular fibrosis, osteopenia, and muscle weakness.

After medical regimens involving rest, physical therapy, splinting, pain medication, and antiinflammatory medication have either failed or reached a plateau, surgical measures may be needed. Swann and colleagues strongly stress the value of soft tissue releases including tenotomy to address joint contractures as the initial surgical treatment. These include soft tissue release procedures at hips, knees, and other sites. At the hip, adductor and psoas tenotomies are performed. Much of the benefit appears to derive from decreasing the intraarticular pressure and diminishing pain. If there has been angular deformity osteotomy may be required. Osteotomy requires more prolonged immobilization postsurgery and is made more difficult by the invariable presence of osteoporosis in particular in a disorder sufficiently marked to lead to the deformity requiring the surgical intervention. Synovectomy is resorted to relatively infrequently in children in comparison to its more extensive use in adult rheumatoid disease. The exception in the opinion of Swann is pauciarticular arthritis. In pauciarticular arthritis, the knee is frequently affected and tends to remain chronically active with warm, thickened synovium, and excess fluid. This is an indication for synovectomy and has been found advantageous in a number of cases. Hip and knee destruction is occasionally so severe that total joint arthroplasty is resorted to in early adulthood [120]. Parvizi et al. reported on 25 consecutive total knee arthroplasties in 13 patients (mean age 17 years) with severe early-joint destruction. At an average followup of 10 years they concluded that "despite a substantial number of postoperative complications, total knee arthoplasty provides relief of pain and improvement of function in this group of adolescent patients with juvenile rheumatoid arthritis."

4.2.1.7 Skeletal Abnormalities

(a) *Valgus Deformity at Knee*: A common skeletal growth manifestation at the knee is a valgus deformity. This can be present during the first decade. An early report of treatment of valgus deformity of the knee in juvenile rheumatoid arthritis by asymmetric stapling was by Laine and Mikkelsen [121]. They performed medial distal femoral stapling in 10 patients to treat valgus deformities between 10º and 25º. The affected leg was also longer so that limb-length discrepancy was also treated. The staples were left in until physiologic position was obtained either before or at skeletal maturity. If there was growth remaining, it appears that the staples were removed. In each instance except one correction into the physiologic range was achieved and no varus overcorrection was noted. Not all patients were followed to skeletal maturity but the report indicated that asymmetric stapling was a relatively simple way to correct for angular deformity without resort to osteotomy. Rydholm et al. also noted that the valgus deformity can be progressive requiring stapling of the physes in asymmetric fashion for correction [122]. Their series reported on stapling for lower extremity length discrepancy and for valgus deformity. Seven patients underwent stapling for bilateral knee valgus deformity in polyarticular disease and 3 had the stapling for unilateral valgus deformity

(2 polyarticular and 1 monarticular). In all, 17 stapling procedures were performed for valgus angulation: stapling of the medial distal femur, 10; medial proximal tibia, 6; and both distal medial femur and proximal medial tibia, 1. The average age at surgery was 10.9 years (range 5°–16 years); the preoperative valgus deformity was 18.9º (range 10°–35º); the postoperative result was correction to 4.7º (0°–20º). Two or three Blount staples per side were used. When angular deformity is seen in the rheumatoid knee, it is almost invariably valgus. On occasion, there is an associated flexion contracture, although most of this is attributed to soft tissue involvement posteriorly rather than to physeal growth asymmetry. The valgus is attributed to some variable form of abnormal or asymmetric vascular stimulation. Brattstrom concluded that hyperemia in the femoral condyle is more pronounced medially than laterally because of asymmetry of the vascular supply [123]. Other theories have involved accelerated metabolism with increased local temperature and oxygen tension; changes in regional blood flow following elevation of the intraarticular pressure; and hyperemia in the joint capsule and the femoral metaphysis.

(b) *Hip Joint Involvement*: The frequency of hip involvement in JRA is approximately 20 %. Hip involvement with JRA can also lead to abnormal growth phenomena. Kobayakawa et al. pointed out the occurrence of femoral head necrosis in JRA and the fact that its extent has been previously underappreciated [124]. The early radiographic findings involve osteopenia and growth disturbance of the femoral capital epiphysis with the trochanter continuing to grow and later findings showing premature closure of the proximal femoral capital epiphysis. A coxa valga deformation of the proximal femur with lateral subluxation and necrosis of the femoral head may also occur. This has been reported previously but generally in association with steroid therapy. They found "obvious radiographic signs of necrosis of the femoral head…in 10 hips in 6 children with a mean age of 3 (1–6) years at the onset of the disease." There were suspicious signs by radiography in 20 hips in 13 children and no radiographic signs of necrosis in 42 hips in 23 children. The mean age at the onset of hip pain was 3, 6, and 9 years, respectively. All of the children with necrosis had been on long-term (>3 months) treatment with corticosteroids, although 8 of 11 and 10 of 18 in the other two groups also had been treated with steroids. In addition to the known growth disturbances of the proximal femoral capital epiphysis and acetabulum which are lateral subluxation of the femoral head, subchondral erosions, joint space narrowing, and acetabular protrusion, this group adds necrosis of the secondary ossification center to the list of sequelae. The changes were similar to those observed in Legg–Perthes disease. Synovial effusion with increase in intracapsular blood pressure might compromise the blood supply by a tamponade mechanism. Hip traction might contribute to the increased intraarticular pressure when, in the presence of a synovitis, the hip was placed in the less desirable extended and internally rotated position. Flexion and external rotation are known to decrease the intracapsular pressure.

Longstanding changes in the hip in persisting JRA were also seen, however, in a second study of 36 children with no significant steroid therapy by Blane et al. [125]. Sixty-eight patients with hip involvement in JRA were followed for at least 2 years. Approximately 50 % (36/68) showed bone and cartilage changes at the hips. They defined changes as primary and secondary, the primary disorders being due to inflammatory destruction of the hip with erosive arthritis and progressive joint space narrowing. The adaptive developmental changes included changes in position from mild valgus to subluxation to dislocation; flattening of the femoral capital epiphysis with wedging of the medial portion and squaring of the lateral portion; acetabular dysplasia; and secondary osteoarthritic changes involving acetabular sclerosis and femoral pseudocyst formation, joint space narrowing, and osteophyte formation.

Patriquin et al. noted the similar long-term radiographic changes of the hip in JRA in a smaller series [126]. They felt that the changes were due to persisting synovitis of the hip joint leading to ischemia of the femoral head secondary to joint distention by both fluid and synovial tissue. Changes noted included coxa magna, a short femoral neck, subluxation of the head combined with cyst-like erosions of the femur and acetabulum, a widened femoral head in the absence of steroid therapy, and joint space narrowing due to destruction of the articular cartilage.

(c) *Joint Contractures*: With severe and frequent joint involvement with poor response to medical management, there is a tendency for the patient to remain nonambulatory for extended periods of time. Joints assume the most comfortable position, invariably in flexion, and persistent contractures can develop. The commonest patterns are knee flexion contractures which can progress to associated posterior subluxation of the tibia and flexion-adduction contractures of the hip.

(d) *Lower extremity length discrepancies*: A retrospective study of patients with the monoarticular and pauciarticular forms of juvenile rheumatoid arthritis has assessed discrepancies in the lengths of the lower limbs [112]. The study included 100 patients with a diagnosis of

juvenile rheumatoid arthritis who were referred to the Growth Study Clinic at the Children's Hospital, Boston. Patients were referred when a limb-length discrepancy had been detected by physical examination. Patients with widely disseminated rheumatoid arthritis were generally not referred. The sex distribution, age at onset of disease, joints involved, incidence of monoarticular and pauciarticular disease, disease activity, and treatment were recorded. The extent of limb-length discrepancies was related to the time of onset of the disease and the course of the discrepancy.

Three groups were considered: Group I, 36 patients who had been followed until skeletal maturity; Group II, 15 patients who had been followed for 4 years or more but had not reached skeletal maturity; and Group III, 49 patients who were followed for <4 years. Many patients in the third group had been referred for a single evaluation, but their records were used to supplement information.

Disease Profile. There were 77 girls and 23 boys. In Groups I and II, the female-to-male ratio was 42–9 (4.7/1), which corresponds well with the predominant female-to-male ratio in monoarticular and pauciarticular arthritis. Seventy-two per cent of the patients in the entire series and 80 % of the patients in Groups I and II had onset of the arthritis when they were <5 years old, as reported in previous series for more severe forms of juvenile rheumatoid arthritis. An additional 4 % had the onset of the disease between the ages of 5 and 9 years.

Involvement was monoarticular slightly more often than it was pauciarticular both in the entire series and in Groups I and II (a ratio of 1.7–1). Ninety per cent of the patients had early involvement of the knee. While this represents a higher incidence than usually recorded, patients usually were referred to the clinic after a discrepancy in limb lengths had been identified, a finding which is most common in patients who had involvement of the knee.

In patients with bilateral disease, one limb generally was much more seriously involved than the other. The knee was involved in 84 of the 100 patients, 65 unilaterally and 19 bilaterally. The ankle was involved in 24 patients, 19 unilaterally and 5 bilaterally. The hip was involved unilaterally in 6 patients and the subtalar joint (foot) unilaterally in 4. For Groups I and II, the analogous figures were: knee involvement in 48 patients, 43 unilateral and 5 bilateral, and ankle involvement in 13, 10 unilateral, and 3 bilateral. Two patients had unilateral subtalar (foot) involvement and 1 unilateral hip involvement.

Medical treatment varied according to clinical symptoms and signs and consisted mostly of rest and acetylsalicylic acid. Orthopedic treatment consisted of immobilization by plaster casts or traction and physical therapy. Only 2 patients had been treated with steroids and neither had an extensive limb-length discrepancy. Only an occasional patient had an aspiration or synovectomy of the knee.

In general, the interval between the onset of the patient's symptoms and the time of diagnosis of arthritis averaged 1.5–2 years, and at the time of diagnosis, an initial stimulation of growth on the involved side usually was evident. If the disease exacerbations occurred frequently or were prolonged (after 6 months) and if during such episodes immobilization treatment was not protracted, regardless of the symptomatic severity of the disease, there tended to be growth stimulation on the involved side. When there was lengthy or frequent immobilization treatment during and sometimes after such exacerbations (for example, 1 year or more), there was inhibition of growth on the involved side.

Skeletal Growth. Of the 51 patients included in Groups I and II, while all had some length discrepancy, in 35 (70 %) a length discrepancy of 1.5 cm or more developed during the study period. Twenty-one patients had a discrepancy between 2.0 and 2.9 cm, and in 3 it was 3.0 cm or more.

In patients with unilateral disease who had the onset of their disease before the age of 9 years, the involved side was almost invariably the longer one (39 of 40 cases). Those who had the onset of disease within the first 3 years of life tended to have a discrepancy >1.5 cm (24 of 34 patients) relatively more often than children 3–8 years old, but overgrowth in the younger children never amounted to more than 3.0 cm. When the disease occurred initially after the patient was 9-years old (5 patients), the involved side usually became shorter (with one exception).

Regardless of age at onset, the major discrepancy that developed did so within the first 4 years after onset of the disease. Thereafter, in the Group I patients, the discrepancy either increased very slowly (6 patients), remained unchanged (14 patients), or decreased spontaneously (12 patients). The other 4 patients, whose discrepancies continued to increase, were patients with late onset of the disease whose epiphyses fused prematurely on the involved side. Continuing involvement of the knee for several years in one patient resulted in a continuing increase with time until a prearrest discrepancy of 2.4 cm was reached, but such an occurrence was unusual.

In the 12 patients whose discrepancies decreased, there was a gradual inhibition of growth in the involved limb over several years. In 7 of the 12, the discrepancy became clinically insignificant. The changes in discrepancy with time were: 2.8–0.3 cm, 2.5–1.2, 2.3–1.3, 2.2–0.4, 2.0–0.2, 1.8–1.4, and 1.5–0.9 cm. In one case, the discrepancy decreased and reversed the side of shortness from 1.1 cm on the right to 1.1 cm on the left.

Epiphyseal Arrest. Of the 35 patients (Groups I and II) having a discrepancy of 1.5 cm or more at some time during

the period of assessment, 15 had surgical epiphyseal arrests. Some of those who did not have arrests refused to have the procedure done despite recommendation by the physician. Twelve of the 15 patients who did have an epiphyseal arrest had the onset of disease before the age of 5 years. No patient who had onset of disease before the age of 9 years had an epiphysiodesis for inhibition of growth of the involved side. When the onset of the disease occurred after the age of 9 years (5 patients), epiphyseal arrest was required on the uninvolved side in 3 patients and will be needed on the ipsilateral side in one. Fourteen of the 15 epiphyseal arrests were performed on patients with disease at the knee.

In patients with the monoarticular or pauciarticular form of juvenile rheumatoid arthritis, who have predominant involvement of the major joints of one lower extremity, the length discrepancy occurs as a result of two factors: (1) a stimulation of the epiphyseal growth plates, predominantly about the knee joint, during the time the disease is active and for some time afterward and (2) inhibition of the growth potential of the involved extremity.

The two epiphyseal growth plates at the knee account for 70 % of the growth potential of the lower extremity. They are sufficiently close to the synovial capsule to be affected by the hyperemia that occurs during the inflammatory process, while not being adversely affected by the concomitant destructive process. Since the knee is commonly involved in the type of arthritis under discussion and so often is involved unilaterally early in the course of the disease, great potential exists for growth stimulation of the involved lower limb.

The severity of the disease often causes a decrease in the use of the involved extremity, either because of the symptoms or the treatment. Such decreased use can explain the gradual reduction in epiphyseal stimulation and eventual inhibition of growth. When the patient has activity of the disease in early adolescence, consequent hyperemia about the knee could cause rapid and premature fusion of one or both of the growth plates, with sudden decrease in growth of the involved lower limb.

The most common and well-defined pattern of development and progression of length discrepancy was ipsilateral lengthening in patients who had the onset of the disease before the age of 5 years. The major part of the discrepancy then occurred within the first few years of the disease. Thirty-nine of the 40 patients with unilateral involvement whose disease began before the age of 9 showed this pattern. Early in the course of the disease the predominant factor is stimulation of the epiphyses about the involved knee joint. This rapid, early epiphyseal stimulation may not be attributable merely to the young age of the patient, but may also be due to the rather long period of time it often takes to make the diagnosis and institute an adequate therapeutic program. In the older child, it may be easier to make the diagnosis, and the child may be more compliant in restricting activities and in carrying out the treatment. This of course cannot be stated with certainty, but is consistent with the results. If true, the importance of early recognition and treatment of the disease can be inferred. The pattern of development of the limb-length discrepancy just described most often is followed by lack of a significant continuing increase in the discrepancy. Although occasionally (in 2 patients in this series) the discrepancy will increase over the ensuing years, in most patients, it will decrease or remain unchanged with time. The thought that some combination of severity of disease activity, region involved, physician's overall treatment, and patient's compliance adds up to a predictable mode of progression of the length discrepancy is appealing, but factors vary from child to child so greatly that data are inadequate to prove the point. However, the study does clearly indicate that in the large majority of patients, significant changes in growth rates are long-term phenomena and are not due to single exacerbations of the disease or to failure of a therapeutic regimen over a short period of time.

Rapid premature closure of the epiphyseal growth plates about the involved joint occurred at the end of growth in 4 children in this series. All had onset of the disease after the age of 9 years and all showed shortening of the involved side. Their length discrepancies ranged from 1.9–5.9 cm, with the two patients who were 9–10 years old at onset of the disease showing larger discrepancies at skeletal maturity than the other two, who were 11–12 years old at onset. Early epiphyseal growth plate fusion has been recognized as a complication of juvenile rheumatoid arthritis for many years, although the cause of this premature fusion is unknown. The phenomenon may also occur in patients with the more disseminated form of arthritis with involvement of multiple joints more frequently than in patients with monoarticular and pauciarticular forms, but if so it usually does not produce a significant limb-length discrepancy because of the relative symmetry of joint involvement.

It was concluded that an alteration in growth of a lower extremity in a patient with monoarticular or pauciarticular juvenile rheumatoid arthritis is common. When a significant limb-length discrepancy develops in a child, the knee joint almost always will have been involved. If the disease begins before the age of 9 years, the involved side will be longer. The maximum overgrowth in this series never exceeded 3.0 cm. In the initial few years following the onset of disease, most of the developing length discrepancy becomes evident. The initial discrepancy, noted within the first 3–4 years after onset, usually remains unchanged or decreases, but on occasion it can increase progressively. The decreases occurred slowly over several years, and in 12 (33 %) of 36 patients in Group I, the decreasing discrepancy rendered epiphyseal arrest unnecessary. No evidence for rapid, definitive premature closure of the epiphyseal growth plate that significantly increased limb-length discrepancies

occurred in the group that had early onset of the disease. In 4 patients, each of whom had onset of the disease after the age of 9 years, rapid premature growth plate closure was evident, and 2 of them had discrepancies of 5.1 and 5.9 cm. The planning for epiphysiodesis by the Green-Anderson method proved satisfactory.

4.2.2 Pigmented Villonodular Synovitis

Pigmented villonodular synovitis is a monoarticular proliferative process of the synovium characterized by a fibrous stroma [1, 127, 128]. It can affect the synovium or the tenosynovium. The deposition of hemosiderin, histiocytic infiltrates and giant cells occurs within the synovial membrane. The most commonly involved joint is the knee with tenosynovial involvement most common in the hand and wrist. There are two basic patterns of involvement, one being localized or pedunculated and the other diffuse. The disorder usually presents with a swollen knee of gradual onset, mild discomfort, a boggy synovium, and the presence of reddish-stained fluid on aspiration. It commonly affects adults in the third and fourth decades but is seen in children on occasion in the second decade with most diagnosed around the time of fusion of the epiphysis or just afterward. The involvement of multiple joints has been reported both in children and adults but is <1 % of cases. In two children, one had involvement of 3 joints and the other 5 [128]. The plain x-ray in the childhood group is almost invariably normal in relation to the bones and will show only the soft tissue swelling if great enough. Cysts or erosions of bone occur in the adult form. The synovial fluid has a deep xanthochromic hue to a bloody dark brown color and has the appearance of a chronic hemorrhagic effusion. The villi are long and tend to become interwoven with each other. On histology, the synovial lining cells are pigmented and 1–3 layers in depth. The treatment varies depending on the age of the patient and extent of involvement. In localized pigmented villonodular synovitis, excision of the abnormal focus either by arthroscopic or open arthrotomy is recommended. Arthroscopic synovectomy is found to be slightly superior to open synovectomy in the diffuse form. Marginal excision is performed for localized disorders. Radiation therapy and radiation synovectomy have been used for the more diffuse variants but are rarely indicated today.

4.3 Neoplastic Disorders of Epiphyses

There is relatively little primary involvement of the epiphyses with either benign or malignant neoplastic disorders. When there is neoplastic involvement of the epiphyses, it can be primary or secondary, involving transphyseal spread from a focus of metaphyseal origin. We will discuss briefly those disorders that involve the epiphyseal region since problems relate not only to the primary lesion but also to possible growth abnormalities owing to their presence in growth sensitive areas. Epiphyseal lesions generally appear radiographically as solitary lucent abnormalities. In a report on 15 solitary epiphyseal lesions from one institution chondroblastoma, osteoid osteoma, eosinophilic granuloma, and enchondroma occurred although most common were foci of subacute or chronic osteomyelitis with one case of skeletal tuberculosis [129]. This is consistent with other reports which will be outlined over the next several sections. Transphyseal spread can occur with unicameral/solitary bone cysts, aneurysmal bone cysts or osteosarcoma.

4.3.1 Primary Involvement of Epiphyseal Regions

4.3.1.1 Chondroblastoma

The one primary tumor of epiphyseal regions in the growing child is the chondroblastoma. This has its origin in the epiphyseal cartilage and is the most common primary tumor of this region of the developing bone [130]. It was defined initially by Jaffe and Lichtenstein in 1942 as a benign disorder [131]. Codman had drawn attention to the disorder previously as a variant of a giant cell tumor in the epiphyses of the proximal humerus. Epiphyses at shoulder, hip, and knee are mainly affected. Pain and limitation of joint movement are the main presenting symptoms. Fifty percent are at the distal femur or proximal tibia and two-thirds involve the lower extremities [132]. The distal femur is the most common site in some series with the proximal tibia next followed by the proximal humerus, distal tibia, and proximal femur. The most common areas in other series involve the proximal humerus (22 %), distal femur (16 %), proximal tibia (14 %), and proximal femoral capital epiphysis and greater trochanteric epiphysis (8 %). Seventy-five percent of the patients are teenagers and 80 % are between 5 and 25 years of age [132]. In a large series of 465 patients, 65 % were between the ages of 10 and 20 years with 4 % occurring in the first decade of life [130]. Another series shows 62 % (29 of 47) of patients between 10 and 20 years of age with none <10 years at presentation [133]. Forty percent of chondroblastomas involve only the epiphysis, 55 % extend into the adjacent metaphysis, 4 % affect the metaphysis alone, and on occasion diaphyseal lesions have been reported [132]. A more recent study also noted relatively frequent metaphyseal involvement of long-bone epiphyseal lesions (12/29, 41 %). This was seen even in young patients (11–14 years of age) with open physes (5/12) with transphyseal involvement. Five of the lesions violated the articular cartilage. The lesion is lytic in radiographic

appearance and will involve the secondary ossification center. The tumors tend to be ovoid or rounded, sharply marginated with a mean diameter of 4.5 cm in 40 lesions (range 1–11 cm) [133]. There is thickening of bone trabeculae around the lesion owing to its slow and nonaggressive growth. Two tissue types are seen—one involving very cellular tissue with little matrix, and the other where the tissue is less cellular and surrounded with a chondroid matrix. The proportion of these tissue types varies from patient to patient and even in different areas of the same tumor. The chondroblastomas are almost always surrounded by at least a thin shell of reactive bone. <50 % of the total lesional tissue is cartilage or chondroid. The lesion contains chondroblasts and osteoclast-like giant cells. All chondroblastomas produce cartilage or chondroid tissue, and the lesion must contain islands of primitive chondroid, fibrochondroid, or hyaline cartilage. An aneurysmal bone cyst component may be identified histologically. The lesion is eccentric in the epiphysis and usually involves less than one-half of its extent. As is frequent with many cartilage tumors, calcific densities within the tumor are often seen. Small punctate calcifications are evident in slightly more than one-half the cases. An open physis is usually present. The lesions are typically benign and not aggressive but all series report local recurrences in the 10–25 % range and rare instances of metastasis. This appears to be more common with hip area lesions (proximal femur and rare pelvis). An open growth plate did not correlate with local recurrence [134]. Inadequate surgery, biologic aggressiveness of the lesion and pelvic location affected local recurrence and metastasis. Treatment is generally surgical with curettage and packing with bone graft or polymethylmethacrylate. Concerns with recurrence, juxtaarticular and juxtaphyseal position have led to some efforts at primary treatment with percutaneous radiofrequency heat ablation with promising early results but no longer followup reports yet [135, 136]. Studies of 116 cases of chondroblastoma from the Dutch Bone Tumor Committee showed very minimal loss of function or growth disturbance with these epiphyseal lesions [137]. It is important to consider the age of the patient in diagnosing the lesion since the most common tumor of epiphyses in adults whose growth plates are closed is the giant cell tumor. The giant cell tumor lacks calcification, occupies more than one-half of the epiphysis in most cases, and has no sclerotic border [130].

4.3.1.2 Osteoid Osteoma

Epiphyseal osteoid osteoma is relatively rare but has been the subject of so many case reports that it is now well defined. The lesions by pathologic assessment are the same as those present in metaphyses and diaphysis. Most epiphyseal lesions involve the lower extremity but upper extremity lesions are also seen. The time to diagnosis is often delayed not by the nature of the lesion but by its position. The time range from symptom onset until diagnosis has varied from 2 to 24 months. Pain often worse at night and relieved by salicylates is identified, but intraarticular and periarticular localization often leads to joint discomfort leading to diagnosis of an arthritis disorder. In some cases a true synovitis develops as noted by Sherman as early as 1947 with a case of osteoid osteoma of the trochlea of the distal humerus in a 13-year-old boy [138]. In an early review of 158 cases, Sherman found only 1 epiphyseal site [139].

The common age of occurrence is between 8 and 16 years of age. There is a clear male predominance. The most common site of occurrence is the knee with most cases at the distal femoral epiphysis and some at the proximal tibial epiphysis. The next area of common involvement is the distal tibial epiphysis with a few cases occurring at the hip (greater trochanter or femoral head). The upper extremity can be the site of involvement with the elbow most common having lesions primarily at the distal humerus (olecranon fossa, trochlea) with rare wrist involvement at distal radial epiphysis [140]. The differential diagnosis includes chondroblastoma, enchondroma, solitary bone cyst, eosinophilic granuloma, and subacute osteomyelitis.

Lower extremity lesions have been reported by Beerman et al. in a 14-year-old male, proximal tibia [141]; Kendrick and Evarts in the distal femur (no age given) [142]; Odaka et al. distal femoral epiphysis in a 9-year-old male [143]; Simon and Beller in a 12-year-old male in the distal tibial epiphysis [144]; Seitz and Dick in an 8-year-old girl distal femur [145]; Micheli and Jupiter in the distal femoral epiphysis of a 15-year-old male [146]; Iceton and Rang in the distal femoral epiphysis of an 11-year-old male [147]; and Van Horn and Karthaus added two cases of epiphyseal osteoid osteoma, one involving an 11-year-old male with a lesion in the lateral part of the distal femoral epiphysis and the other a 15-year-old male with a lesion in the distal tibia [148]. Regarding the upper extremity, Blair and Kube reported an osteoid osteoma in a distal radial epiphysis in a 15-year-old boy [140]; Sherman a trochlear lesion in a 13-year-old boy [138]; Cassard et al. 3 osteoid osteomas of the distal humerus olecranon fossa [149]; and Zarezadeh et al. 2 cases of involvement of the trochlea at the elbow [150].

The bone scan is extremely useful for diagnosis and localization. Subsequent MR imaging or CT is also helpful, if not essential, for precise localization especially since with surgical excision or curettage it is better not to injure either the articular cartilage or the physis.

Surgical treatment is either by complete excision or by curettage in those regions close to the physis. Excellent results usually with immediate relief of symptoms are reported with epiphyseal lesions. Complete excision of the nidus and surrounding sclerotic bone [en bloc resection] is

effective but protection is needed until the defect fills in. Others will curette the nidus under radiographic or CT-guided control [burr-down technique]. Increasing experience and favorable results have led to CT-guided percutaneous radiofrequency thermal ablation as the main treatment for osteoid osteoma although there is limited experience with epiphyseal lesions [151, 152]. Spontaneous regression has been well documented but takes a considerable period of time averaging 30 months in one study and 33 in another. NSAIDs are used to control pain while waiting for resolution [153].

If the nidus is located near a growing epiphysis, it may cause an acceleration of bone growth [130]. Overgrowth phenomena have not been reported with an intraepiphyseal osteoid osteoma, but some authors have commented on this phenomenon with metaphyseal lesions in particular where the symptoms are longstanding prior to diagnosis in those with several years of growth remaining. Habermann and Stern described an osteoid osteoma of the tibial metaphysis occurring in an 8-month-old male with slight overgrowth [154].

4.3.1.3 Eosinophilic Granuloma

Eosinophilic granuloma is a benign disorder due to granulomatous histiocytic lesions which appear radiographically as lytic lesions of bone. It is part of a larger entity referred to as Langerhans cell histiocytosis which includes three clinical syndromes with recognizable but indistinguishable histology. These are eosinophilic granuloma involving predominantly osseous or pulmonary regions; Hand–Schuller–Christian disease with multiple organs affected including the skull base, and Letterer–Siwe disease the most severe, typically, affecting the abdominal viscera [155]. The histopathology is characterized by two predominant cell types, eosinophils and mononuclear histiocytes. The disorder may be single or multiple, but occurs mainly in the shafts of long-tubular bones in metaphyses or diaphyses or in the skull, ribs or vertebrae. The occurrence in growing epiphyses is rare but does occur [156, 157]. Both solitary and multiple lesions occur. The lesions are radiolucent and well circumscribed and on occasion demonstrate a thin bone rim of sclerosis within the secondary ossification center. They are either central or peripheral. The age range varies from 2.5 to 8 years with a mean of 5 years. Most of the cases are male. Bones involved have been the proximal femur, distal femur, proximal tibia, and distal tibia. This corresponds with the overall demographics of eosinophilic granuloma which is found more frequently in males, has its peak incidence between the ages of 5 and 10 years, and is almost always confined to children <15 years of age. The cause remains unknown with no evidence found yet for neoplastic, infectious, or genetic causes.

Leeson et al. described 3 additional cases [156]. Their lesions involved a 3–year old, 5-month-old male with a lytic defect in the femoral head that appeared to extend across the physis into the proximal femoral metaphysis; a 2-year old, 7-month-old female with a circumscribed lytic lesion in the medial distal tibial epiphysis with subsequent transphyseal spread to the metaphysis; and a 7-year-old boy also with involvement of the proximal femoral epiphysis with a well-marginated round, radiolucent lesion without transphyseal extension. Two months later, the lesion had crossed the physis into the neck. Serial x-rays indicate that the disorder begins in the secondary ossification center of the epiphysis and then with time passes in a transphyseal fashion toward the metaphysis. Leeson et al. reported that 5 of the 10 lesions in the literature demonstrated transphyseal extension with each of the 5 considered to be epiphyseal in origin. Caballes et al. reported an epiphyseal lesion of the proximal left femur in a 12-year-old male [157]. Treatment involves open biopsy because of the essential need to establish the diagnosis followed by a curettage. Bone grafting may be required for larger lesions [158]. Efforts to protect the physis are mandatory. Ghanem et al. reviewed 56 patients with Langerhans cell histiocytosis, 26 of whom had a solitary bone lesion with no systemic involvement and 13 with multiple bone lesions with no systemic involvement. These 39 patients thus had eosinophilic granuloma. There were no epiphyseal lesions noted and many patients healed the bone lesions spontaneously with no treatment. Epiphyseal lesions were confined to a few of the additional 17 patients with bone and systemic involvement (not true eosinophilic granuloma) who were all treated with chemotherapy and/or radiation [159]. Usui et al. described 7 additional cases, one of which (distal femur) extended into the metaphysis damaging the growth plate. The other 6 lesions were all confined to the epiphyses (proximal femur 4, distal femur 1, and proximal tibia 1) [160].

4.3.1.4 Solitary Enchondroma

Solitary enchondromas originating in the epiphyses are rare. A review of 761 patients referred to the Armed Forces Institute of Pathology with a final diagnosis of enchondroma analyzed for enchondromas of the long bones that originated in the epiphysis. All had a histopathologic diagnosis. Thirty-three patients had epiphyseal enchondromas but only 11 had open physes [161]. Of these 11 the mean age was 13.3 years (range 7–16 years) and 4 had metaphyseal extension. For the entire series, the mean size was 2.7 cm in the widest radiographic dimension. Sites were proximal humerus 7 and 1 each in greater trochanter, distal femur, proximal tibia, and distal fibula. Mineralization was present in 6 of the 11. The lesion was centric in 6, eccentric in 5. Treatment was by curettage and bone graft. Occasional

enchondromas were also seen in cases of Ollier's disease, multiple enchondromatosis [162].

4.3.2 Secondary Involvement of Epiphyseal Regions from Primary Metaphyseal Foci of Benign and Malignant Disorders

4.3.2.1 Unicameral Bone Cyst

The most common site of the unicameral bone cyst is the proximal humeral metaphysis. Over 50 % of cases are located there with another 25 % at the proximal femur. The distribution established in a larger series of 175 patients with unicameral bone cysts by Neer et al. was proximal humerus 54 %, proximal femur 18 %, proximal tibia 6 %, distal tibia 5 %, distal femur 3 %, and many other bones with occasional involvement [163]. The proximal humerus/proximal femur pattern of frequency is seen in essentially all studies. The cyst is considered to be active if immediately adjacent to the undersurface of the physis and latent if there is metaphyseal bone between the physis and the lesion. Those older than 10 years of age heal their cysts at a higher rate then those under 10 years [163]. Cohen's hypothesis that the cyst occurs due to obstruction to the drainage of interstitial fluid remains credible, if unproven, and also serves as the rationale for decompression/drainage treatments [164]. Involvement of a cyst through the physis into the epiphysis was for a long time considered to be rare but is now recognized to occur in as many as 10–20 % of cases either spontaneously, subsequent to one or more pathologic fractures, and sometimes with steroid therapy. Growth slowdown (shortening) or varus deformity of the proximal humerus can occur with or without epiphyseal involvement. Many examples of epiphyseal cysts with growth deformity in the absence of any treatment have been reported. In these, however, the likely explanation is the occurrence of fracture of the cyst and adjacent physis allowing either for premature closure of the physis due to the fracture with subsequent spread of the cyst or spread of the cyst in relation to transphyseal discontinuities. Also common is damage to the physis during the course of treatment of active lesions against the physis involving either curettage and bone grafting or injection of such agents as steroids. Following growth plate damage, the cyst can be seen subsequently within the epiphysis. Cysts are described occasionally within the epiphyseal region after skeletal maturity, but in the absence of growth deformity would be postulated to have occurred quite late.

Nelson and Foster reported 5 cm of humeral shortening in a 15-year-old female with a large proximal humeral bone cyst which had expanded into the epiphysis and was associated with an almost fully closed physis [165]. They felt that a proximal humeral injury a few years previously represented a pathologic fracture of the cyst with physeal damage. Cohen presented a case of premature proximal humeral physeal closure with a cyst treated nonoperatively [164]. Moed and La Mont presented 3 cases of premature physeal closure of the proximal humerus, each associated with a fracture of the cyst and no surgical intervention [166]. Malawer and Markle reported a unicameral bone cyst of the proximal femoral metaphysis communicating across the open physis with the secondary ossification center of the epiphysis in a 14-year-old male [167]. They reviewed previous reports where epiphyseal involvement with a unicameral bone cyst had been described and, in these, most of the patients were older. Of the 8 lesions including their own, 3 involved the proximal femur, 1 the distal femur with 2 each in the proximal humerus and proximal tibia. One cyst in a 6.5-year-old female in the proximal tibia subsequently healed with no shortening or deformity. The next youngest patient was a 15-year-old female whose proximal humeral physis was closed but 2 cm shortening indicated that the disorder was present during the growing years. Capanna et al. described 12 cysts with epiphyseal involvement across an open growth plate (in over 500 cases), ten in the proximal humerus and 2 in the proximal femur [168]. Three had no pathologic fracture and 9 had 1 or more fractures. In 4, a growth disturbance was found. Shortening when present was 2.5–4.5 cm. Proximal humeral varus was always present ranging from 18° to 90° with a mean of 39°. The lesions tend to penetrate centrally and spread medially. Additional cases: 13-year-old male, proximal humerus, 3 pathological fractures, varus deformity [169]; growth arrest at proximal humerus in 10 % (5 of 51 consecutive patients) not caused by iatrogenic damage of surgery with grafting although 3 had steroid injections, all presenting with pathologic fracture, humeral discrepancies from 4.0 to 6.5 cm, and proximal humeral varus deformity [170]; and 8 patients with epiphyseal involvement (7 proximal humerus, 1 proximal femur), all with more than 2 pathologic fractures and 7/8 with shortening 2–11 cm, mean 4.6 cm [171]. In all reports functional limitation did not develop even with shortening and varus deformity. Ovadia et al. indicated that cysts with epiphyseal involvement should be considered as a more aggressive variant. They did not respond as quickly or as completely to treatment with steroid (methylprednisolone) injections or grafting with autologous bone marrow (as pure metaphyseal lesions had) [171].

Violas et al. reported 4 cases of proximal humeral simple bone cysts of the metaphysis with considerable shortening and varus deformity, all with one pathological fracture, 3 of whom were treated with steroids and 1 with saline injections [172]. The number of cases in their unit was not described so the frequency of occurrence is not known. These cases did not involve epiphyseal extension but all show the significant growth damage that can occur. The ages at occurrence and

growth problems at maturity were 6 years, 7 cm, no varus or valgus; 4 years, 13 cm, considerable varus leading to valgus osteotomy; 8 years, 10 cm, no varus; and 9 years, 6 cm, varus deformity. As for the association with steroid therapy, Campanacci et al. described 141 cysts (mostly localized at the proximal humerus) and treated with one or more cortisone injections where 28 (20 %) had developed limb-length discrepancy [173].

Treatments. The wide variety of treatments in use previously and currently indicates lack of a superior approach. Results are good with these approaches but a fairly high recurrence (or failure of full resolution) rate and occasional cases of growth deformity with each approach persist. These include curettage of the cyst with insertion of bone graft, injection of steroids (methylprednisolone) at repeated periods of time, injection of bone marrow or bone morphogenetic protein to enhance healing, decompression of cyst with indwelling cannulated screw(s), instillation of "substitute" bone scaffolding such as calcium tri-phosphate, and even flexible intramedullary rod insertions from distal to proximal.

Factors to be considered re shortening and deformity with unicameral bone cysts:

Growth problems can occur prior to or in the absence of any treatments. These are invariably attributed to the fractures that occur at the cyst sites and could exend into the physis. Increased cyst pressure could cause local erosion and subsequent perforation of the physis. Growth problems can occur or be worsened in cases where epiphyseal involvement has occurred.

Growth problems can occur with overly aggressive surgical management by curettage (damaging the physis) or excessively tight bone graft packing (adjacent to the physis).

Growth problems have been reported by several authors after steroid injections. It needs to be recognized, however, that these cases were also associated with pathological fractures (and in fact essentially all unicameral cysts are diagnosed in relation to pain episodes—i.e., fractures).

Growth deformity is more likely: the younger the patient (especially 4–7 years of age since so much growth remains), the more active the lesion (the closer it is to the physis), the more aggressive the therapy by surgical curettage and bone grafting or by multiple steroid injections, and the more frequent the fractures.

In an effort to allow resolution of the lesion with minimal to no growth deformity the following steps can be considered:

Treat the pathological fracture conservatively by immobilization until comfortable. Some cysts will demonstrate bone formation that not only heals the thinned cortices but also begins to fill in the cystic space.

Try to defer intervention until the cyst has improved from an active state (immediately adjacent to the physis) to a latent state (with bone interposed between the undersurface of the physis and the cyst).

An integral part of any intervention is multiple punctur-ings of the cyst wall to decompress any fluid under pressure.

If curettage and some or all of bone grafting/bone marrow-BMP insertion/bone substitute insertion are done the periphyseal region must be avoided.

If steroids are used, they should be reserved for the latent phases. Since steroids damage articular cartilage and are no longer recommended for direct injection into joints in children, adolescents or young adults, it is reasonable to infer that (in the active state) they could damage physeal cartilage by direct contact.

The concepts of relieving intralesional pressure by multiple transcortical drilling or by an indwelling cannulated screw and enhancing bone repair by microfractures of the cyst wall or "diaphyseal-end" autografts remain safe approaches.

4.3.2.2 Aneurysmal Bone Cyst

Aneurysmal bone cysts in skeletally immature patients almost invariably involve the metaphyseal regions with transphyseal spread into the epiphysis infrequent. Capanna et al. found 9 cases of aneurysmal bone cyst arising in juxtaepiphyseal regions with gross invasion of the growth plate and lesional presence in the epiphysis [174]. Five of these had premature growth plate fusion. The patients were seen in an assessment of 198 cases of aneurysmal bone cyst. The ages ranged from 6 to 16 years but almost all were in the second decade. A wide array of bones were involved with approximately half showing some shortening of 1–4 cm.

Reviews of most large series generally show virtually no lesions crossing the physis in skeletally immature patients. Carlson et al. reported 1 patient out of 26 with an aneurysmal bone cyst crossing the proximal femoral physis to extend into both the capital femoral and greater trochanteric epiphyses [175]. Dyer et al. described physeal bridging in a metatarsal cyst in a one-year-old girl [176]. They also reviewed the English literature over a 25-year period and found 223 cases of primary aneurysmal bone cyst described in 4 papers in which the status of the growth plate was adequately described. In only 1 of these cases did the aneurysmal cyst cross an open plate into the epiphysis (proximal femur).

One reported case of spread from a metaphyseal focus through the growth plate into the secondary ossification center of the epiphysis was in a 10-year-old girl at the proximal fibula [177]. Following removal of the entire proximal end of the fibula, gross hemidissection revealed blood-filled spaces with obvious cystic extension through the center of the growth plate to replace most of the fibular ossification center. The growth plate itself had decreased organization in the hypertrophic zone. The central quarter of

the plate had been destroyed, but the periphery persisted although it was somewhat attenuated and abnormal. The growth plate was relatively intact even immediately adjacent to the area being bridged by the cyst. Once within the secondary ossification center, however, the cyst lining had completely displaced the adjacent bone plate and the epiphyseal blood supply along the germinal zone of the physis. There was only a small area of transphyseal bone bridging.

Primary aneurysmal bone cyst of the epiphysis. Chan et al. recently reported what they believe to be the first primary epiphyseal aneurysmal bone cyst which developed in a 3-year-old boy in the proximal tibial epiphysis [178].

Treatment was by curettage, high speed burring, electrocauterization, and 5 % phenol painting of the cyst wall. A second case in a distal tibial epiphysis of a 13-year-old boy was reported by Kerimoglu et al. [179]. There was no metaphyseal involvement.

The tumors are eccentrically located within cortices and a blowout appearance. Primary treatment is usually by curettage and bone graft. A review of 150 patients from the Massachusetts General Hospital published in 2005 actually showed mean age of 18 ± 12 years (3–62) with most common sites tibia, femur, fibula, and pelvis. There was no mention made of transphyseal spread or epiphyseal involvement [180].

Cottalorda et al. reviewed 156 cases from multiple centers in France and a literature review of 255 additional cases totalling 411 cases in children and adolescents [181]. No mention was made of epiphyseal involvement although analysis was limited to location by bone only. The lesions were most prominent in the first 2 decades of life (mean age 10.2 years), rarely seen after age 30 years, can involve essentially any bone but are most common in femur, tibia, spine, humerus, pelvis, and fibular. Treatment is generally by curettage and bone grafting.

4.3.2.3 Osteogenic Sarcoma

Although the large majority of metaphyseal osteosarcomas had long been considered to remain within the metaphyses, there have been several well-documented cases of transphyseal spread. Simon and Bos reported a retrospective macroscopic and microscopic review of 26 macrosections of entire metaphyseal, growth plate, and epiphyseal tissues from patients with osteosarcoma who had been treated between 1926 and 1960 [182]. Their study required the availability of at least one good macrosection of the whole tumor which contained a well visualized and active physis from a patient with high-grade metaphyseal osteosarcoma. The results in the 26 patients showed that in only 3 was the physis not perforated by tumor tissue. In 4, there was only microscopic perforation, but in 19, there was transphyseal spread evidenced both by microscopic and macroscopic examination. In some instances, there was more than one site of extension of the metaphyseal tumor into the ossific nucleus. Metaphyseal spread occurred through the center of the physis in 12 cases, the periphery in 9, and the region beneath the perichondrial ring into the margins of the ossific nucleus in 6. The tumor tissue invariably perforated the physis along with a series of vascular channels. In some instances, the physis was intact except for the transphyseal vascular penetration, but in others it was focally destroyed by the tumor mass. The authors concluded that the physis appeared to have a tendency to act as a barrier to tumor spread but did not restrain the tumor in most cases such that epiphyseal invasion of the tumor tissue was extremely common in general and was extensive in more than one-half of the cases.

These findings were similar to an assessment by Enneking and Kagan who found that 21 of 28 skeletally immature patients had physeal perforation by osteosarcoma tissue in the proximal tibia and distal femur [183]. They define an open physis as regularly oriented cartilaginous cells with the typical zones of an epiphyseal plate and more than 6 cells comprising the zone of hypertrophy. They defined a closing plate as having histologic evidence of decreased cellular proliferation and hypertrophy with plate narrowing and some early transverse osseus trabeculae. Of 24 cases with open plates, only 7 showed no evidence of tumor in the epiphysis with 17 showing tumor which was anywhere from microscopic to 100 % invasion of the epiphysis with an average roughly calculated at 25 %. Of the 4 cases with closing plates, all showed involvement of the epiphysis with tumor. There were two patterns of transphyseal tumor spread. The most common was direct spread across the central portion of the growth plate with tumor proliferating through vascular channels. The adjacent cartilage was not destroyed in early instances, but was at later time periods. The ability of the physis to at least temporarily contain the tumor was shown by the fact that in such cases, the opposing metaphysis was almost entirely filled with tumor. On occasion, the tumor extended beneath the perichondrium, circumvented the plate, and penetrated the lateral margin of the epiphysis. The then current imaging methods involving x-rays and bone scans were frequently inaccurate in assessing transphyseal spread.

Ghandur-Mnaymenh et al. also found transphyseal spread of osteosarcoma to be extremely common [184]. In 14 cases of osteosarcoma of long bones in patients ranging in age from 10 to 19 years with open physes, the physeal cartilage was not crossed in only 2 cases. In 12 cases, the tumor crossed the cartilage plate partially or completely remaining in the epiphysis in 7 and actually crossing the articular cartilage and involving the joint in 5.

Jesus-Garcia et al. assessed 25 patients with osteosarcoma and open epiphyseal plates, mean age 12.2 years [185]. Histopathologic examination showed transepiphyseal extension in 21 patients. The incidence of transphyseal

spread in the four published series (total of 93 cases) was 83 % indicating that transphyseal spread of osteosarcoma is the rule rather than the exception. Histologic sections showed that increased vascularity on the metaphyseal side occurred initially followed by osteoclastic and chondroclastic activity at the physeal plate with subsequent tumor tissue invasion. Blood vessels appeared to be part of the tumor stroma extending deeply into the cartilage with progressive advance of the osteosarcoma through the plate.

When limb-saving procedures are planned in association with chemotherapy, the importance of careful assessment of the possibility of transphyseal spread by CT and MR imaging is evident. In one paper assessing 25 patients, histopathologic spread was found in 21 (84 %) but was detected radiographically in only 11 (44 %) [185]. MRI is currently the best method to evaluate local extension prior to tumor resection, especially to assess the feasibility of conservative surgery [186, 187]. The study specifically, assessing MRI for detecting epiphyseal extension of osteosarcoma, concluded that static MRI most accurately detected epiphyseal extension [186]. Static MR images refer to T1-weighted and short tau inversion recovery (STIR). MRI is so sensitive in detecting changes that a major concern is to increase accuracy of tumor identification and not interpret edema, hematopoietic marrow, or angiogenesis as tumor involvement. Dynamic contrast-enhanced MR findings (DEMRI) can help make these distinctions but for clinical decision making static MRI is still preferable. Careful preoperative assessment is needed to determine margins for limb-sparing surgery for osteosarcoma and other malignant tumors. Epiphyseal and joint preservation are even more valuable functionally as long as tumor can be effectively removed. Recent studies have shown the feasibility of transepiphyseal resection of knee region high-grade metaphyseal osteosarcoma with preservation of distal femoral and proximal tibial articular portions of the epiphysis and intercalary allograft reconstruction [188]. Thirteen patients undergoing this approach showed eleven to be disease free at a mean followup time of 63 months.

4.4 Osteomyelitis and Septic Arthritis

4.4.1 Primary Subacute/Chronic Epiphyseal Osteomyelitis

Epiphyseal osteomyelitis occurring as a primary entity is a well-defined although infrequent occurrence. The common site for long-bone osteomyelitis in the growing child is metaphyseal. Episodes of primary epiphyseal osteomyelitis tend to be subacute or chronic in their presentation. As with most osteomyelitis disorders, they occur at those regions where growth is most active—these being the distal femur, proximal tibia, distal tibia, and proximal humerus. They present with discomfort, a slightly decreased range of motion, a several day to several week history, and a low-grade temperature elevation. The primary abnormality on blood testing is an elevated ESR and perhaps a slightly elevated white blood cell count. There may be atrophy of the muscles surrounding the joint. The main radiographic finding is a focal, relatively circumscribed, and generally eccentric region of lysis within the secondary ossification center. Depending on the degree of chronicity, there may be some surrounding sclerosis, but this is usually not marked. King and Mayo reported 2 cases of primary subacute epiphyseal osteomyelitis, one in the distal femoral epiphysis and the other in the distal tibial epiphysis [189]. Green et al. reported 8 cases one of which was in the proximal femoral epiphysis, 5 in the distal femoral epiphysis, and 2 in the proximal tibial epiphysis [190]. All patients were <5 years of age. Andrew and Porter reported 3 patients with localized primary subacute epiphyseal osteomyelitis [191]. These were in a 4-year-old girl in the distal femoral epiphysis, a 3.5-year-old girl in the distal femoral epiphysis, and a 9-year-old girl in the distal tibial epiphysis. In none of the above–mentioned 13 cases was there any long-term damage to the epiphysis or adjacent joint. Rosenbaum and Blumhagen described 10 cases (in 9 patients) at the characteristic sites: 7 distal femur, 2 proximal tibia, and 1 proximal humerus [192]. At 8 sites, the lesion was limited to the epiphysis, while in 2 there was an adjacent metaphyseal lesion. Sorensen reported 20 patients from a literature review with hematogenous osteomyelitis involving only the epiphysis with lytic lesions almost all (20/21) at the knee distal femoral or proximal tibial sites [193]. Kramer et al. have also reported osteomyelitis of the distal femoral epiphysis in an 11-year-old boy with a slightly more acute onset [194]. In more recent studies similar findings continue: Rasool reports 2 cases of epiphyseal primary subacute hematogenous osteomyelitis in children (proximal femur, distal femur) [195]; Hempfing et al. in the distal femur of a 2-year-old boy [196]; and Schmidt and Glorion cases in the distal femoral epiphysis of an 8-month-old boy, proximal femoral epiphysis in a 3-year-old boy, and proximal tumerol epiphysis in a 12-year-old girl [195–197]. While plain radiographs eventually show circumscribed, noncentric lytic epiphyseal lesions earlier diagnosis is favored by a positive bone scan and CT or MR imaging.

Published series show the same distribution of organisms as is found with the more common metaphyseal osteomyelitis [198]. The most common infections are caused by staphylococcus aureus with occasional examples of H-influenza and streptococcus. Treatment is by curettage and intravenous antibiotics followed by oral antibiotics. Biopsy diagnosis is stressed but, once identified as bateriologic, systemic antibiotics alone have been effective in some. Great care must

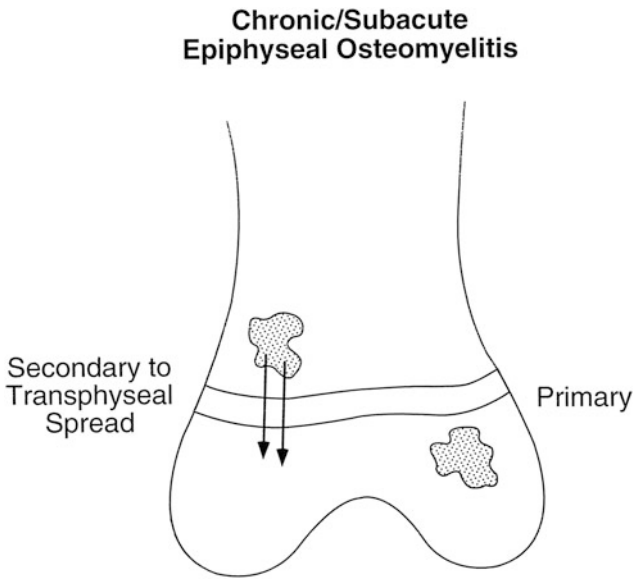

Fig. 4.8 Epiphyseal involvement in subacute and chronic osteomyelitis can be either primary or secondary to transphyseal spread from a metaphyseal focus

be taken not to damage the physis surgically. These foci of infection tend to heal uneventfully with no serious long-term sequelae. Figure 4.8 shows how the epiphyseal foci of subacute or chronic osteomyelitis can be primary or secondary to transphyseal spread from the metaphysis.

4.4.2 Epiphyseal Osteomyelitis Secondary to Transphyseal Spread from Subacute or Chronic Metaphyseal Foci

Epiphyseal osteomyelitis occurs more commonly secondary to a primary subacute or chronic metaphyseal osteomyelitis which has undergone transphyseal spread (Fig. 4.8). The subacute or chronic metaphyseal focus is also referred to as a Brodie's abscess. Harris and Kirkaldy-Willis demonstrated a subacute pyogenic abscess crossing the epiphyseal plate of the distal tibia in a 13-year old [199]. Robertson published 8 cases of epiphyseal osteomyelitis, most of which appeared to have larger metaphyseal components [200]. He defined involvement of 2 in the distal tibial epiphysis, 2 in the distal lateral femoral epiphysis, 2 in the distal fibular epiphysis, and 1 each in the distal ulnar and terminal phalangeal (finger) epiphysis. He clearly defined the involvement of epiphyseal cartilage and secondary ossification center bone. Gledhill reported transphyseal spread of a distal tibial metaphyseal subacute osteomyelitis across the physis into the epiphysis [201]. Examples of metaphyseal abscesses crossing the epiphyseal plate were also described by Gillespie et al; 2 of 57 Brodie metaphyseal abscesses crossed the epiphyseal plate, while 2 of their 110 cases appeared to be primary within the epiphyseal bone [202]. Roberts et al. described a subacute osteomyelitis of the lateral proximal femur that crossed the physis passing into the greater trochanter in a 2.5-year-old girl [203]. The relative infrequency of epiphyseal involvement in chronic and subacute osteomyelitis, however, is shown by Boriani who reported 181 cases of Brodie's abscess with no cases in which the lesion involved the epiphyseal plate [204].

Other reviews of foci of chronic circumscribed osteomyelitis that traversed the epiphyseal plate have been presented. Kandel and Mankin presented 9 patients with subacute or chronic pyogenic abscesses of the long bones with circumscribed lesions in the metaphyseal regions [205]. Three of these traversed the epiphyseal plate allowing for intraepiphyseal involvement but it was noted that in no case did any negative growth sequelae occur, as evidenced by absence of stimulation, retardation, or angular deformity. Two of 3 patients were sufficiently old at 15 and 16 years of age that growth sequelae would not have been expected but they did have symptoms for 6 and 15 months, respectively, prior to diagnosis. Even when the epiphyseal plate was crossed in a 10-year-old child, growth sequelae did not occur since only a narrow region of the central portion of the physis had been damaged. Bogoch et al. presented 6 cases of localized transgression of the epiphyseal plate, in patients with considerable growth remaining, with no subsequent growth disturbance seen [206]. Surgery was performed in 4 of the cases while medical treatment was performed in the other 2. Most episodes of transphyseal transgression occur near the end of growth limiting growth sequelae. Four of the cases in this series, however, occurred in children <10 years of age. Jani and Remagen used the term primary chronic osteomyelitis to describe 3 cases of transphyseal spread of metaphyseal foci into the epiphysis with no negative growth sequelae [207]. Hempfing et al. showed two cases of subacute osteomyelitis with epiphyseal and adjacent metaphyseal involvement (crossing the growth plate) in a 2-year-old girl, proximal femur, and 7-year-old girl, distal femur [196]. Even though there may be large lytic defects in both the metaphyseal and epiphyseal bone, the passage through the physis itself appears to be through a relatively small and even narrow focus such that cure of the infection appears to leave the growth potential intact. The factors to be considered for making an assessment of growth potential following transphyseal spread involve the age of the patient, the position of the transphyseal spread, and the extent of the transphyseal defect. The first two are readily ascertainable while the latter would require MR imaging.

4.4.3 Acute Neonatal/Infantile Osteomyelitis and Its Damaging Effects on Epiphyses

Great damage to the epiphyses has been documented with osteomyelitis of an acute nature in the infant. The epiphyses can be damaged extensively by acute infection of the bone which occurs in a highly specific time frame, namely the neonatal period concentrated in particular from birth to 4 weeks of age. The use of the term infantile to qualify the age at which osteomyelitis occurs is variable but generally refers to the first year of life. The younger the patients, in general, the worse the prognosis for epiphyseal damage. Damage occurs by two specific mechanisms which are often combined in the same region (Fig. 4.9). The first involves transphyseal spread of infection from its metaphyseal localization through the physis and into the epiphysis in association with persisting open transphyseal vessels remaining open from the fetal developmental period. The second mechanism involves a septic arthritis in association with metaphyseal osteomyelitis which can occur following passage of organisms from the metaphysis to the joint in intracapsular epiphyses or from the epiphyses into the joint after transphyseal spread. On occasion acute primary septic arthritis appears to occur in which the vascular spread of the organism is initially to the synovium and then into the joint. Each of these mechanisms will be referred to in the subsequent discussion which will focus on septic arthritis of the hip of infancy, neonatal involvement of the distal femoral epiphysis and knee joint, and sepsis of other growth regions.

Prior to development of antibiotics neonatal osteomyelitis, by which is meant infection in the first 4 weeks of life, frequently resulted in death owing to the severity of spread and frequent multibone involvement [208–210]. Green and Shannon noted in their series of infants with osteomyelitis under 2 years of age published in 1936 that there had been joint involvement in all but one instance where there was eventual residual deformity [210]. Weissberg et al. studied 17 infants, 1–28 days of age, with osteomyelitis and noted that joint involvement was present in 12 of the 17 and that eventually bone deformity was present in 10 patients most with a significant functional deficit [211]. In 14 of the 17 infants, the illness was not accompanied by systemic signs or symptoms and delay in diagnosis was usually seen since help was not sought until local signs became apparent. These involved swelling, discomfort, and decreased motion of the extremity. Radiographic changes of the bone were often dramatic at time of initial presentation with marked femoral periosteal elevation, soft tissue swelling, localized bone resorption, and subperiosteal new bone formation. In many instances, the joint space was widened and there was often frank subluxation or dislocation in particular at the hip and knee. They reviewed several studies of neonatal osteomyelitis, published between 1940 and 1965. Three of the studies mentioned associated joint involvement with septic arthritis: one with the joint involved in 12 of 29 cases; another with the joint involved in 2 of 4 cases; and a third study in which joint involvement was seen in each of 3 cases [212–214]. Epiphyseal separation can also occur after neonatal osteomyelitis and septic arthritis at proximal and distal femur [215].

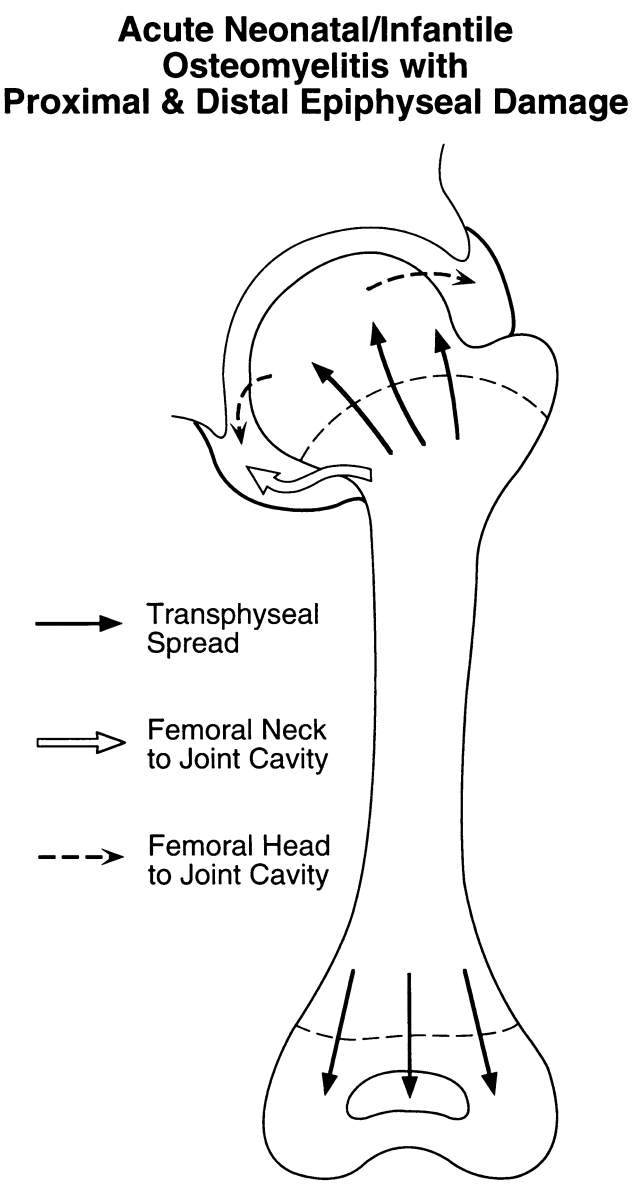

Fig. 4.9 The long-term effects of an acute neonatal/infantile osteomyelitis of the proximal and distal epiphyseal–metaphyseal region of the femur are shown

4.4.3.1 Acute Septic Arthritis of the Hip of Infancy and Childhood

(a) *General overview*: Septic arthritis of the hip of infancy is a rare but potentially devastating disorder which can occur in one of 3 ways: (i) from spread of a metaphyseal focus of osteomyelitis through the physis into the femoral head and then into the joint; (ii) from spread from an osteomyelitic focus within the neck directly into the joint cavity leading to an immediate septic arthritis; and (iii) due to primary hematogenous joint infection without initial foci of adjacent osteomyelitis.

Septic arthritis of the hip has a history of causing severe growth sequelae. In the preantibiotic era a review of 113 cases by Badgley et al. [208] and 65 cases by Slowick [216] showed major complications to include: pathologic dislocation of the hip joint, avascular necrosis (sequestration) of the femoral head, epiphyseal separation, resorption (disappearance) of the head, bony ankylosis, fibrous ankylosis, and shortening. These sequelae were seen throughout the childhood years. With antibiotics and earlier diagnosis, the most severe problems are now concentrated in those with neonatal sepsis and those affected within the first 2 or 3 years of life.

The one region where transphyseal spread of metaphyseal osteomyelitis is commonly documented is at the proximal femur during the first year of life. The spread is attributed to the persistence of transphyseal vessels from the fetal period which allow for direct communication between the metaphysis and the epiphysis. It is for this reason that primary proximal femoral osteomyelitis in the neonate is potentially so severe. Spread of infection can occur into the epiphysis damaging the growth plate and through the lateral walls of the neck passing directly into the joint leading to a septic arthritis since the epiphysis at the proximal femur is entirely intracapsular. After the first year of life, there is little tendency to transphyseal passage of infection although the risk of septic arthritis of the hip in association with proximal femoral osteomyelitis remains high because of the passage of organisms through the thin cortex of the neck which leads to their immediate presence within the joint.

There is considerable variability throughout vertebrates in terms of the persistence of transphyseal vessels as a remnant of epiphyseal development. They are only infrequently seen in murine species and the rabbit, but are commonly seen in the pig and lamb even several months after birth. Such vessels have been documented commonly in human and other species in the late fetal and early postnatal time periods [217].

The damage done to the epiphyseal apparatus of the femoral capital epiphysis by infection can be extensive and can occur rapidly over several hours to a few days in childhood septic arthritis of the hip. Diagnosis is frequently delayed for several days in those children affected in the first few months of life since they are almost always afebrile with little tendency to leucocytosis or elevated ESR values. The commonest mode of presentation in this age group is listlessness and decreased use of the extremity on the involved side, referred to by some as 'pseudoparalysis.' A recent study separated those having the disorder from 0 to 4 weeks of age from those from 1 to 3 years of age. The prognosis was clearly worse in the younger age group and also in those associated with osteomyelitis of the proximal femur. In a preantibiotic era 1936 study, Badgely reported a 12 % mortality in septic arthritis of the hip with only 6.2 % of those surviving having normal hips [208].

Blanche studied osteomyelitis in the first year of life in 25 patients in whom a bacteriologic diagnosis had been made between the years 1934 and 1950 [209]. The age range was from 14 days to 9.5 months but 23 of the 25 were seen within the first 2 months of life, 13 under 1 month of age and 10 from 1 to 2 months of age. Many patients had no fever at all and the systemic temperature was rarely over 100 °F. Local symptoms predominated involving swelling, loss of function of an extremity, and discomfort with movement. In the 25 patients, 13 had a single focus of infection and 12 had multiple foci. The femur was the commonest site by far with 22 of 50 known lesions present there. The next commonest bone involved was the humerus with 7, followed by the tibia with 5, and lesser involvement of other bones. Proximal involvement of the femur was seen in 16 and of these there was an associated septic arthritis of the hip in 11 cases. Distal femoral involvement was frequently associated with growth damage to the distal physis and epiphysis. Intraarticular infection rapidly destroyed the cartilage and frequently caused disruption of the joint, pathologic dislocation, and serious proximal femoral growth disturbances.

The main prognostic feature in terms of ultimate normal development and function is the quickness with which treatment is instituted. In the study, 16 neonates were affected from 0 to 4 weeks of age of whom 11 were premature. In 14 of the 16 patients, the septic arthritis was secondary to an osteomyelitis close to the joint with 10 patients having primary osteomyelitis of the femoral neck and the other an osteomyelitis of the acetabulum. In the second group of 13 children affected between 1 month and 3 years of age, negative sequelae were secondary to avascular necrosis of the femoral head along with lytic damage of articular cartilage, bone, and physeal cartilage. The greater trochanter appears relatively spared.

Hallel and Salvatti defined results into 3 groups following septic arthritis of the hip in infancy [218]. In Group 1, there was a normal femoral head or a head only mildly deformed with a coxa magna. In Group 2, there was a deformed small head/neck component with varus malposition. In Group 3,

there was complete absence of the head and neck owing to lytic destruction. The femoral head may be in normal position, subluxed, or dislocated. Major predisposing features of neonatal septic arthritis were an indwelling umbilical catheter, prematurity, and septicemia. The earlier treatment began, the better the result. Treatment involves open arthrotomy combined with intravenous antibiotic coverage and maintenance of the hip in the reduced position using either a hip spica or Pavlik harness during the healing phase.

Vidigal and Jacomo reported on 14 neonates with septic arthritis of the hip which had been diagnosed late, meaning that diagnosis was made and surgical drainage carried out more than 4 days after the onset of symptoms with the average delay of 9 days [219]. The age of their patients at admission averaged 17 days with a range between 9 and 30 days. In 11 of the cases, the organism was staphylococcus aureus with one each of staphylococcus albus, enterobacter, and streptococcus hemolyticus. Radiographic features at time of diagnosis include a normal appearance in a few but often subluxation, dislocation, and dislocation with periosteal elevation of the proximal femur (associated osteomyelitis) or lysis of the acetabulum (osteomyelitis). Only one hip was normal at followup. Three patients died. The radiographic features of the femoral head seen after long-term followup for neonatal septic arthritis involved 7 in which the femoral head was destroyed and dislocated, 2 in which it was deformed and subluxated, 2 in which it was subluxated, 1 in which it was deformed and dislocated, 1 in which there was avascular necrosis and subluxation, and 1 which was normal.

Nade reviewed septic arthritis of infancy and childhood well stressing the gradual improvements in treatment from the 1800s to the start of the antibiotic era in the 1940s–1950s and beyond [220]. The disorder early on was often life and limb threatening. Surgical drainage and antisepsis limited those events but destruction of the joint was common. Antibiotics, more aggressive surgical drainage and earlier diagnosis and treatment continued to improve results but delay in treatment, especially with neonatal involvement still destroys or seriously damages the growth potential.

Organisms involved. Organisms are identified by bacteriologic assessment of joint fluid or tissue obtained by aspiration or open procedure or by blood culture. Many cases of hip joint sepsis still yield no causative organism at initial assessment. Nade in 1983 (reviewing several studies) reported failure to detect an organism in 25/133 (19 %), 46/117 (39 %), and 19/45 (42 %) of cases [220]. Similar percentages of relatively low rates of organism detection persist more recently: Welkom et al. detected an organism in 61/95 (64 %) [221], Chen et al. in 25/33 (76 %) [222], Journeau et al. 18/43 (42 %) [223], and Samora and Klingele (57 %) [224].

The infectious organisms have remained similar. The most common causative organism in acute septic arthritis in all age groups is staphylococcus aureus [220–224]. Another very common one is haemophilus (H) influenza, especially in the very young between 6 and 24 months of age [220, 221]. Other organisms are identified such as streptococcus pneumoniae (under 2 years of age), group A streptococcus (older than 2 years of age), E. coli, proteus, salmonella, staphylococcus albus, and many others.

The well-accepted triad of treatments for septic arthritis of childhood involves (i) *drainage of the joint*, (ii) *antibiotics*, and (iii) *joint rest* in a comfortable position. There are many approaches, however, to each of these components.

Drainage has been done by needle aspiration (often repeated) or arthrotomy (with irrigation, debridement, leaving the capsule open but closing the skin). Open drainage is rarely considered to be necessary today. Antibiotics are given either parenterally (intravenous) or orally with joint irrigation with antibiotics no longer considered necessary. Resting the affected joint is necessary both for comfort and to prevent displacement but length of time and supportive devices vary with relatively early range of notion exercises encouraged to prevent stiffness. Nade expanded the criteria to include immediate arthrotomy, complete skin closure without drainage, immobilization of the joint, and antibiotics.

(b) *Negative growth sequelae following septic arthritis of the hip*: Eyre-Brook [225] and Sharrard [226] listed the sequelae of hip sepsis as follows: destruction of capital epiphysis with dislocation of the hip; destruction of capital epiphysis with the femoral neck remaining in the acetabulum; destruction of the femoral head–neck growth plate with the femoral head remaining in the acetabulum connected to the neck by a fibrous union; and recovery with only a coxa magna seen. More formal classifications were subsequently formulated to aid in management.

Hunka et al. developed a radiographic classification based on 10 children with disease onset mostly before 18 months of age [227]. A study by Choi et al. evaluated residual deformity and late treatment of 34 hips of 31 children who had septic arthritis when they were <1 year of age [228]. They evolved a classification of the sequelae into 4 types which incorporates well observations made over several decades including those of Hunka et al. [227]. Forlin and Milani felt that the previous classifications were too complicated and difficult to apply in young children [229]. Their classification based on 41 hips with negative sequelae was based on 25 neonatal cases and 16 between 1 and 3 months of age. There were type 1 and type 2 hips each with A and B subtypes. Grade 1 hips were reduced with the femoral head preserved (1A) or absent (1B). Grade 2 hips were dislocated with the femoral head preserved (2A) or absent (2B). The end responses can be extremely variable owing to the time that diagnosis is made, the age of the patient and the type

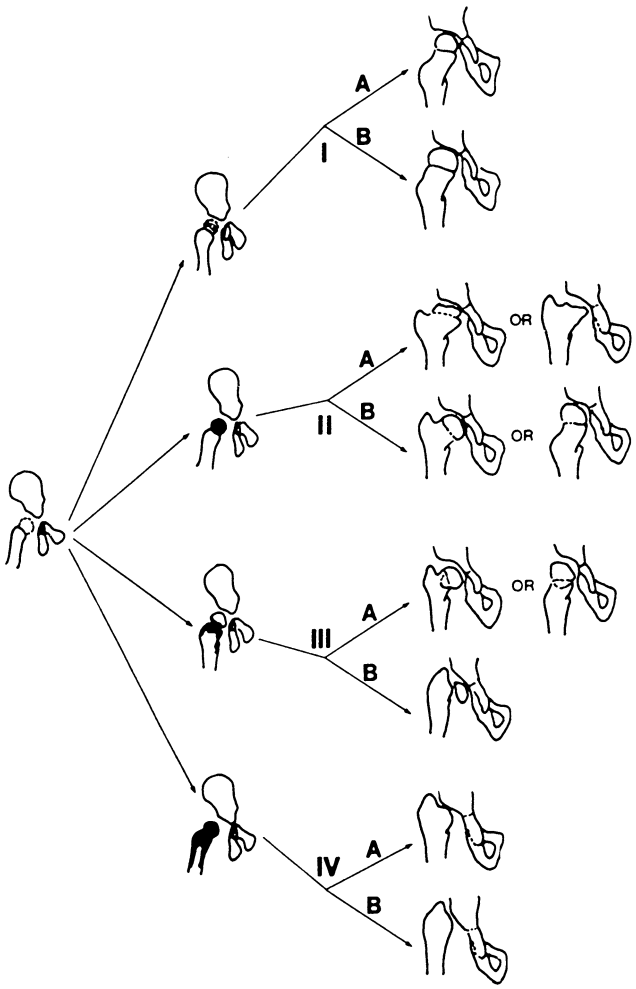

Fig. 4.10 The classification of the sequelae of septic arthritis of the hip in infancy developed by Choi et al. is shown [228]. (Reprinted with permission from Choi et al. Sequelae and reconstruction after septic arthritis of the hip in infants. J Bone Joint Surg Am. 1990;72A:1150–1165)

and effectiveness of the initial treatment used. The classifications of the sequelae are illustrated in Fig. 4.10 and listed in Table 4.3. An example of a damaged proximal femur is shown in Fig. 4.11a. Figure 4.11b (i) and (ii) shows a completely displaced necrotic femoral head denuded of cartilage both articular and physeal at time of removal at arthrotomy after several weeks of symptoms.

(c) *Pathoanatomy of Septic Arthritis of the Hip of Infancy*:

(i) Smith (1874)

Septic arthritis of the hip in infancy was clearly outlined by Smith in 1874 describing acute arthritis in infants in 21 patients, 13 of whom died, and 8 who healed with severe disability [230]. Smith differentiated the "acute arthritis of infants" from any of the other recognized joint affections of childhood. The disorder occurs "in the first year of life and is characterized by the suddenness of its onset and the rapidity of its progress and termination." He concluded that "it is very dangerous to life and intensely destructive to the articular ends of the bones which of course at this period of life are largely cartilaginous." The disease "rarely produces anchylosis but leaves a child with a limb shortened by loss of part of the articular end of some bone and with a weakened flail-like joint." His 21 cases all occurred within the first year of life with 8 in infants under one month of age and 19 of 21 under 6 months of age. The disease first attacked at the hip, shoulder, or knee, and in the absence of effective treatment often involved more than one joint. At postmortem examination, he "found in all instances a considerable and rapid loss of substance in the articular end of one of the long bones entering into the joint affected." In some, the absorption or ulceration proceeded from the joint surface toward the deeper parts, while in others the destruction of tissue had commenced in an abscess within the articular end of the bone which then progressed outwards. This often leaked into the joint by a small opening near the margin of the articular cartilage. He defined the term subarticular abscess referring to abscess cavities formed beneath the articular cartilage either in the cartilaginous or osseous structure of the end of the bone. Smith stressed that "in many cases, the formation of a subarticular abscess in the bone must have been the first step in the joint affection since while the articular end of the bone was extensively excavated, the aperture through which the abscess had burst into the joint was a mere pinhole and though the joint contained pus, the articular cartilage was apparently healthy."

Smith's description of the pathoanatomic findings remains valid today and underscores the need for rapid, accurate diagnosis, and treatment. A brief summary of his descriptive findings at postmortem in several cases of septic arthritis of the hip follows.

[Case 3] The head and part of the neck of the right femur were completely removed by ulceration giving the appearance

Table 4.3 Classification of sequelae: septic arthritis of the hip in infancy

Type	Sequelae
IA	No residual deformity
IB	Mild coxa magna
IIA	Coxa breva with deformed head
IIB	Progressive coxa vara/valga
IIIA	Slipping of femoral neck with severe anteversion or retroversion
IIIB	Pseudarthrosis of femoral neck
IVA	Destruction of femoral head and neck with small medial remnant of the neck
IVB	Complete loss of femoral head and neck and no articulation of the hip

From Choi et al. J Bone Joint Surg Am 1990;72:1150–1165; [228]

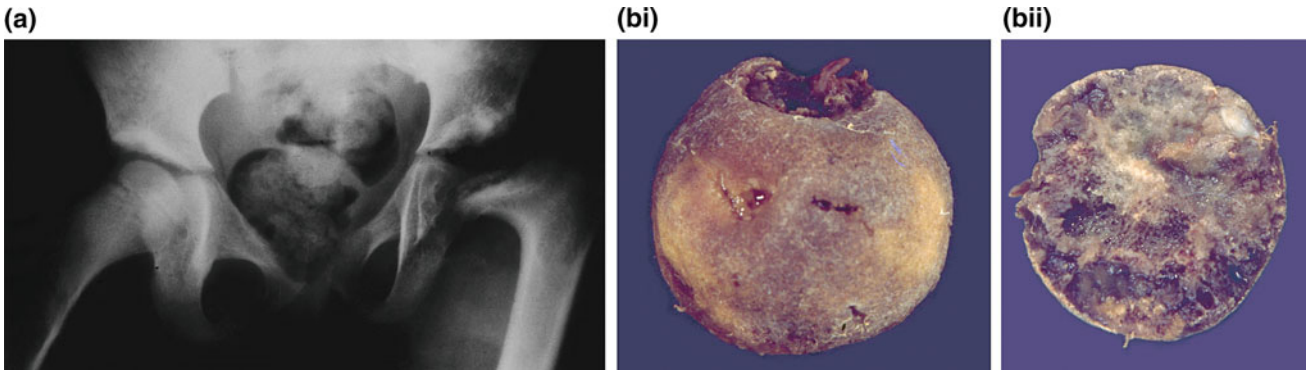

Fig. 4.11 **a** Radiograph illustrates damage caused by neonatal septic arthritis of the hip. The involved femoral head has been almost completely destroyed; the neck is short and wide and greater trochanter overgrowth is marked. **b** A completely displaced and markedly damaged femoral head from a 7-year old with chronic previously untreated septic arthritis of the hip is seen. The femoral head was completely displaced from the neck lying free in the hip joint surrounded by pus at time of arthrotomy. The head was removed and found to be completely avascular and necrotic. Both the articular cartilage (i) and physeal cartilage (ii) have been almost completely resorbed. **c** A detailed algorithm for diagnosis (*white background*) and treatment (*gray background*) of septic arthritis in childhood has been presented by Rutz and Spoerri [247]. (Reprinted with permission from Rutz and Spoerri, Septic arthritis of the pediatric hip. Acta Orthop Belg. 2013;79:123–134. Copyright 2013 Acta Orthopaedica Belgica)

of destruction proceeding from the articular surface to the deeper part of the bone. In the opposite left hip, however, the process of destruction appeared to begin within the bone and pass toward the joint surface, where the end of the bone contained a well-defined subarticular abscess opening by a small hole in the joint. The right hip was filled with pus, the synovial membrane thickened and vascular, the capsular ligament perforated by abscess, no ligamentum teres, and the head of the femur had been completely removed. All the acetabular cartilage had been destroyed. The left hip also contained pus, but the synovial membrane, articular cartilage, and ligaments appeared healthy. There was a small ragged hole at the margin of the articular cartilage which leads by a narrow sinus into a well-defined abscess cavity containing pus. This was situated partly in the ossifying cartilage and partly in the cancellous bone.

[Case 4] A huge right thigh abscess leads to death 18 days after the patient presented for medical care. The right hip joint was full of pus. The ligamentum teres had disappeared, the capsular ligament had ulcerated, the rim of the acetabulum was destroyed by ulceration, the synovial membrane was thickened and vascular, and the head and neck of the femur had disappeared completely.

[Case 5] There was left hip joint swelling and discomfort with an abscess found in the hip joint at postmortem. The ligamentum teres had disappeared, the capsule was opened by ulceration, the cartilage of the acetabulum was in places totally destroyed, and the head of the femur was absorbed having lost approximately 2/3 of its structure.

[Case 6] The left hip was full of pus, the ligamentum teres had given way, and the cartilage while intact had lost its pearly appearance.

[Case 8] A patient, aged 7 weeks at presentation, died 6 weeks after onset of symptoms with a right hip abscess. Postmortem examination showed the synovium in the right hip joint to be swollen and vascular, the ligamentum teres had disappeared, approximately one fourth of the head of the femur had been resorbed, and the articular surface was covered with punctate ulcerations. One of the small ulcers passed through a minute sinus to a cavity in the cancellous bone just beneath the ossifying cartilage. This cavity which was approximately one inch in its longest diameter was lined by a thick false membrane. The osseous nucleus and the cartilaginous head of the bone were similarly excavated and communicated by a pin hole opening in the articular cartilage with the cavity of the joint. The acetabulum was shallow, widened laterally with its sharp edge absorbed, and its cartilage gone.

[Case 9] There was a right hip abscess with the hip joint full of pus. The capsule was widely opened by ulceration. The ligamentum teres had disappeared, and the acetabulum was denuded of cartilage. The head and upper part of the neck of the femur had been completely absorbed.

Smith indicated "that many children not only survive the attack, but recover with useful joints." He described a 6-month-old female who developed a left hip abscess which drained spontaneously. At 6 years of age, there was 1.5–2 inches of shortening, the thigh muscles were smaller, and the limb was everted in walking and somewhat flail. What remained of the head of the femur was dislocated and easily mobile. He described other cases with survival and reasonable function although rarely with a normal joint. The problems were related to limb shortening; multiple scars where the abscesses had drained either spontaneously or by

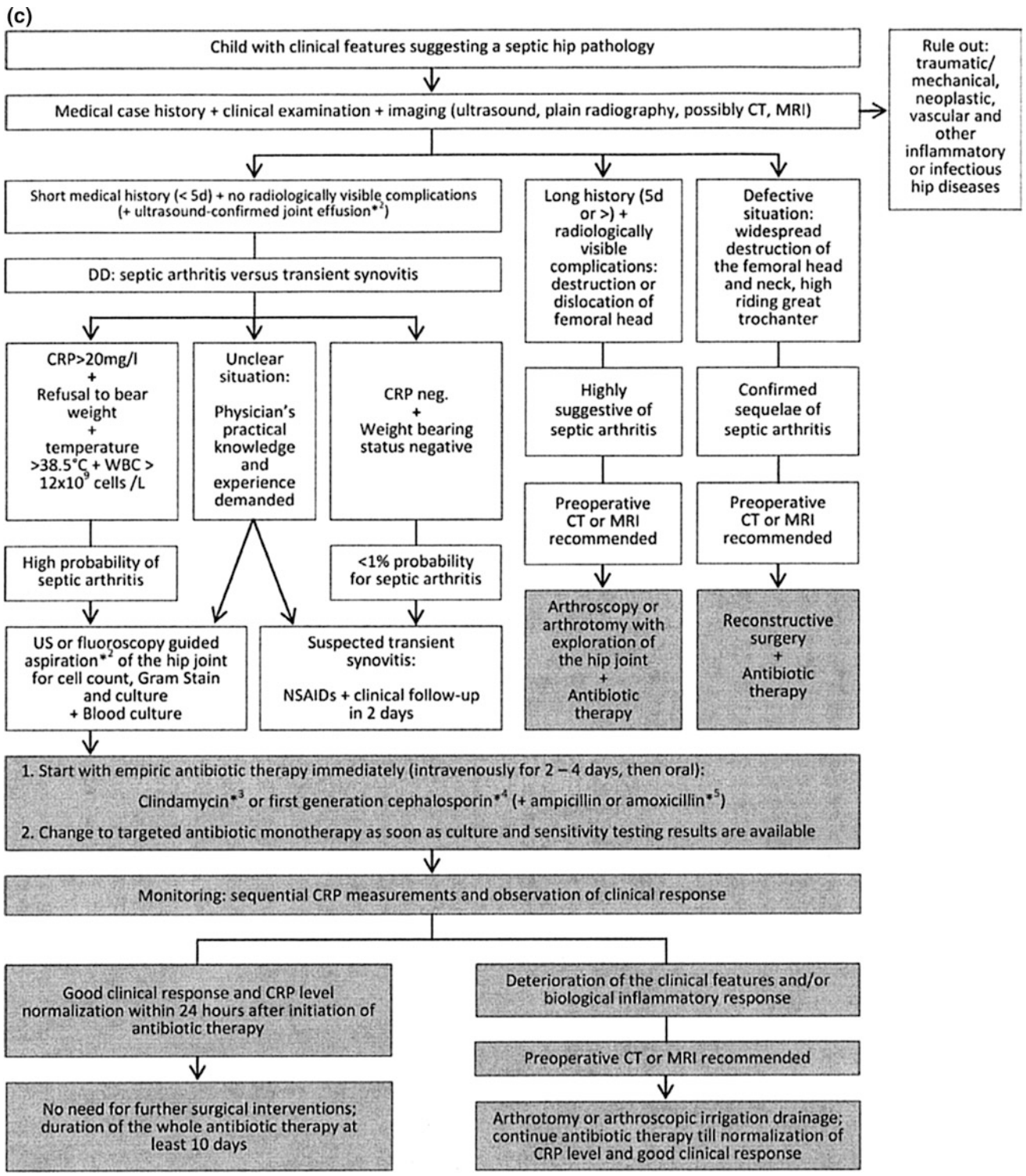

Fig. 4.11 (continued)

surgical intervention—a tendency to a dislocated or dislocatable head of the femur—movements of the joint that were abnormally free and considerable limping.

(d) *Diagnostic considerations for septic arthritis of the hip*: In the first year of life clinical signs include listlessness and pseudoparalysis of the lower extremity observed as

a disinclination to move the limb. Temperature elevation is not common in the neonate under 1 year of age. Swelling and warmth of the thigh are relatively late findings owing to the deep position of the hip joint. After 1 year of age and especially in those already walking findings are more clear and include limping or loss of ambulation; pain in hip, thigh, or inner knee regions; decreased hip flexion, internal rotation, and adduction on physical examination; temperature >38 °C; leucocytosis with white blood cell count >11,000 cells/mm^3; elevated ESR >20–40 mm/hour; C-reactive protein >1–2 mg/dL; hip ultrasound showing intraarticular fluid; and hip radiograph showing 2 mm or more widened joint space or lytic bone lesions of metaphysis, secondary center or acetabulum. The main differentiation needed is from transient synovitis of the hip discussed in detail below in Sect. 4.4.5.

(e) *Treatment approaches*: The long-term sequelae of a septic arthritis of the hip can be extremely severe so early diagnosis and aggressive therapy are needed. There is universal agreement that the best results even leading to complete cure with no long-term sequelae are seen with early diagnosis and prompt treatment. By "early" is meant within 3–5 days of the onset of symptoms. The treatment triad of joint drainage, antibiotics, and joint immobilization (rest) is also widely agreed to but approaches to those concepts vary [220, 224]. Open arthrotomy is preferable to joint aspiration for the hip. Arthrotomy releases intraarticular pressure, provides a channel through which subsequently developing pus can easily escape (by not completely closing the capsule), and allows for accurate bacteriological diagnosis. Maintenance of the femoral head in the fully reduced position within the acetabulum by hip spica immobilization minimizes the likelihood of a septic dislocation [231, 232]. Intravenous high-dose antibiotics are used to clear osseus and soft tissue infection. While urgent treatment is carried out once the diagnosis is suspected, it is becoming apparent that treatment by arthrotomy and appropriate antibiotics within 5 days of the onset of symptoms should lead to an uncomplicated recovery [233]. A recent prospective study of 38 patients in South Africa from September 2004 to December 2005 involved 40 hips with proven hip sepsis diagnosed by arthrotomy with bacteriologic and histologic confirmation [233]. All patients treated within five days of onset of symptoms by arthrotomy and antibiotics had full and uncomplicated recovery (14 hips, 34 %) while those treated later had complications (25, 66 %) with followup at a mean of 8 months. Complications included one death, avascular necrosis of the femoral head (11, 29 %) in which four had the femoral head completely destroyed, joint stiffness and pain (8, 21 %) of whom four had chondrolysis, one acetabular erosion, and coxa vara (3, 8 %) due to pathologic fracture or slipped upper capital femoral epiphysis or both. Patients in this study were drawn from a wide geographic area with many from economically disadvantaged areas.

Treatments of the long-term sequelae have been described in several reports and are outlined in Table 4.4 [208, 218, 225, 226, 228, 234–238]. To these can be added the advanced hybrid Ilizarov method which addresses both hip reconstruction and femoral lengthening with good success [239, 240]. Treatments include: open reduction (OR), OR with Dega osteotomy, OR with Dega and proximal femoral varus osteotomy, OR with innominate osteotomy, valgus proximal femoral osteotomy, acetabular shelf procedure, distal transfer of the greater trochanter, ipsilateral femoral lengthening, or contralateral femoral epiphyseodesis.

(f) *Summary of current approaches to septic arthritis in children*: The management of septic arthritis in children has been assessed in an extensive review of the English language literature [241]. Multiple investigational methods in use are needed for diagnosis; single investigations, including joint aspiration, are not sufficiently reliable for conclusive diagnosis. These have been reviewed in the previous sections and included: history, concentrating on determining the earliest time of onset; overall patient appearance (listlessness, lack of energy); temperature pattern; blood tests including white blood cell count with differential, erythrocyte sedimentation rate (ESR) and C-reactive protein; imaging including plain radiographs and hip ultrasound: and bacteriologic assessment using joint fluid and blood cultures.

Removal of joint fluid for diagnosis (bacteriology) and treatment is agreed upon but approaches (especially initial ones) vary between needle aspiration, arthroscopy, and open surgical arthrotomy. Many still favor open hip arthrotomy with irrigation and leaving part of the capsule open since the long-term sequelae of growth damage are so severe. There is no widespread agreement as to which approach is best, although needle aspiration/irrigation is usually reserved for the very early stages, although it can be repeated if symptoms persist. Journeau et al. [223] and Chen et al. [222] favor the aspiration approach. El-Sayed et al. compared results of open hip arthrotomy versus arthroscopic drainage with 10 patients in each group and found similar results with either approach (although this is a small series) [242].

Table 4.4 Late operative treatments for severe sequelae of infantile septic arthritis of the hip

1. Excision of damaged femoral head
(i) for necrotic, completely separated femoral head lying free in joint (septic epiphysiolysis)
(ii) to remove projections and allow for repositioning procedures
2. Adductor/Iliopsoas tenotomies
• for adduction, flexion contractures
3. Open reduction
(i) femoral head into acetabulum–after septic pathologic dislocation
(ii) femoral neck into acetabulum–after severe head destruction
(iii) greater trochanter into acetabulum–trochanteric arthroplasty
4. Greater trochanteric interventions
(i) trochanteric arthroplasty (see above)
(ii) distal transfer of greater trochanter
(iii) greater trochanteric epiphyseal arrest–all to increase hip stabilization, minimize Trendelenburg gait
5. Proximal femoral osteotomy
(i) varus osteotomy
• following lateral subluxation, or partial premature lateral physeal closure
(ii) valgus osteotomy
• to better position head into acetabulum following complete or medial premature physeal closure with persisting trochanteric growth
• to support and align lower extremity in relation to the hip joint, disregarding shape, and position of head but correcting the adduction position of femur
(iii) extension/derotation osteotomy
• to correct additional deformities sometimes present with (i) or (ii) above
6. Acetabuloplasty
• shelf, Pemberton, Salter, Chiari, other
7. Epiphyseal Arrest
• for lower extremity length discrepancy
• contralateral distal femur ± proximal tibia
8. Ipsilateral tibial lengthening
• for lower extremity length discrepancy
• femoral lengthening rarely done because of hip instability
9. Contralateral femoral shortening
• for severe lower extremity length discrepancy
10. Bone graft for proximal femoral pseudoarthrosis
• often accompanied by osteotomy
11. Hip arthrodesis
• for painful ± unstable hip not amenable to above approaches

Derived from [208, 218, 225, 227, 228, 231, 232, 234, 238, 241]

Paakkonen et al. showed that hip joint aspiration followed by antibiotics was successful without resort to surgical arthrotomy in 81 % of 62 patients with pediatric nonneonatal septic arthritis of the hip [243]. All cultures were positive with staphylococcus aureus in 71 %. [Delay did not seem to affect those eventually needing arthrotomy due to slow response.]

Givon et al. treated septic arthritis of the hip by repeated ultrasound-guided aspirations in 34 children with no complications seen [244]. Arthrotomy was needed in some (six) followed by aspiration, in four arthrotomy followed aspiration, and in 24 aspiration only was done.

A similar revision of time needed for parenteral antibiotics has occurred, with a clear tendency to turn to oral antibiotics earlier. This is very variable since the type of antibiotic is dependent on the organism identified, cases when no organism is identified (tendency to broad spectrum coverage), the sensitivity of any organism, the response

Table 4.5 Differential diagnosis of the irritable hip in children

Infectious	Septic arthritis
	Tuberculosis
	Lyme disease
	Osteomyelitis
Inflammatory	Transient synovitis
	Juvenile rheumatoid arthritis
	Rheumatic fever
Traumatic/mechanical	Fractures
	Slipped capital femoral epiphysis
	Muscle injuries
	Contusions
Vascular	Legg–Calvé–Perthes disease
	Haemoglobinopathies (hemophilia, sickle-cell disease)
Neoplastic	Benign tumors with impending fractures
	Malignant tumors
	Leukemia
	Lymphoma

Modified from Rutz and Spoerri: 247

initially, and even the medical delivery system since the availability of out-patient intravenous therapy might predispose to longer use of that method. Paakkonen and Peltola have pointed out the value and safety of earlier switch to old agents in non-neonatal septic arthritis starting as early as 2–4 days after IV therapy, four times a day [245, 246]. Septic arthritis of the hip (i) in the neonatal time period (birth–4 weeks) or even within the first year of life, (ii) clearly associated with a proximal femoral osteomyelitis, or (iii) presenting with a >5 day history regardless of age have a poorer prognosis and in the opinion of many warrant more aggressive intervention (arthroscopy or arthrotomy) and more prolonged parenteral antibiotics.

In efforts limiting the time of antibiotic therapy, Paakonen and Pettola have reported a total course of as little as 10 days [246].

Organisms. The commonest organism remains staphylococcus aureus followed by respiratory pathogens streptococcus pyogenes, streptococcus pneumonia, and haemophilus influenza type b.

Antibiotics. Coverage often begins before organisms are determined (after aspiration/blood culture) but should include agents for the common organisms listed above. Antibiotic choice varies greatly by regional preference. A common protocol in many centers is 3–5 days intravenous followed by 3–4 weeks orally. It has been found that CRP is a very sensitive indicator of response while ESR levels lag clinical findings considerably [246]. Once CRP has declined below 20 mg/L healing is considered to be well underway to almost complete.

Diagnostic Criteria. A literature review of articles on septic arthritis of the pediatric hip covering 53 papers from 2002 to 2012 listed the key diagnostic findings as: CRP >20 mg/L, nonweight bearing status, temperature >38.5 °C, and white blood cell count >12 × 109 cells/L offered a predictive probability for septic arthritis of 87 % [247]. The entire entity was reviewed concentrating on research from the first decade of the twenty-first century. Most cases previously occur in healthy children. Associate predispositions include young age (neonatal to under 2 years), respiratory problems, umbilical artery catheterization, and instrumentation of the urinary or gastrointestinal tracts.

In neonates and infants generalized malaise, poor appetite and irritability are (in retrospect) common, while fever is sometimes delayed. Pseudoparalysis is seen in nonambulatory age groups with the involved extremity lying in hip flexion, external rotation, and abduction with limited passive motion. A detailed flow chart of diagnostic and treatment options has been presented (Fig. 4.11c). A differential diagnosis of the irritable hip in children must be considered (Table 4.5). Differentiation is most commonly needed between septic arthritis and transient synovitis of the hip which is discussed in detail in Sect. 4.4.5.

Imaging. Plain radiographs of the hips, while always done, are not helpful for early diagnosis of septic arthritis unless there are bone lysis collections seen in the proximal femur. Ultrasound is the best way to define a joint effusion but cannot distinguish between septic arthritis and benign synovitis. MRI is not used routinely or available in many primary care facilities worldwide.

Diagnostic hip joint needle aspiration is done in essentially all centers. If signs point to a likelihood of septic arthritis, broad spectrum antibiotic therapy is started immediately after aspiration. The response of the patient clinically as well as the CRP value over the first 24 h of therapy guides subsequent management. It is increasingly recognized that a CRP >20 mg/L and refusal to bear weight in the ambulatory age group are highly suggestive of septic arthritis.

4.4.3.2 Septic Arthritis of Joints Other Than the Hip and Their Sequelae in Relation to Epiphyseal Development

In a large study of 102 cases of septic arthritis of childhood, the hip was most commonly affected both in the 0–3-year-old age group and in the 3 years and older group [248]. There were 42 joints involved in the 0–3-year-old group: hip—18/42, 43 %; knee—15/42, 35 %; ankle—5/42, 12 %; wrist—2/42, 5 %; and shoulder 1, elbow 1–2 % each. The same distribution continued in the older age group.

(a) *Knee*: After the hip, the next most frequently involved joint is the knee. Smith described the effects of septic arthritis of the knee in infancy as defined at postmortem examination [230]. The medial condyle of the femur was involved with "a large ragged hole in the cartilage of the internal condyle, large enough to admit one's finger; this led into a deep excavated cavity in the bone and ossifying cartilage; this cavity occupied a large part of the articular part of the femur of which little remained but the shell." In another case, both knees were involved. Postmortem examination on the right showed the joint to be partially ankylosed and the synovial membrane thickened and a pinkish color. The opposing surfaces of tibia and femur were firmly adherent by infected granulation tissue and "could not be separated by tearing." The articular surface of the femur was deeply excavated by ulceration. On hemisection, there was a small circular cavity within the cartilaginous end of the femur which led by a pin hole sinus through the condyle into the joint. The opposite knee was filled with pus. The synovial membrane was thickened and vascular and the cartilage surface of the femur was irregularly absorbed to a depth of half inch or more. There was a fold on the anterior surface of the lateral condyle one by fourth inch wide and half inch deep lined by vascular tissue. Hemisection showed a cavity in the lower end of the femur partly in the bony secondary center and partly in the ossifying cartilage.
With septic arthritis of the knee, the distal femur suffers more growth-related sequelae than the proximal tibia. Angular deformities due to partial distal femoral physeal destruction are far more common than complete symmetric growth cessation. The most damaging growth sequelae continue to follow neonatal sepsis and, to a lesser extent, those affected within the first 2 years of life. At later ages, earlier diagnosis and more effective treatment minimize negative sequelae. A large study of 96 septic knees in childhood demonstrated far more serious growth sequelae in patients who were 24 months of age or younger at the time of diagnosis [249]. In 50 knees assessed in detail in those within 2 years of age, 26 had no deformity at followup and 24 did. Fifteen had a varus deformity, average 14º, and range 5°–30º, and 9 were in valgus with an average of 22º and a range from 5º to 40º. Seventeen of the knees had flexion contractures averaging 12º with a range of 5º–25º. Central growth retardation of the distal femoral physis was noted in almost every case where metaphyseal changes were accompanied by deformity. The secondary ossification center was also delayed in appearance or if present was partially lysed. The tibia was less often and less severely affected than the femur.

(b) *Disturbed Distal Femoral Epiphyseal Growth After Infantile Osteomyelitis*: The vital anatomic finding underlying the possible spread of metaphyseal osteomyelitis through the physis and into the epiphysis directly in the newborn period is the persistence of transphyseal vessels during this time frame. Neonatal osteomyelitis thus can damage epiphyses directly at the proximal femur and also in other large physes with the two most commonly affected being the distal femoral and proximal humeral. Infection at the distal femur has the next greatest tendency after the proximal femur to lead to major growth complications. Ogden and Lister performed a histopathologic study of hip, shoulder, and knee from a child who died at 27 days of age with multifocal osteomyelitis [250]. The distal femur epiphysis demonstrated severe destruction with complete physeal separation. Metaphyseal trabecular bone was clearly affected and was being destroyed. The distal femoral growth plate had been completely destroyed and the hyaline cartilage of the epiphysis was diffusely invaded. Serial sections demonstrated an inflammatory exudate that could be traced along the cartilage canals from the metaphysis through the physis into the secondary ossification center of the epiphysis. The trabecular bone in the secondary ossification center was also being destroyed by the inflammatory process. Examples of distal femoral epiphyseal damage following neonatal infection were also reported by Banks et al., [251] and Halbstein [252]. A study by Bergdahl et al. documented that neonatal osteomyelitis led to a high rate of negative long-term sequelae [253]. Particular risk factors include large vessel and umbilical catheterization, a gestational age of <37 weeks or birth weight of <2,500 g, and more generalized indications of systemic illness such as the respiratory distress syndrome, hyperbilirubinemia, perinatal asphyxia and the need for an emergency cesarean section. In the study of 40 patients with 71 sites of infection, the most commonly involved regions were the knee in 19 (27 %), the hip in 17 (24 %), the shoulder in 9 (13 %), and the ankle in 6 (8 %). Any joint can be involved but these four accounted for the highest involvement.
Papers discussing osteomyelitis of the long bones in infancy in the preantibiotic era stressed high mortality, while information analyzed subsequent to antibiotic use noted diminished mortality but increasing episodes of disturbed epiphyseal growth [203]. Roberts clarified the severity of growth problems at the knee with a study of 14 children who had bone infection present within 6 weeks of birth. One patient presented at 3 months. In 13, the distal femur was involved while in only two was damage seen at the upper tibia. Involvement of two or more sites was

noted in five of the 15 patients. In spite of seemingly adequate treatment, growth sequelae were seen in virtually all instances. Major problems involved shortening which was present in all and angular deformity which was present in most. Instability of the joint and diminution in the ranges of movement were seen frequently as well.

Two major points are noted with neonatal infection in relation to the appearance of the epiphyses. 1. There is often considerable lysis followed by delay in formation of the secondary ossification center in particular of the distal femoral epiphysis. Many have commented that the radiographic damage often looks greater than subsequent films at skeletal maturity indicate. The crucial factor is thus not only the appearance of the secondary ossification center, but also the presence, viability, and structure of the cartilage mass of the entire epiphysis. It is not infrequent after an infection that reossification occurs several years after the normal pattern if the cartilage model has managed to survive. There is often indication of the presence of the cartilage model based on the range of motion and function of the joint. This can be readily determined either by arthrography or magnetic resonance imaging. 2. Growth may continue in a relatively normal fashion for several years after the infectious insult but then slow down well before skeletal maturation leading to further shortening and angular deformity over the final years of growth. These patients should thus be followed to skeletal maturation. It is rare for the entire physis and epiphysis to be completely destroyed, and corrective surgery and limb lengthening should lead to a reasonably functioning knee at skeletal maturity. Owing to the fact that most of the growth of the lower extremity occurs at the knee the amount of shortening can be extensive. In Roberts' series, several patients had discrepancies between 10 and 14 cm with many from five to nine cm shorter on the involved side.

Langenskiold also reported several cases of growth disturbance of the distal femur after neonatal osteomyelitis [254]. His cases had onset of infection between 10 days and 4 weeks. The medial epiphysis was affected in 3 cases and the lateral in 4. The disorder led to partial closure of the growth plate seen in a range from 6 to 12 years of age. Growth and subsequent damage of the epiphysis were unpredictable on the basis of plain radiographic findings in particular during infancy and the early years of life. The maximum shortening documented was variable depending on the nature of the involvement and ranged from 3 cm to as great as 19 cm.

(c) *Shoulder*: A case of arthritis of the shoulder was described by Smith with pus in the joint [230]. The cartilage over the glenoid cavity had disappeared and the bone beneath was roughened. The head of the humerus was wasted, ulcerated, and deformed by absorption on hemisection. An irregular cavity was exposed between the ossifying cartilage and the shaft of the bone.

Examples of septic arthritis of the shoulder with long-term sequelae continue to be described. A large series from Poland indicated that 18 % of septic joints of childhood were at the shoulder [255]. In a review of 46 septic shoulders in 42 patients <18 months of age who were followed for an average of slightly under 7 years, only 7 % of the humeral heads were entirely normal radiographically. Although length discrepancies did occur, the mean amount of shortening was only 2.4 cm after several years but one patient experienced a 9 cm shortening. There were few complaints about the length either from functional or cosmetic viewpoints. The initial appearance of the secondary ossification centers in the humeral head was slowed by the infection, while in those patients where they were already present at the time of infection they usually disappeared for months to years. There was no specific pattern to the negative sequelae which occurred. There was a continuum of distortion of the shape of the humeral head from normal to knob-like, with various amounts of flattening, reorientation of the tilt of the head, and degrees of forking or saddling of the epiphysis.

Schmidt et al. reviewed nine children diagnosed with septic arthritis of the shoulder [256]. Eight of the nine were under 18 months of age at time of diagnosis. Involvement was felt to be owing to transphyseal spread from metaphyseal vessels, secondary to metaphyseal perforation into an intraarticular part of the joint, and also spread from the bicipital synovial sheath which can be affected and which passes over the joint. Growth sequelae were relatively rare and all patients developed a satisfactory pain-free range of motion. Even if varus of the proximal humerus and some shortening occur these rarely present the clinical difficulties inherent with similar lower extremity damage.

(d) *Wrist*: Septic arthritis of the wrist is extremely rare but can on occasion lead to negative growth sequelae [257]. Damage can involve lysis of the secondary ossification center and destruction of all or part of the radial growth plate.

(e) *Long-term sequelae of childhood septic arthritis*: Involvement of major joints other than the hip with septic arthritis, in particular the knee, shoulder and ankle, after the first year of life is due primarily to direct joint involvement rather than through transphyseal spread from metaphyseal foci. The physes are extracapsular and transphyseal vessels in the human postnatal age group are infrequently documented after 1 year of age. There is also a tendency for septic

arthritis in these joints to be diagnosed sooner than the hip because they are more superficial and swelling and redness are more readily seen. After sepsis within the first 2 years of life in particular, even if it appears to have been treated effectively, it remains important to follow the growth pattern for several years and to skeletal maturity if possible. Peters et al. assessed several cases of neonatal joint sepsis other than the hip where growth sequelae were not apparent for several years [258]. It was often not clear retrospectively whether the damage resulted from a metaphyseal osteomyelitis or a primary septic arthritis. Four distal femurs suffered growth sequelae with a partial growth plate arrest leading to shortening and valgus deformation. There were four proximal humeral deformities, all varus; one distal radial shortening with ulnar prominence; and one distal humeral shortening. Growth plate arrest following sepsis often extended beyond the area of bone bridging with the adjacent physeal tissue fibrous rather than cartilaginous. Gillespie has analyzed cases of septic arthritis of major joints in childhood in terms of residual disability [248]. In the hip, 17 of 41 cases (41 %) had an unsatisfactory result; in the ankle 2 of 13 cases (15 %) were unsatisfactory; and in the knee, only 3 of 37 cases (8 %) were unsatisfactory. Long-term assessment is also important because of the potential for radiographic improvement of the involved epiphyseal region several months to years after the infection. There is often lysis of bone of the secondary ossification center and/or the adjacent metaphysis even though the cartilage model is intact. The infection can cause necrosis of bone with subsequent reabsorption but delayed new bone formation. In younger epiphyses where the secondary center has not yet formed, vascular damage can lead to a marked delay in formation of the center but the cartilage model can continue to grow. Studies to assess the cartilaginous structure of an epiphyseal region using either arthrography or MR imaging are essential to assess growth potential where bone deficiency by plain radiography is seen.

4.4.4 Summary of Effects of Epiphyseal and Metaphyseal Infection on Epiphyseal Growth

The three possible growth effects of juxtaepiphyseal pyogenic infections are stimulation of growth, retardation of growth, and angular deformity [259]. The nature and extent of lower extremity length discrepancies in relation to septic arthritis of the hip and osteomyelitis of growing bones are summarized below and reviewed in greater depth in Chap. 6.

4.4.4.1 Osteomyelitis

Overgrowth of a long bone that is the site of osteomyelitis was found in 18 of 35 patients (21 %) in Wilson and McKeever's series [260]. This occurred almost always when the osteomyelitis was metaphyseal and damage to the physis had not occurred. Trueta and Morgan stated that overgrowth following osteomyelitis lasts until medullary recanalization occurs by which time the sequestra would have been resorbed and a normal vascular pattern would have been reestablished [261]. The maximum overgrowth was 2.0 cm, but most patients had only a few millimeters. In chronic recurrent osteomyelitis of childhood, however, overgrowth will persist. When an infection is localized eccentrically beneath the epiphyseal plate, then growth stimulation can also be asymmetric and angular deformities may occur. The same percentage of patients had growth retardation when chronic infection damaged the physis. In the modern era, diagnosis of metaphyseal hematogenous osteomyelitis within a few days of onset followed by intravenous antibiotics and transcortical decompression drilling, if needed, has led to rapid cure, and growth sequelae are now much less frequently encountered.

4.4.4.2 Septic Arthritis of the Hip

Damage to the femoral capital epiphysis in septic arthritis can produce serious length discrepancies. Such discrepancies tended to increase with time, but a type I pattern was seen in only 42 % of the patients, and most commonly when the infection had occurred relatively late, after the age of 7 or 8 years [262]. An assessment of pattern development in this group was obscured more often than in other groups because of the necessity for early and often frequent surgical intervention, although femoral osteotomy was done infrequently in growing children.

Even with complete destruction of the physis, however, femoral shortening did not invariably become worse with time, particularly in the younger patients. When the greater trochanter overtakes the involved femoral head in height, the femur resumes a somewhat more regular growth pattern as the greater trochanter and distal femoral physes are normal, thus accounting for the type II and III patterns seen. Studies of growth sequelae of septic arthritis of the hip of infancy by Betz et al. [234], Choi et al. [228], and Hallel and Salvati [218] documented mean length discrepancies of 3–3.5 cm from injury to the proximal femoral growth plate and an additional 2.5 cm if there was hip instability.

The type-IV growth pattern was limited almost exclusively to abnormalities of the proximal end of the femur such as occur with septic arthritis of the hip. In patients in whom damage was relatively mild, premature fusion of the proximal femoral capital physis has been noted years after the infectious insult. The premature fusion can be detected 2 or 3 years prior to skeletal maturation by the progressive change in the

relationship of the level of the greater trochanteric physis to that of the proximal femoral capital physis. It is, therefore, extremely important to continue periodic assessment of these children by monitoring carefully the relationship of the head and neck to the greater trochanter until skeletal maturity, even if the discrepancy has been in a plateau phase for several years. Although the average increase in the late phase was only approximately one centimeter, this amount can convert a clinically insignificant discrepancy to one of 2.4 cm or more, and thus warrants special consideration.

4.4.5 Transient Synovitis of the Hip in Children and Its Differentiation from Septic Arthritis

4.4.5.1 Overview

Transient synovitis of the hip in children is a benign self-limiting disorder. It presents clinically in a similar fashion to an early septic arthritis of the hip; however, the potentially devastating damage of sepsis to the hip has made early differentiation of the two of prime importance. The terms "observation hip," "irritable hip," and "toxic synovitis" are also used to refer to the transient synovitis entity. Adams studied 50 patients, all admitted to hospital, with an average followup of 6.5 years (range 1–15 years) [263]. Most occurred between 5 and 10 years of age with considerable involvement also between 1–5 and 10–15 years. The male–female ratio was 3:2 with equal side involvement. The onset of symptoms was acute in 28 and gradual in 22. Some injury was present in 6 and limping alone without pain was seen in only 4. All had spasm of the hip muscles, especially flexors, and adductors with decreased ranges of motion. Fever of 100°F or greater was seen in only 2, white blood cell count of >12,000 in only one (the patient also had an upper respiratory infection), and the erythrocyte sedimentation rate was over 5. In the 10 hips aspirated, 5 retrieved fluid but all cultures were normal. Symptoms settled within a few days. There was "no evidence" that the condition progresses to more serious disorders. The synovitis usually lasted for a few weeks and was followed by complete resolution. Studies from the 1930s to recent times continually reinforced these findings.

4.4.5.2 Clinical Prediction Algorithms

The presence or absence of several of the diagnostic factors in the 2 entities was then compared to see if clinically helpful prediction algorithms could be established. Large studies deigned to differentiate between transient synovitis and septic arthritis using various clinical, laboratory, and radiographic results had relatively poor ability to distinguish between the two because of substantial overlap between the various criteria. Individual variables even in large studies continued to show overlap between the two groups. The works of Molteni [264] reviewing 97 cases of nonspecific arthritis and 37 cases of septic arthritis of several large joints and of Del Beccaro et al. assessing hip involvement demonstrated this predicament [264, 265].

(a) Kocher et al. 1999. Kocher et al. reviewed the value of several criteria in differentiating between septic arthritis of the hip and transient synovitis [266]. The diagnoses were explicitly defined by white blood cell counts in joint fluid, cultures of blood and joint fluid, and clinical course. Of the many factors in the two clinical entities, four independent multivariate clinical predictors were identified to differentiate between the two conditions: fever, nonweight bearing, erythrocyte sedimentation rate of at least 40 mm per hour, and serum white blood cell count of more than 12,000 cells per cubic millimeter. The predicted probability of septic arthritis was determined for all 16 combinations of these 4 predictors and was calculated as <0.2 % for no predictors, 3.0 % for 1 predictor, 40.0 % for two predictors, 93.1 % for 3 predictors, and 99.6 % for all four predictors. By combining these variables, a highly accurate diagnostic capability was revealed. Joint aspiration was performed in 168 hips. Univariate analysis in 82 patients with septic arthritis differed significantly ($P < 0.5$) from 86 with transient synovitis in the differentiating features for such criteria as erythrocyte sedimentation rate (51.6 ± 23.5 vs. 21.3 ± 12.5 mm per hour), serum white blood cell count (15,000 ± 5700 vs. 9900 ± 3100 cells per cubic mm), temperature (38.7 ± 1.0° vs. 37.4 ± 0.6 °C), nonweight bearing status (78 patients, 95 % vs. 30 patients, 35 %), history of fever (82 % vs. 8 %), and joint effusion on radiographs (77 % vs. 38 %). The simplified algorithm based on the number of multivariate predictors appeared able to overcome substantial overlap between the entities in the intermediate ranges of the variables. It was the independent multivariate predictors that allowed for the more clear cut differentiation.

(b) Eich et al. 1999 [267]. Eich et al. found that a CRP (C-reactive protein) >2.0 mg/dL was seen in all 8 patients with septic arthritis but in only 14 % of those with transient synovitis. They studied 14 patients referred for acute hip pain. An elevation of ESR >55 mm/hr was found on all patients with septic arthritis. Radiographs were not found to be helpful in the initial evaluation and were not recommended except in those under 1 year of age (to look for signs of abuse or associated osteomyelitis) and over 8 years of age (concern for slipped epiphyses). Hip ultrasound was valuable and all children with septic arthritis had a hip effusion shown by ultrasound. They concluded that, in differentiating septic from nonseptic conditions, rectal temperature > 38 °C,

ESR > 20 mm/hr, and CRP > 2.0 mg/dL had good discriminating power along with hip ultrasound.

(c) Jung et al. 2003 [268]. Jung et al. studied 97 patients with transient synovitis of the hip and 27 with septic arthritis of the hip using univariate and multivariate regression analysis of several parameters. The retrospective study showed that 5 multivariate indicators for differentiation were more predictive of septic arthritis: temperature > 37 °C, ESR > 20 mm/hr, CRP > 1 mg/dL, serum wbc count > 11, 000 cells/m^3, and a joint space difference > 2 mm on plain hip radiographs. An algorithm for probability of septic arthritis was established; all 5 predictors led to a 99.1 % likelihood of septic arthritis. They concluded that patients with 4 or 5 predictors had a high probability of having septic arthritis of the hip and thus warranted further study such as hip joint aspiration.

(d) Levine et al. 2003 [269]: Levine et al. assessed the value of C-reactive protein (CRP) compared to ESR as an early indicator for septic arthritis of the knee and hip. Patient base of 133 included all who underwent joint aspiration for synovial fluid analysis and culture in workup for acute nontraumatic pain and had a CRP level drawn within 24 h of presentation. Septic arthritis was diagnosed in 39 (21 %). Both CRP and ESR were independent predictors of disease but CRP was a better predictor. Both, however, were better as negative predictors. If the CRP is < 1.0 mg/dL, the probability that a patient does not have septic arthritis is 87 %, and if the ESR is < 25 mm/hr, the probability of not having septic arthritis was 85 %. C-reactive protein was discovered in 1930 and is an acute-phase reactant produced in the liver in response to tissue injury, inflammation, or infection [270]. Levels begin rising within 6–8 h of the onset of disease.

(e) Luhmann et al. 2004 [271]. Luhmann et al. applied the clinical prediction algorithm criteria of Kocher et al. to their group of 165 hips with transient synovitis and septic arthritis retrospectively. They also used arthrocentesis (hip aspiration) information to categorize their patients as having true septic arthritis (20), presumed septic arthritis (27), or transient synovitis (118). When the four independent multivariate predictors of septic arthritis of Kocher et al. were present, the predicted probability of the patient having septic arthritis was only 59 % compared to the 99.6 % predicted probability described by Kocher et al. The best model to describe their (Luhmann et al.) population was based on 3 variables: a history of fever, serum total white blood cell count > 12000/mm^3, and a previous health care visit, with these increasing the probability to 71 %.

(f) Kocher et al. 2004 [272]. In a second study, Kocher et al. applied their four independent predictors of septic arthritis of the hip prospectively. A history of fever, nonweight bearing, ESR > 40 mm/hr, and a serum white blood cell count of > 12,000 cells/mm^3 were used. Using the area under the "receiver operating characteristic curves" the original study was 0.96 with a slight decrease to 0.86 in the second study. For a patient with all 4 predictors, the previous predicted probability of septic arthritis was 99.6 and 93.0 % in the second study. For 3 predictors, the previous value of 93.1 % decreased to 72.8 %.

(g) Caird et al. 2006 [273]. Caird et al. assessed their patient population prospectively using five criteria for the multivariate analysis in 48 patients: fever > 38.5 °C, elevated C-reactive protein, elevated ESR, elevated serum white blood cell count, and refusal to bear weight. The C-reactive protein level (> 2 mg/dL) was the only risk factor strongly associated with the outcome at a 5 % significance level. The five together, however, predicted a probability of 98 %.

h) Sultan et al. 2010 [274]. Sultan et al. tested the same five clinical predictors as Caird et al. but in a primary referral general hospital rather than in a tertiary referral center as done in the previous studies. The predicted probability decreased again to the 60 % range. This was attributed to the much lower prevalence of septic arthritis in a primary referral center (= wider differential than simply septic arthritis versus transient synovitis).

(i) Singhal et al. 2011 [275]. A large study in a primary referral center assessed 29 septic arthritis and 282 transient synovitis cases. CRP was the strongest and most significant independent predictor of septic arthritis. The inclusion of CRP into other models (variable numbers of criteria) eliminated the significance of other variables. If both weight bearing status and CRP were negative, the predictive probability of septic arthritis was <1 %.

Summarizing, CRP is the single most valuable determinant of a septic arthritis.

4.4.5.3 Treatment of Transient Synovitis

Once the diagnosis is made treatment and followup are still needed. Since the disorder is transient and self-limiting the management consists of rest and gradual resumption of activity once hip motion is full and there is no more discomfort or limping. Hip traction is rarely used at present out of concern that it might worsen the hip problems since traction pulls the hip into extension which can increase intraarticular pressure and conceivably induce avascular necrosis. Synovitis of the hip with effusion is most comfortable with the hip flexed, slightly abducted, and externally rotated. This stresses/stretches the hip capsule least and is the position of comfort the child will assume on his or her own. Bed rest, no or limited ambulation, and protected walking with crutches are variants of treatment dictated by the clinical situation. Resolution usually occurs in 1–3 weeks. Recurrent

episodes are usually due to premature activity but three recurrences or more lead one to suspect other disorders such as juvenile rheumatoid arthritis or Legg–Perthes disease.

4.4.6 Overview of Findings in Childhood Hip Pain and Limping Re "Arthritis"

A child presenting with limping and hip pain requires careful assessment and early diagnosis so that optimal management can be instituted. Although the main differentiation is between transient synovitis and septic arthritis of the hip, other disorders need to be considered (Table 4.5). A prospective study of all children in three counties in southeastern Norway (containing about one fourth of the country's population) over 12 months (in 2004–2005) was designed to assess all children under 16 years of age with possible or evident arthritis and/or osteomyelitis [276]. The area pediatricians, general practitioners, orthopedic surgeons, and rheumatologists were requested to refer patients the same day they presented to the local hospitals. Inclusion criteria were strict and similar to those in North American studies. The annual incidence of arthritis was 71/100,000 children. Transient arthritis, juvenile idiopathic arthritis, postinfectious arthritis, and septic arthritis occurred in a ratio of 43, 14, 9, and 5 per 100,000. Transient arthritis was the most common variant by far. The incidence of all types was much more common under the age of 8 years. In that time frame, boys were affected more than girls. The median age of occurrence was lowest (youngest) in septic arthritis.

Other groups assessed patients in the same time frame studying transient synovitis (97 patients) compared with septic arthritis (27) [268]; transient synovitis (118) compared with septic arthritis (97) [271]; and transient synovitis (103) compared with septic arthritis (51) [272]. The mean ages of occurrence for septic arthritis (SA) and transient synovitis (TS) are almost the same in most series although SA tends to occur at a slightly earlier age in some. The transient synovitis (TS)/septic arthritis (SA) ages are listed as follows: 5.3 years/5.3 years; 7.5 years/4.6 years; 6.7/5.7 years; and 5.3 years/6.0 years [268, 269, 271]. In the Norwegian study, the TS occurred between 2 and 5 years of age with SA median age at 1.9 years (before age 3 in 10 of 12).

Not all hips with true or presumed septic arthritis show bacterial growth on synovial fluid or blood culture. The defining laboratory finding is a white blood cell count of ≥50,000 cells/mm^3. Most groups classify the disorders as follows: true septic arthritis-bacterial growth on synovial fluid culture, or bacterial growth on blood culture and synovial fluid white blood cell count of >50,000 cells/mm^3; presumed septic arthritis-synovial fluid white blood cell count of ≥50,000 cells/mm^3 with no bacterial growth on synovial fluid or blood culture; and transient synovitis–synovial fluid white blood cell count of ≤50,000 cells/mm^3, no growth on synovial fluid or blood culture, and no resolution of symptoms with antibiotic treatment [266, 271, 276].

4.4.7 Tuberculosis

4.4.7.1 Overview

Skeletal tuberculosis in the growing child commonly affects the spine and the epiphyseal regions of long bones where it presents as a combined epiphyseal osteomyelitis and septic arthritis [1]. It is still seen in many regions of the world and even in relatively advanced industrial nations, particularly in children with other debilitating disorders such as malignant diseases, immunosuppression, and diabetes. Tuberculosis persists globally due to such factors as increased drug resistance, HIV-positive and AIDS disorders, migration, poverty, crowded living conditions, and difficulty carrying out TB control programmes in the poorer regions of Africa and Asia. Multidrug-resistent (MDR) and extensively drug-resistant (XDR) tuberculosis remain a severe threat with an estimated 440,000 new cases globally of MDR tuberculosis in 2008 [277]. There were 9.4 million estimated new cases in 2008 with 1.8 million estimated deaths per year. It has been estimated that there are over 1.3 million infected children globally under the age of 15 years. Approximately 1 % of cases of tuberculosis have skeletal involvement. Associated pulmonary TB is seen in <50 % of the cases.

The spine is most commonly affected in childhood skeletal tuberculosis followed by the hip and knee joints [1, 278–284]. In a review of 219 patients with skeletal tuberculosis in Malaysia seen between 1968 and 1976, the disorder was spread almost evenly over several age groups from the first to the sixth decade [281]. From birth to age 19 years, there were 67 patients (31 %) and the spine was affected in 35/67 (52 %). In the entire series, the spine was most commonly affected (128/219, 58 %) followed by the hip (37/219, 17 %), knee (17/219, 8 %), ankle (13/219, 6 %), and wrist (8/219, 4 %). A similar disease distribution was reported at varying ages in a Japanese study of 914 lesions; spinal 61 %, hip 14 %, knee 8 %, and foot 5 % [280]. The onset of joint symptoms tends to be gradual with discomfort, swelling of the joint, periarticular muscle atrophy, low-grade temperature elevations, and decreased function. Involvement of the hip is particularly common and much of the early confusion involving what has come to be known as Legg–Perthes disease was due to of the fact that many of the clinical symptoms were similar, and tuberculosis was very common world wide in the first decades of the twentieth century.

Diagnosis is made by a positive tuberculin skin test, and the demonstration of tubercle bacilli is either on bone or synovial biopsies or following growth of the organism. Although skeletal tuberculosis is relatively common, it is

still infrequent in the overall spectrum of tuberculosis. The primary tuberculous focus occurs almost always in the lung and heals in many leaving only a fibrous scar. The second stage involves a postprimary reinfection which might then be associated with spread throughout the body. Involvement of any specific organ is referred to as the tertiary stage of tuberculosis. Primary foci of tuberculous infection are not known to appear in the skeletal system. Tuberculous infections in skeletal parts reach that area by the bloodstream from an already existing extraskeletal tuberculous disease focus. In children, the nidus of tuberculosis occurs through hematogenous spread.

4.4.7.2 Age Incidence

Tuberculosis is rarely seen during the first year of life. Statistics indicated that "in the first half of the twentieth century… in about 50 % of all cases, the subjects were between 3 and 15 years of age" [1]. Currently childhood tuberculosis is highest between 1 and 4 years of age, declines between 5 and 10 years of age, and begins to rise again in incidence at 15 years of age [285]. Children younger than 15 years contribute to 15–20 % of global tuberculosis although it is suspected that childhood cases are "grossly underdiagnosed and under-reported" [286]. The most common areas of involvement are the vertebral column, hip, and knee. The joints of the lower extremities are affected much more commonly than those of the upper extremities. The clinical characteristics of a tuberculous skeletal infection are much more indolent than those of a septic arthritis or osteomyelitis. Involvement is almost always monoarticular.

4.4.7.3 Radiographic Changes

The radiographic characteristic of long-bone tuberculosis is a periarticular osteopenia with the presence of a lytic lesion within the secondary ossification center. There is almost invariably an increase of joint fluid due to synovitis. Swelling of periarticular soft tissues is seen with joint involvement which generally results in a combined epiphyseal osteomyelitis and septic tuberculous arthritis. There may be narrowing of the joint space. There is resorption of subchondral bone and adjacent trabeculae by granulation tissue with minimal to absent bone reaction and no formation of sequestra. Osteoporosis can be marked. Wedge or cone-shaped areas of destruction are often seen in epiphyseal ends of the bone. There is a tendency toward involvement of bone on both sides of the joint. Sclerosis adjacent to the lytic lesions can be seen with prolonged partially controlled involvement as can osteophyte formation.

Ultrasound can be helpful to demonstrate joint effusion and soft tissue masses. CT defines bone tissue destruction well. MRI is indicated more often since it visualizes not only long bone and marrow changes but also soft tissue masses, cartilage damage, synovitis and pannus, and bone erosion.

4.4.7.4 Histopathology

Skeletal involvement occurs following hematologic spread. Approximately 1 % of tuberculosis cases show some skeletal localization [282]. The tendency is for the disease to begin in the articular or epiphyseal end of a bone, break into the joint where it becomes a septic arthritis, and then involve the synovial membrane. On occasion the synovial membrane can become infected directly by hematogenous spread. In the long-tubular bones, the tuberculous process usually originates at the epiphyseal subarticular end of the bone and spreads through the cartilage surface to involve the synovium. Tubercle formation occurs in the marrow with the trabeculae of spongy bone affected secondarily. There is necrosis and resorption of the cancellous trabeculae with circumferential spread of the lesion. In the hip, the bone of the secondary ossification center is affected as is that of the acetabulum. The joint often shows destruction of the articular cartilage with the femoral head covered by a pannus of tuberculous granulation tissue. Tuberculous synovitis is seen frequently, associated with inflammatory thickening of the periarticular connective tissue and fat. Synovial membranes are extremely thickened and the articular cavity will contain a large amount of necrotic material. Synovial involvement is associated with partial or complete erosion and destruction of the articular cartilage with the tuberculous granulation going both over the surface of the cartilage and along its subchondral region.

The triad of changes in tuberculous arthritis includes juxtaarticular osteoporosis, peripheral osseous erosions, and gradual narrowing of the joint space [287]. The seat of primary infection is in the bone in some cases and in the synovial membrane in others. In the early stages, therefore, the articular cartilage is not affected and remains alive. It is attacked secondarily by tuberculous granulation tissue either along its free junctional surface with the bone and synovium or along the region of its attachment to subchondral bone. The initial destruction of cartilage is usually by granulations growing from the synovium onto the periphery of the cartilage where it is not immediately adjacent to cartilage from the opposite bone. The second region in which granulations develop is the peripheral portion of epiphyseal bone beneath the articular cartilage. A thin layer of subchondral granulation forms which absorbs the subchondral bone and the deeper layer of cartilage leading to detachment of overlying cartilage along with necrosis. Marginal undermining of the articular cartilage may also be seen by tuberculous granulations growing in from the synovium. The subchondral bone can be affected in two ways. In small focal areas, the bone may be broken down rapidly as the focus spreads

leaving a cavity filled with tuberculous granulations or necrotic debris. In other cases, large areas are involved and the tuberculous tissue of the cancellous spaces undergoes early necrosis and caseation leaving the dead bone trabeculae practically intact. The overlying cartilage is then affected secondarily due to subchondral bone collapse similar to what is seen in osteonecrosis where the cartilage is initially unaffected. Secondary changes along the articular surfaces of the bones developed from spread of the tuberculous infection from the primary point of involvement.

In the spine, the mycobacteria are preferentially deposited in the vertebral bodies adjacent to the anterior part of the vertebral end plate. The posterior elements are rarely involved and the intervertebral disk is involved only late in the disease. Infection can break though the cortex and spread into the soft tissues to form paravertebral or epidural collections. Involvement of adjacent vertebral bodies can lead to kyphotic collapse [288]. In a study of 53 children with tuberculous spondylitis, below 13 years of age, kyphosis developed in 79 % with contiguous involvement of two or more vertebral bodies in 85 % and intraspinal or paraspinal abscess/soft tissue spread in 98 % [289].

TB osteomyelitis can be multifocal but is usually a solitary focus. Skull vault, hands, feet, and ribs can be affected. "Spina ventosa" refers to TB osteomyelitis with bone destruction, periosteal thickening, and fusiform expansion of the bone. This term refers to lesions other than of spine and epiphyseal joint involvement. In 42 children with tuberculous osteomyelitis, there were 50 osseous lesions, with most (n = 25) in the metaphyses. The involvement was cystic (n = 26), infiltrative (n = 10), focally erosive (n = 8), and spina ventosa (n = 6) [290].

The most common region of tuberculous skeletal involvement after the spine and hip is the knee. Other areas of involvement are the tarsal, carpal, and elbow bones. Shoulder involvement is less frequently seen than at the elbow. Involvement is in the head of the humerus and the lesion spreads to the articular cavity. In joints which go on to stabilize in the absence of full healing, fibrous ankylosis tends to develop. Cartilage is not regenerated and in preantibiotic days, there was often some degree of fibrous or bone ankylosis.

In skeletal tuberculosis, the tubercle is the characteristic pathologic finding associated with tuberculous granulation tissue and, later on, caseation necrosis, and eventual fibrosis. Except for the vertebral lesions, the majority of cases of skeletal tuberculosis involve a joint. There is almost invariably an associated tuberculous synovitis and osteomyelitis of the epiphyseal region. Virtually all metaphyseal and epiphyseal foci sooner or later involve the adjacent joint. Transphyseal spread from the metaphysis is seen. The epiphyseal focus extends into the adjacent joint near the synovial-cartilage junction. In association with synovial involvement, there is early invasion of the articular cortex at the joint margins. The tuberculous granulation tissue erodes through the edge of the cartilage to create a focus of advancing damage. There is subchondral granulation resulting in fibrous tissue deposition. Eventually, the zone of calcified cartilage and the noncalcified articular cartilage are slowly resorbed. Subchondral marrow fibrosis is seen. The articular cartilage is also resorbed from the surface beneath the granulation tissue creeping over it. Resorption and destruction of cartilage occur first at the margins of the joint and then move progressively onto the weight-bearing surfaces. Within the bone itself, the dead trabeculae remain of normal thickness, whereas those at the periphery in the more viable regions tend to become thinner in association with decreased use and increased vascularity. The phrase "kissing" sequestra has been used for many decades to describe the pathologic findings in tuberculous osteomyelitis and arthritis. These refer to secondary sequestra formed directly opposite each other in opposing epiphyses at sites of maximum pressure stress. In the preantibiotic era, there was very little, if any, tendency for tuberculous joints to heal with preservation of a useful range of motion. Healing occurred initially by a fibrous ankylosis which in turn sometimes became a bony ankylosis. In most the healed joint became a mass of dense fibrous adhesions with a fibrotic synovium. Figure 4.12 illustrates the pathophysiological changes of the joint and epiphyseal regions in tuberculous disease.

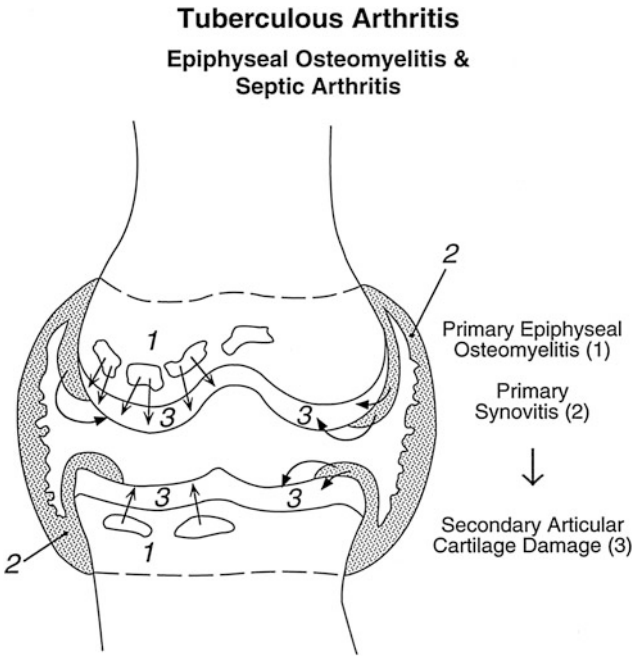

Fig. 4.12 Tuberculous involvement of the joints is a combined epiphyseal osteomyelitis and tuberculous septic arthritis. The pathophysiologic changes are illustrated here

4.4.7.5 Treatment

Treatment for skeletal tuberculosis became effective with the development of streptomycin in the early 1940s. Streptomycin alone soon led to resistance and antituberculous antibiotic regimens in the 1950s used a combination of isoniazid, aminosalicylic acid, and streptomycin and in the 1960s a regimen of streptomycin, isoniazid, and ethambutol. Rifampicin was added to the triple regimen of streptomycin, isoniazid, and ethambutol in the 1970s. In the 1980s, the recommended regimen was revised to isoniazid, rifampcin, pyrazinamide, and ethambutol. This is still the first-line treatment: standardized short-course chemotherapy-rifampcin and isoniazid for six months supplemented with pyrazinamide and ethambutol in the first two months. Relapse and resistance are increasingly common with this regimen, however, and a large array of second-line drugs is used with only partial effectiveness [291].

With skeletal involvement, the drug regimens were used in combination with splinting followed by physical therapy for range of motion of the joints. Repair was improved with debridement of the fibrotic, necrotic infected tissue whether this was in the joint or within the adjacent bone. For children in the acute stages of the disorder, antibiotic therapy alone was often sufficient. Since development of the infection, however, tended to be indolent and discomfort much less than that associated with pyogenic bacteria many patients were already in the subacute or chronic phase when diagnosis was made. The combination of joint and bone debridement in combination with antibiotic therapy and rehabilitation with earlier focus on range of motion activities tended to improve results greatly. Kondo and Yamada were early proponents of focal debridement [280]. In large joints all loose cartilaginous fragments, loose devitalized bone fragments, and necrotic or devitalized infectious tissues were removed surgically. They felt that the combined therapy greatly improved results. Debridement was especially indicated during the later chronic stages of the disorder in particular when abscesses or sinuses were present which markedly limited access by systemic antibiotics. An extensive study also from Japan by Katayama et al. strongly supported the triple therapy antibiotics along with surgical synovectomy and joint and bone debridement to physically remove all gross tuberculous foci in particular those regions that communicated with the joint space [279]. Synovectomy alone was commonly resorted to within the knee joint. They felt that these treatments improved the likelihood of retention of joint motion even though completely normal joints were rarely achieved with chronic disorders.

Wilkinson also resorted increasingly to synovectomy of the knee and hip in combination with chemotherapy to improve joint healing and function [283, 284]. Care was taken to distinguish the tuberculous joint from pyogenic arthritis even when there was extensive involvement with synovial swelling and lytic areas of bone since the articular cartilage tended to survive much better in tuberculous than in the pyogenic infection. Synovectomy and even removal of the overlying pannus layer in combination with chemotherapy led to some remarkable recoveries in tuberculous arthritis. Wilkinson recognized that in tuberculous arthritis both synovium and bone were involved by the time the disease had become recognizable clinically. On the basis of extensive clinical experience, he noted the pathologic involvement at hip and knee to be definable into four groups according to the tissues involved [284]. The first group involved those with disease of both synovial membrane and cartilage. The cartilage involvement tended to be around the periphery of the articular surface. The next group had disease of the synovial membrane, cartilage, and bone. This involved considerably advanced disease with frequent destruction of the joint and subluxation or dislocation of the femoral head in the hip. The third group involved disease of the synovial membrane and bone with little evidence of cartilage loss. The fourth group had mainly bony changes with no change in the joint found at operation. In those with disease of the synovium and cartilage, the synovium was always more markedly involved being thickened and vascular and encroaching on the periphery of the cartilage. In some cases, the synovium spread over the cartilage almost to the center of the joint. Cartilage laceration also occurred over subchondral tuberculous foci with diseased tissue attacking from bone into cartilage from below. Pannus formation was also observed spreading from the periphery onto the cartilage surface. Even when pannus covered the cartilage, the cartilage beneath was often intact. Disease of synovium, cartilage, and bone was seen, generally, where the patient was older and destruction more severe. Chemotherapy was combined increasingly with synovectomy and joint debridement and many joints which appeared initially quite damaged were restored to reasonable function for several years. Debridement and curettage of adjacent bony foci was frequently needed. In terms of bone surgery, osteotomy was required in more severe cases and although arthrodesis was resorted to early in the series at progressively later time periods the combination of antibiotics and more vigorous and early surgery limited the number of arthrodeses needed. Wilkinson stressed, as had others, that there was a tendency for the articular cartilage to survive even in joints which appeared severely affected by tuberculosis. Pannus if possible was removed and if it was of relatively recent origin the cartilage showed excellent tendency to regenerate. Synovectomy was helpful since synovial persistence in a thickened state delayed cartilage nutrition. In addition, the presence of pannus also delayed joint recovery.

Tuli has reviewed evidence that uptake of drug at foci of tuberculous lesions in the skeleton is surprisingly high and stresses the value of the drug over surgical intervention.

He supports the primacy of antitubercular drugs, repetitive active, and assisted exercises for the involved joint from the very beginning, and rest in the functional position between exercises. Surgical intervention is reserved for those with chronic synovitis not responsive to medical management. Management is predicated to a great extent on economic and social factors. Where there are no specific constraints to active therapy it appears that optimal antibiotic use, early physical therapy to stress range of motion and surgical debridement with any evidence of slowness of repair would be the optimal approach.

4.4.7.6 Long-Term Followup of Childhood Tuberculous Joint Infection

Chow and Yau studied 30 cases of tuberculosis of the knee followed for an average of 15 years with the majority having developed the disease during childhood [292]. In 75 % of the patients, the infection occurred before the age of 18 years. The peak year of incidence was four years with the large majority of cases occurring from one year to 11 years of age. Treatment varied between conservative and operative, but all had chemotherapy. In those patients treated operatively, synovectomy and debridement followed by cast immobilization and bracing was the usual approach. On occasion, the destruction was sufficiently great that immobilization was continued to the point of ankylosis. Conservative treatment involved chemotherapy with casting and bracing alone. In patients in the childhood group, deformities commonly seen involved varus deformity of the knee, flexion contractures, and lower extremity shortening. In 6 instances, there was varus deformity which was mild in two simply leading to loss of the normal valgus angle, 10° in two cases, and 30° in two additional cases. The flexion contractures of the knee were seen in 12 cases: 10° in 6, 20° in 5, and 30° in 1. Significant clinical shortening was demonstrated in seven cases with the amounts being 2.5 cm in 2, 5.0 cm in 4, and 7.5 cm in 1. Most of the abnormal deformities occurred in association with each other. There were 13 knees with no deformity and an otherwise excellent result. On occasion, extensive regeneration of the bone occurred even though much of the epiphyseal subchondral bone appeared lytic at diagnosis. At review, roughly 25 % of the joints were radiologically normal. Of those with abnormalities, the most common were described as "congruous incongruity in which the joint space was well preserved although it was irregular in outline with a matching pattern of irregularity in the two opposing surfaces of the tibia and femur." Other x-ray abnormalities were osteophytes, osteoporosis, a smaller epiphysis, chondral calcinosis, abnormal patellae, and loose bodies. Of note was the fact that "as the child grew older, the previously destroyed bone and perhaps the overlying articular cartilage showed a remarkable power of reconstitution."

4.5 Hematologic Disorders

4.5.1 Hemophilia

4.5.1.1 Overview

Hemophilia is a sex-linked recessive bleeding disorder caused by a group of inherited blood coagulation factor deficiencies, the two commonest being factors VIII or IX [293–297]. It is an inherited tendency in males to bleed. Prior to the onset of effective therapy for this disorder, damage to the joints and epiphyseal ends of the bone was extensive, and treatment methods involving surgery and physical therapy were not curative. Lethal hemorrhage was frequently seen following major trauma or after surgery performed where the diagnosis was not recognized [298, 299]. The natural history of the disorder has changed significantly following factor replacement therapies over the past several decades, but considerable morbidity and some mortality persists. Larsson has documented the dramatic change in life expectancy with hemophilia in Sweden where detailed statistics have been available since the eighteenth century [300]. The median life expectancy of patients with severe hemophilia increased from 11.4 years from 1831 to 1920, to the mid 20 s from 1921 to 1960, and to 56.8 years from 1961 to 1980. The AIDS crisis then led to a significant decline in median life expectancy in the United States and Western Europe from 1981 to 1990 prior to recognition of its cause and avoidance of infected blood.

Hemophilia A, the most common hereditary coagulation disorder, is due to a deficiency in the factor VIII clotting factor, is seen throughout the world, and has an incidence of two per 10,000 male births. It is an X-linked recessive disorder which affects males only and is transmitted by females. The disorder is the result of a new mutation in approximately 33 % of new patients, so a family history is often not obtainable. It is due to the absence, severe deficiency, or defective functioning of the plasma coagulation factor VIII (sometimes referred to as the antihemophilic factor). Several different mutations cause the disorder which accounts for the variable clinical severity. Hemophilia B (Christmas disease) is indistinguishable clinically from hemophilia A, is also transmitted as an X-linked disorder, and is the result of a deficiency in the factor IX clotting factor. It is the result of a new mutation in approximately 20 % of new patients. The gene is located near the tip of the long arm of the X chromosome at Xq 26–27. Genetic defects of factor IX include partial and total deletions, point mutations, frameshifts, and premature stop codons.

Hemophilia was described as an inherited sex-linked disorder by John Otto of New Hampshire in 1803 [301]. For several decades, however, no connection was made between the bleeding disorder and the joint swelling and degeneration. It was not until the 1860s that this correlation even

began to be considered [299]. The factor VIII deficiency (hemophilia A) occurs in approximately 85 % of cases and the factor IX deficiency in 15 %. The normal plasma levels of F VIII and F IX range from 50 to 150 %. Three severities of disorder are defined for both factor VIII and IX deficiencies. Those with a mild disorder have above 5 % factor activity in the blood; moderate 1–5 % factor activity; and severe <1 % factor activity. The distinction is extremely important since mild and moderate hemophilia A rarely lead to joint bleeding. It has been estimated that in hemophilia A the severe–moderate–mild distribution is 70–15–15 % and in hemophilia B it is 50–30–20 % [293]. When unusual bleeding is encountered in a male patient, screening laboratory tests include a normal platelet count and prothrombin time but a prolonged activated partial thromboplastin time. Specific factor assays are then needed to determine the deficiency differentiating hemophilia A from hemophilia B. Patients with von Willebrand's disease also have factor VIII deficiency due not to a defect in the X chromosome but to the indirect consequence of qualitative or quantitative changes in plasma von Willebrand factor [302]. Factor VIII circulates in the plasma with von Willebrand factor in a noncovalent complex but the two factors are distinct proteins.

Much of the improved treatment of hemophilia comes from the molecular understanding. Some patients, however, remain resistant to therapy because of the presence of inhibitors which are antibodies developing against exogenous factor VIII or IX [293, 303]. These inhibitors are present in 20–50 % of people with severe hemophilia and are suspected when good responses to therapy are not achieved with restoration of appropriate levels of factor.

The clinical hallmarks of hemophilia A are joint and intramuscular hemorrhages, easy bruising, and prolonged hemorrhage after trauma or surgery although there is no excessive bleeding after minor cuts or abrasions. Other sites of bleeding are subcutaneous, mouth–neck–throat, gastrointestinal, genitourinary, and intracranial (after head trauma) or spinal cord (after trauma). Hemarthroses account for 75–85 % of bleeding episodes in patients with severe hemophilia. Intraarticular bleeding is highly characteristic of factor VIII and IX deficiency and is not seen in other blood clotting factor deficiencies. The joints most frequently involved are the knees, elbows, and ankles with occasional involvement of shoulders and hips. In a small series of 44 patients hospitalized with hemarthrosis, Eyring et al. reported an incidence of knee 62 %, ankle 20 %, elbow 15 %, hip 2 %, wrist 1 %, and shoulder 0.5 % [304]. Houghton and Duthie reported joint involvement as follows: knee 328 (44 %), elbow 190 (26 %), ankle 106 (14 %), sternoclavicular 33 (5 %), shoulder 25 (3 %), wrist 20 (35 %), hip 19 (3 %) and hand 17 (15 %) [305]. The ankle is the commonest joint experiencing hemarthrosis in the second decade. Gamble et al. noted intraarticular bleeding to be most common in the knee in those under 10 years of age but in those between 11 and 19 years of age the frequency of hemarthrosis of the ankle was two and half times that of the knee [306]. Hemarthroses tend to be noted when the child first begins to walk and are generally spontaneous. The joint bleeding is associated with discomfort and limitation of motion and then with inflammation and synovitis. This establishes a vicious cycle which leads to more hemarthrosis. Ultimately hemophilic arthropathy damages and destroys the cartilage narrowing the joint space, and is associated with small subchondral bone cysts, osteopenia, and contractures. Many patients have one joint recurrently affected and then referred to as a target joint.

4.5.1.2 Gene Abnormalities

The gene that codes for factor VIII is at the tip of the long arm of the X chromosome [293, 295, 297, 307]. It is one of the largest human genes comprising nearly 186 kilobases and constituting nearly 0.1 % of the X chromosome. The initial studies of mutations were performed by screening genomic DNA digested with restricted enzymes. By 1991, more than 150 different mutations had been identified in hemophilia A. With a few exceptions, deletions in the factor VIII gene cause a severe form of hemophilia A. Nonsense mutations also cause severe hemophilia. Over 80 point mutations and 70 gene alterations have been identified in the factor VIII gene which underscores the wide range of clinical variability. Characterization of factor VIII mutations has been slow because of the extremely large size of the gene and the variable mutations which are reflected in the fact that hemophilia A is a clinically heterogeneous disorder. An inversion in the factor VIII gene at intron 22 was identified and found to account for as many as 40 % of all severe hemophilia A gene abnormalities.

The factor IX gene is smaller comprising of 34 kilobases [294]. More than 300 unique mutations have been found; of families with moderate–severe disease, 95 % have different mutations. No link between factor VIII and IX genes has been found.

With pedigree analysis and laboratory studies involving plasma levels of factor VIII and von Willebrand factor, it is now possible to determine carrier or noncarrier status for women with >95 % accuracy in roughly 80 % of women who are evaluated. DNA analysis has recently been used to determine carrier status. Ultrasound-assisted fetoscopy has made it possible to obtain fetal blood samples in the eighteenth–twentieth week of pregnancy and prenatal diagnosis of hemophilia has become feasible with the advent of factor VIII immunoassays. More recently, prenatal diagnosis during the eighth–tenth week of pregnancy has become possible through DNA analysis of amniocytes or chorionic-villus material.

4.5.1.3 Musculoskeletal Damage: Arthropathy, Pseudotumor, Neuropathy, Contractures, Volkmann's Ischemia, Fractures, Ectopic Ossification

The major orthopedic problem in hemophilia is intraarticular bleeding with subsequent hemarthropathy [296, 308–313]. This is generally associated with muscle atrophy and a tendency to joint contractures. The most commonly involved joints are the knees, ankles, and elbows. Characteristic knee deformities accompanying hemophilic arthropathy involve a flexion contracture, genu valgum, and external rotation of the tibia. In long-established cases, there is posterior subluxation of the tibia. The knees tend to be "knobby" owing to irregular overgrowth of the epiphyses, overgrowth of the periphery of the patella and periarticular muscle atrophy. The ankle shows diffuse osteopenia, collapse of the superior surface of the talus, a valgus tilt of the ankle joint and a mild equinus deformity. The elbow develops a progressive flexion contracture. Other less common disorders involve: bleeding surrounding and into the bone, primarily proximal femur and ilium which leads to the formation of a lytic lesion referred to as a hemophilic pseudotumor; bleeding into muscle and soft tissues which can lead to neuropathies in particular of the sciatic and femoral nerves; episodes of Volkmann's ischemia of the forearm and occasionally of the calf; fractures, generally of the distal one-half of the femur associated with chronic knee arthropathy, stiffness, and osteopenia; and ectopic ossification, usually in the pelvis. Rodriguez-Merchan has provided an excellent overview of the musculoskeletal complications of hemophilia [314].

4.5.1.4 Hemophilic Arthropathy

Joint involvement is rare in the first year of life and generally begins in the second year with onset of walking. The knee is most commonly affected followed by the ankle and elbow joints. Small joints of the fingers and toes are only rarely affected. In most hemophiliacs, a single joint tends to be affected repeatedly and is referred to as a target joint.

(a) *Clinical Stages*:
   (i) *Three stages of hemophilic arthropathy (Koenig)*: Koenig in 1892 was one of the first to recognize that the joint abnormalities of hemophilia following the hemarthrosis represented a specific pathoanatomic entity, not simply a variant of rheumatologic or arthritic disease that just happened to occur in hemophiliacs. He divided the disorder into three stages [299]. The first stage due to initial bleeding was referred to as the stage of true hemarthrosis; the second stage was the inflammatory stage with a panarthritis with reactive inflammation throughout the involved joint with proliferation of the synovial membrane; and the third stage was one of regression or wasting away of the joint with destruction of the joint surfaces, contractures causing permanent deformity, and ankylosis. The initial symptoms were often vague with apparent spontaneous but rapid onset of the hemarthrosis occurring without trauma, usually without associated pain, and with a surprisingly good range of motion retained. The deterioration of function occurred gradually after several bleeding episodes. Aspiration yielded bloody fluid. Koenig was able to diagnosis a "bleeders' joint" of hemophilia "due to the patient's pallor, the sudden appearance of the fluid effusion, lack of pain in the joint, and the freedom of movement."
   (ii) *Four grades of hemophilic arthropathy (Depalma and Cotler)* [309]: The four grades were Grade 1. Intraarticular hemorrhages that have not resulted in any functional joint impairment. There are no or only minimal radiographic changes. Grade 2. The affected joint presents a slightly reduced range of motion but the joint space is well preserved; there is no irregularity of the subchondral bone and the spongy trabeculae are only somewhat more prominent. Grade 3. There is fixed deformity of the joint associated with periarticular muscle atrophy, pericapsular and capsular thickening, irregular articular surfaces, and subchondral cysts with marginal spur formation. Grade 4. The deformity is pronounced and fixed with marked periarticular muscle atrophy. The articular bone ends are irregular and deformed with increased radiolucency and narrowing of the joint space. With time, the bone ends, particularly at the knee, tend to flatten and widen and subluxations are common. Fibrous ankylosis may lead to bony ankylosis. Marginal exostoses are seen.

(b) *Gross Pathologic Findings*: Koenig described changes observed in three cases of open arthrotomy or postmortem examination [299]. Joint aspiration in the early phase yielded blood. This was still found a few weeks after onset of bleeding but some blood clots were free in the joint while others were attached to the capsule. With time the capsule was thickened and its inner lining discolored with a blood colored fluid. Fibrous deposits were noted to occur both on the capsule and on part of the cartilage surface of the distal femur. Even at this stage, "the cartilage starts to change, to become fibrous, and the strangely sharp-edged defects described below start to develop." In the second stage, he noted that if no new bleeding had taken place, the contents of the joint are "not purely blood but bloody serous or purely serous with a slightly brown color."

At arthrotomy in these joints a "great number of brownish synovial tufts was particularly noticeable." There was a villous appearance of the synovium with red-brown, brown, or gray discoloration. There were changes in the cartilage; "all over it has lost its white color and its shine; it is discolored a dirty red-brown or gray-brown." The cartilage became fibrous. "The truly characteristic changes consist in strangely sharp-edged defects, small and big, deep and on the joint surface with gnawing defects to the cartilage in various spots of the joint but mostly at the same places where the fibrous deposits are found." There was a characteristic central position of the defects in which "we have found no actual changes on the edge of the cartilage surface as is the case in arthritic deformity." With histologic sections, there was granular blood pigment in both the cartilage and the synovium. The third stage was referred to as "regressive metamorphosis." Scarring and shrinking of the connective tissue set in with super-added mechanical influences. The joint continued to degenerate and became stiff and deformed. There was fibrous and then bony ankylosis and fibrosis and tightening of the capsule. Flexion contractures and slight valgus deformation of the knee joint followed. Key provided another description of the hemophilic joint [298]. At operation (for a mistaken diagnosis of traumatic arthritis), it was noted that the synovial membrane was unusually dark in color. Blood without clots escaped once the arthrotomy had been made. The synovial membrane was dark chocolate in color and the joint cavity was filled with hypertrophied synovial folds and villi. The articular cartilage on femoral, tibial, and patellar surfaces was yellowish brown in color, and there were many areas in which the cartilage was either thinned or had entirely disappeared. The underlying bone was covered by a chocolate-colored connective tissue. The areas of cartilage erosion were irregular in size and contour but were sharply demarcated. Some of the synovial villi were pedunculated while others were sessile. Many of the synovial folds branched extensively giving areas of a moss-like structure. The villi were markedly friable. DePalma and Cotler provided an excellent description of the gross pathology [309]. Postmortem study of two shoulders showed one to be perfectly normal and the other with marked abnormalities. The affected side was totally degenerated. There was no trace of hyalin cartilage and the subchondral bone was eburnated and covered with numerous crater-like defects varying in size and shape. Subchondral cystic regions were seen that communicated with the joint cavity. Many of the defects in the cancellous bone had a smooth, firm compact inner surface indicating that the contents of the cyst were under great pressure. There was considerable erosion of both cartilage and bone elements along the superior and posterior borders. The soft tissues of the joint were discolored. The synovial membrane was thin with only minimal villus formation noted at this stage. The ligaments were thicker and broader than normal. In the knee joint, the entire synovial lining was discolored in varying shades of reddish brown. The entire thickness of both menisci and the quadriceps tendon was permeated by blood pigments. The articular cartilage was similarly discolored, swollen, wavy, and shredded. Numerous fine villi covered its surface. The cartilage was markedly pitted and also exhibited clefting, but there were no areas of erosion to the level of the subchondral bone. There was no eburnation. The synovial membrane and subsynovial tissues were thickened markedly. Numerous fine villi extended from the synovium. The intercondylar notch was filled with thickened hyperplastic synovial tissue.

(c) *Pathogenesis of hemophilic arthropathy*: Clinical swelling of a joint is rarely documented before 12 months of age and most of the bleeding episodes become prominent at 4–5 years of age. It is usual that the first massive hemarthrosis can be resorbed with no apparent sequelae. It is the recurrent intraarticular bleeding that becomes problematic. The three-stage progression of the disease outlined by Koenig remains accurate today—hemarthrosis, inflammatory panarthritis, and regressive stages [299]. The repeated insults of numerous and frequent hemorrhages can be either massive or small and subclinical. When the stages of chronicity begin the synovium is involved first followed by the cartilage and then the bone. The subsequent synovial hyperplasia serves as a deterrent to effective resorption of blood from the joint cavity with repeated episodes. Bleeding occurs more frequently with even minimal trauma since the thickened synovium is hypervascular. Organization of the subsynovial granulation tissue further worsens the process by producing dense scar tissue. Pannus ensues covering the periphery of the articular cartilage and leading to underlying cartilage degeneration. Occasional osteophytes are seen at the periphery. The subchondral and cancellous bone tends to atrophy. There is coalescence of small marrow spaces forming larger cystic spaces. There is proliferating vascular connective tissue in some of the cysts while in other areas, there is blood clot associated with intraosseous bleeding. Most cysts eventually gain communication with the joint cavity as the overlying cartilage degenerates. Articular cartilage degeneration is an invariable part of the picture with marked fibrillation of the collagen fibers and in some areas focal full thickness defects. In some cartilage areas, cellular elements have disappeared almost completely. In

areas where the entire thickness of the cartilage has been destroyed, surface tissue is replaced by vascular granulation tissue extending from the marrow. With cartilage destruction, the joint space narrows. In the final or third phase of Koenig, the bleeding episodes diminish since the synovium has become so thickened and sclerotic that vessel involution has occurred. By this time, joint cartilage can be nonexistent and bone on bone crepitus is very painful, motion is limited, contracture deformity is great, and function markedly diminished.

An overview of the pathogenesis of hemophilic arthropathy has recently been presented by Roosendaal and Lafeber centering on the damaging effects of intraarticular blood on the articular cartilage and on the synovium [315].

(d) *Histopathologic Findings*: The early synovial reaction to intraarticular bleeding resembles the changes occurring with rheumatoid arthritis. Initial hemarthroses are quickly resorbed with no clinical sequelae. With multiple bleeds, however, resorption is slower and persisting intraarticular blood and blood clot lead to the development of progressively severe changes. The synovial lesion is characterized by hemosiderin deposition and fibrovascular proliferation. There is inflammation, reactive proliferation, and brownish discoloration of the synovial membrane which eventually leads to osteoarticular changes. The synovial membrane with time becomes hypertrophic, thickened with villous proliferation, increased vascularity, and round cell infiltrates (Figs. 4.13 and 4.14). The blood products are resorbed by the synovium, but it is the overload of iron which appears to be most damaging to the synovial cells. Hemosiderin accumulates within synovial villi. Synovial cells that absorb too much iron disintegrate, releasing lysosomal enzymes that destroy articular cartilage and further irritate the synovium. Chondrocytes are also damaged directly by the iron. The synovium gradually becomes fibrotic and in end-stage disease, loses the capacity for excess bleeding and causing joint distention.

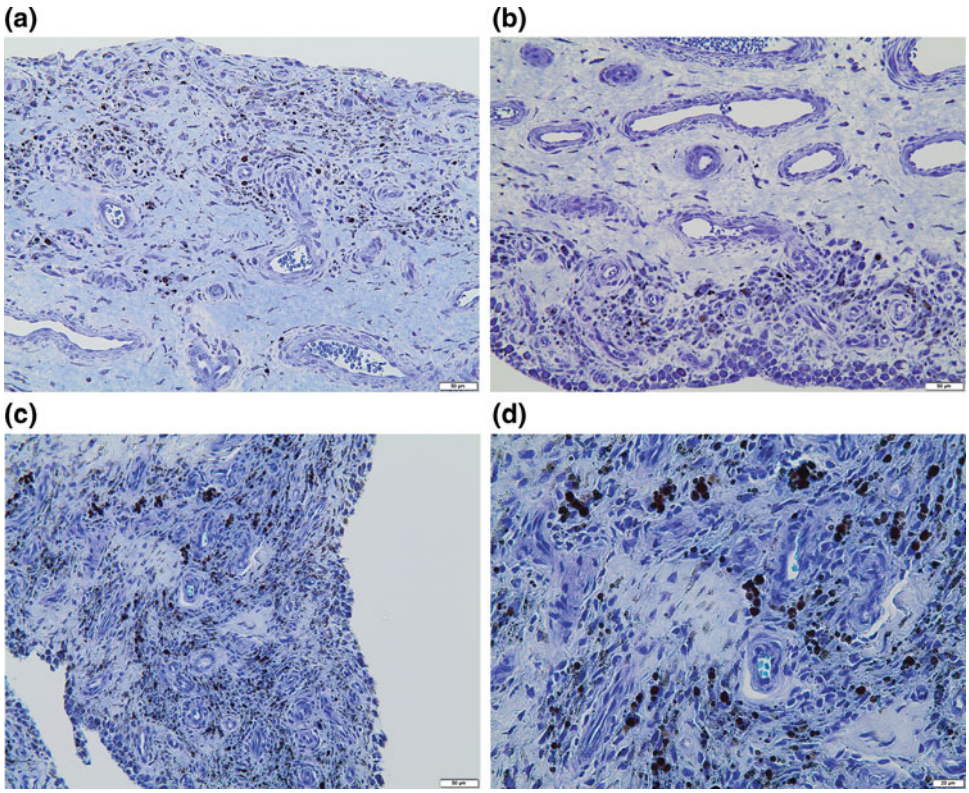

Fig. 4.13 Histologic sections (**a**–**d**) of tissue from knee synovectomy in a patient with hemophilia illustrate characteristic findings in advanced involvement. Chronic repetitive bleeding has led to marked thickening of the synovium (**a**, **b**) with the surface showing multiple folds (**b**) of hypertrophic synovium. The deeper tissue is markedly fibrotic (**a**–**d**) and often shows retained iron deposits (**a**–**d**). More superficially the thickened surface synovium is markedly hypercellular with arterial and arteriolar vessels numerous and thick walled (**a**, **b**). Cellular inflammation (*round cells*) is marked with a high level of iron deposits (dark staining accumulations) both intracellular and within the collagenous scar tissue in the extracellular space (**b**–**d**)

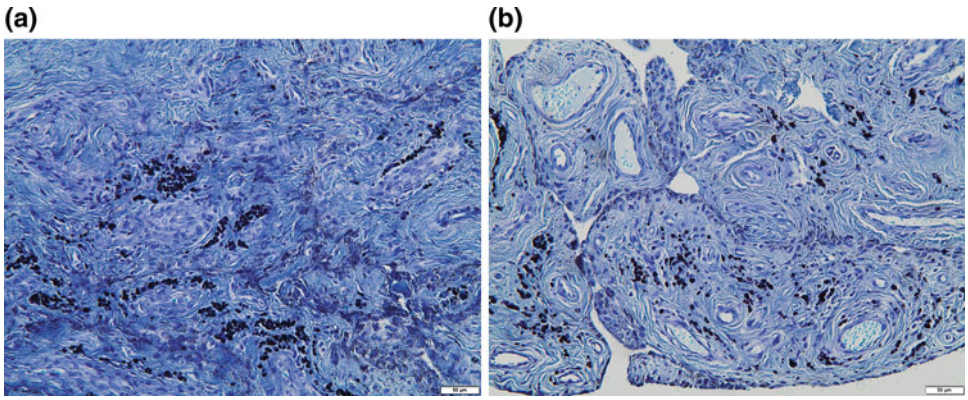

Fig. 4.14 Synovial tissue removed at open ankle synovectomy for hemophilic arthropathy is shown in **a** and **b**. The findings are the same as those described in Fig. 4.13 above

These changes are soon followed by articular cartilage degeneration from superficial to deep. A brownish pannus covers the cartilage from the periphery. If full thickness focal regions of cartilage are lost, the subchondral bone becomes exposed and thickened. Subchondral cysts form, and there may be collapse of the articular surfaces. Subchondral cysts are often found to begin with intraosseous hemorrhage that breaks down the atrophic bony trabeculae and can reach giant proportions. Coalescence and collapse of these defects produces marked deformities of the bone ends and flattening and incongruity of the articular surfaces. The cysts are formed by destruction of the overlying subchondral bone and cartilage by vascular connective tissue originating in the marrow spaces immediately adjacent to the subchondral bone. Cartilage surface pitting and focal erosion occur. The entire hypervascular process is associated with osteopenia of the underlying trabeculae. The capsule of the joint becomes thickened. The subchondral cystic cavities communicate at times with the joint space and contain fresh clot as well as fibrous tissue.

Key defined the microscopic anatomy with findings similar to those reviewed above [298]. The synovium was thrown into innumerable folds and villi. The subsynovial tissues were thickened by cellular proliferation and edema, and filled with granules of yellowish-brown pigment. The changes were seen universally throughout the joint lining. The surface synovial cell layer was from four to 10 cells in thickness. Many of the cells had pigment granules. There were also phagocytic cells or macrophages also loaded with pigment. The subsynovial layer was markedly thickened and composed of a well-vascularized component, increased collagenous tissue, and macrophagic cells. Beyond this the capsular tissues were markedly thickened and fibrotic. The margin of the articular cartilage was invaded at its periphery by the vascular synovial and subsynovial tissue. The surface of much of the cartilage had undergone fibrosis with little evidence of hyperplasia. The underlying bone was extremely atrophic and in many places the cartilage virtually rested upon the bone marrow and the cancellous bone of the epiphysis.

Speer has delineated the early pathogenesis of hemophilic arthropathy in particular in relation to the evolution of the subchondral cysts (Fig. 4.15) [312]. His study was based on patients undergoing synovectomy of the knee. Six of the nine patients were in the younger age group showing early stage changes, but all had had more than two episodes of hemarthrosis in the affected knee and chronic synovitis of >6 months duration which was not responding to therapy. The changes described are similar to those reviewed above. He noted osteochondral defects at central load bearing areas of the femoral condyles with the surrounding articular cartilage relatively spared. The flattened or gently curvilinear space at the bottom of each osteochondral defect was 3–7 mm below the surface of the joint and was invariably depressed below the contour of the normal subchondral bone plate. Fluid filled osteochondral cysts were seen in several patients; the surface layer of which was continuous with superficial zones of

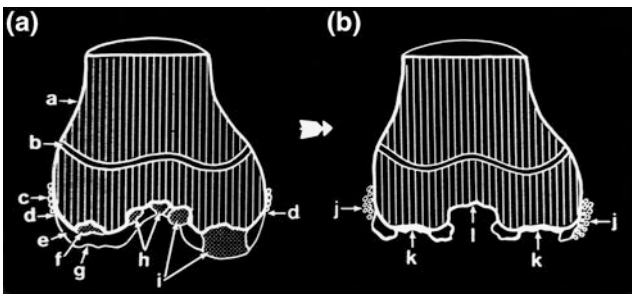

Fig. 4.15 Early **a** and late **b** arthropathic changes of distal femur in hemophilia are illustrated (from the work of Speer [312]). **c/j** synovitis; **f/h** subchondral cyst; **g** chondrolysis, fibrillation; i osteochondral cyst; **k** bone sclerosis; **l** widened notch. (Reprinted with permission from Speer D, Early pathogenesis of hemophilic arthropathy. Clin Orthop Rel Res. 1984;185:250–265. Copyright 1984 Wolters Kluwer Health)

the articular cartilage. The cysts when unroofed contained a dark viscous fluid with no evidence of bone or cartilage. Although a pannus was seen, it was not as vascular or as advanced as that in rheumatoid arthritis. In addition, at the osteochondral junction, the fibrovascular pannus appeared to invade the articular cartilage from the surface, but the marrow cavity itself did not show cystic or fibrous changes in contrast to early rheumatoid arthritis. Eventually the fibrous pannus extended to the margin of the osteochondral defects in the central parts of the condyles. At the bases of the osteochondral defects, there were thickened sclerotic laminated bone plates depressed below the plate of the normal subchondral bone. It was Speer's feeling that "a subchondral cyst evolves as an expanding hematoma that aggressively destroys the subchondral bone and the overlying articular cartilage before eventually communicating with the joint space. The subchondral cyst progressed to an osteochondral cyst and then to an osteochondral defect." Since these cysts occurred in the intracondylar notch in the central portion of the condyles, they related to the characteristic radiographic findings. He defined five mechanisms by which the articular cartilage was destroyed in hemophilic arthropathy: (1) enzymatic digestion of articular cartilage due to production of proteolytic enzymes including collagenases during the chronic synovitis stage; (2) direct cellular destruction of articular chondrocytes by phagocytic and other cells; (3) direct damage to articular chondrocytes by "blood or other tissue products"; (4) mechanical factors of load pressure, abrasion, and abnormal loading secondary to contractures and osteopenia; and (5) changes resulting from the subchondral hemorrhagic cysts.

He states that "the cyst of hemophilic arthropathy is the result of subchondral hemorrhage." An inciting event for the subchondral cyst was fracture of the subchondral bone plate with a resulting subchondral hemorrhage. The osteopenic bone would increase the likelihood of fracture. The hemophilic arthropathy begins in the center of the condyle and moves progressively outward which is different from the progression of rheumatoid arthritis from the periphery toward the center. Owing to its position, the subchondral cyst expands with its hematoma by direct bone and articular cartilage tissue destruction until rupture into the joint space occurs. The subchondral cyst thus paves the way for eventual joint destruction as the articular cartilage which is initially intact overlying it subsequently collapses. In summary, the evolution of hemophilic arthropathy begins in the synovium with acute and chronic synovitis. Subchondral cysts develop following subchondral hemorrhage with osteolysis and/or collapse resulting in flattening of the condyles and widening of the intercondylar notch. Fibrillation and wear of the joint surface then occur on both a chemical and mechanical basis. The subchondral cysts expand with lysis of overlying cartilage to form an osteochondral cyst. This can be associated with full thickness articular cartilage loss. In the later stages, chronic synovial fibrovascular pannus grows to undermine the osteochondral junction of articular cartilage peripherally. Bone sclerosis occurs at the base of the osteochondral defects. There is further widening of the intercondylar notch due to further subchondral osteolysis and/or collapse with overlying articular cartilage loss.

Stein and Duthie reported on chronic end-stage hemophilic arthropathy analyzing 44 tissue specimens from 39 adult patients during reconstructive joint surgery [313]. The mean age of patients having hip, knee, and ankle procedures ranged from 20.5 years for knee synovectomies to 41.5 years of age for total hip replacements. Specimens were obtained from 21 knees, 15 hips, 6 ankles, 1 foot, and 1 wrist. Their assessments understandably showed extensive damage of both the hemophilic synovium and articular cartilage. The synovial lining became progressively fibrotic and the hyalin cartilage disintegrated and eventually disappeared. Both mechanical and chemical processes were considered to cause degeneration of cells but enzymatic processes in particular appeared primarily responsible for degradation of the cartilage matrix. Synovial changes worsened with age. In those <20 years of age, there was marked villous proliferation while in all adult patients, the synovium was progressively replaced showing marked thinness, an increasing tendency to avascularity and eventual fibrous thickening. In the younger age groups, the lining cells of the synovium were heavily filled with hemosiderin. There was inflammation around the synovial hemosiderin deposits. Subsynovial layers were almost totally free of hemosiderin. The cartilage was thinned and degenerated. Fibrous tissue invaded from the synovial regions at the periphery of the joint and from the underlying subchondral bone and marrow. Pyknotic chondrocytes were frequently seen. The cellularity of the cartilage was increased in some areas with chondrocyte clones but in general was decreased with destruction and disappearance of damaged chondrocytes. Connective tissue often covered and partially replaced the superficial layer of the original articular cartilage. Histochemical stains revealed hemosiderin in both the superficial synovial membrane and also within chondrocytes of the articular cartilage. They concluded that the synovial membrane underwent extensive fibrosis

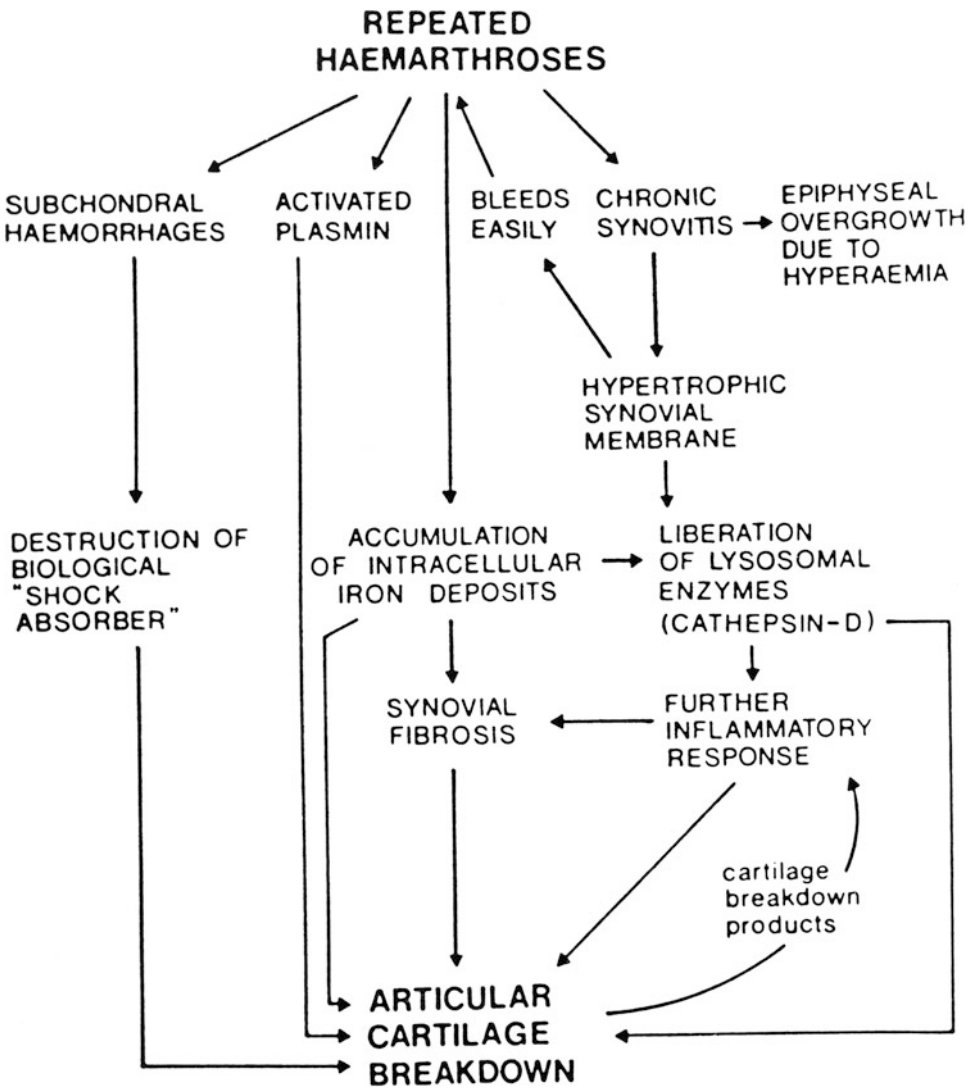

Fig. 4.16 The pathogenesis of chronic hemophilic arthropathy is outlined (from Stein and Duthie [313])

with time, scar tissue replacing the entire thickness including the lining layer. The architecture of articular cartilage was severely disrupted. Chondrocytes degenerated. At one stage, they were irregularly dispersed in the matrix and aggregated in cell clusters referred to as clones. With time, many areas of matrix were acellular. Fibrous tissue then invaded the cartilage both from the subchondral bone and from the periphery of the synovial lining. Iron deposits were seen both in the synovial cells and even within chondrocytes. All cells containing iron deposits eventually showed degeneration and disintegration. All mechanical, chemical and particular enzymatic effects of the hemophilic arthropathy led to articular cartilage breakdown. This is illustrated in Fig. 4.16 from their work.

(e) *Experimental studies on animal joints and human synovium*: Hooiveld et al. induced changes in the beagle knee joint to simulate recurrent hemophilia hemarthrosis [316]. They injected autologous blood three times per week for 4 weeks in eight mature dogs knees. Some knees were loaded for walking while others were not. Analysis was performed on cartilage and synovium after 10 weeks. Those joints which had undergone joint loading had many more negative effects than those subjected only to blood injections alone. Proteoglycan turnover was markedly increased in the weighted cartilage with both increased synthesis of proteoglycan and increased release (loss) of proteoglycan from the cartilage matrix. This response was similar to articular cartilage damage in osteoarthritis. Histology showed adverse effects on cartilage matrix and synovial inflammation. The study showed that it was not the presence of blood alone in the joint that induced hemophilic arthropathy changes.

The authors also reviewed other investigative studies on hemophic joints. The feeling is increasing that

changes seen are more similar to degenerative osteoarthritis than they are to inflammation as in rheumatoid arthritis. It is not the synovitis that causes the problem but rather the blood that directly has adverse effects on the cartilage. Chondrocyte apoptosis appears to be triggered by the exposure to bleeding. Based on their study, however, loading of the affected joint worsened the bleeding sequelae.

Roosendaal et al. examined sections of synovium from six human hemophilic joints with arthropathy [317]. Brown tissue with hemosiderin (iron) deposits was compared with normal appearing synovium from the same joint. The hemosiderin-stained synovium showed a significantly higher inflammatory activity than the normal appearing synovium. Tissue cultures showed the abnormal appearing tissue to be synthesizing much more 1L-1, 1L-6, and TNFα indicating greater catabolic activity (1L = interleukin, TNF = tumor necrosis factor).

(f) *Radiologic Findings*: The striking radiographic changes of hemophilic arthropathy were recognized early and in great detail [318]. Some felt that the radiographic features of hemophilia, once it entered the nonacute phases, were sufficiently characteristic to allow diagnosis to be made radiographically. These included generalized osteopenia, markedly increased density of the synovial tissues, enlargement of the epiphyseal bone in comparison to the normal side, narrow joint spaces, roughened articular surfaces, cystic lesions in the subchondral region, and widening and deepening of the intercondylar notch of the femur. Several observers had noted clinical evidence of joint involvement in hemophilia before the age of 10 years with Thomas reporting 89 % of 98 hemophilic patients so involved [319]. In Thomas' study of 98 hemophiliacs prior to the era of blood and factor replacement, 78 % gave a history of joint involvement and 61 % had permanent deformities. The distribution of joints affected was knees 68 %, ankles 56 %, elbows 53 %, hips 16 %, fingers 15 %, wrist 5 %, and toes 2 %. In the earliest stages with acute hemarthrosis, soft tissue swelling could be noted but the radiograph was otherwise unremarkable. As the arthropathy worsened with recurrent bleeds, the soft tissue hypertrophy led to increased density radiographically and this was often increased because of the high iron content of the synovial and subsynovial tissues. The joint space was often reduced because of degeneration of the articular cartilage. The articular surfaces of the bones became irregular, and there were focal subchondral bone cystic defects noted.

Pettersson et al. based their classification on radiographic changes previously described including intraarticular effusion, periarticular soft tissue thickening, periarticular soft tissue calcification, synovial thickening and increased density, enlargement of the secondary ossification centers of the epiphyses, periarticular osteoporosis, narrowed joint spaces, irregularity of subchondral surfaces, subchondral sclerosis, subchondral cysts, incongruence between articular surfaces, erosions of joint margins, and Harris lines [320, 321]. The radiologic classification of changes was based on the above criteria that could be quantified radiologically and each finding was allotted 0, 1, or 2 points according to severity. The sum of points allotted to a given joint at each examination led to its score. The radiologic evaluation classification recommended by the orthopedic advisory committee of the World Federation of Hemophilia is shown in Table 4.6.

A widened intercondylar notch of the distal femur seen on the anteroposterior radiograph is a characteristic finding in hemophilia after recurrent hemarthroses. There can also be broadening of the radial head at the

Table 4.6 Radiologic evaluation recommended by the Orthopaedic Advisory Committee of the WFH

Type of change	Finding	Score (points)
Osteoporosis	Absent	0
	Present	1
Enlarged epiphysis	Absent	0
	Present	1
Irregular subchondral surface	Absent	0
	Partly involved	1
	Totally involved	2
Narrowing of joint space	Absent	0
	Joint space > 1 mm	1
	Joint space < 1 mm	2
Subchondral cyst formation	Absent	0
	1 cyst	1
	>1 cyst	2
Erosions of joint margins	Absent	0
	Present	1
Gross incongruence of articulating bone ends	Absent	0
	Slight	1
	Pronounced	2
Joint deformity (angulation and/or displacement between articulating bones)	Absent	0
	Slight	1
	Pronounced	2

Possible point score: 0–13 points

elbow. Other radiographic findings included soft tissue swelling, osteopenia, and overgrowth of the epiphysis. Later bone changes included subchondral cysts, marginal erosions, subchondral surface irregularity, widening of the intercondylar notch of the distal femur, squaring of the patella, enlargement of the radial head, and widening of the trochlear notch of the olecranon. The latest stages are characterized by articular cartilage joint space narrowing, flexion contractures, and angular deformity.

Another radiographic classification has been defined by Arnold and Hilgartner [322]. Stage 1. There are no skeletal abnormalities visible on radiographs but there is soft tissue swelling due to hemarthrosis or periarticular bleeding. Stage 2. Subacute hemarthropathy. There is osteoporosis particularly in the epiphyses along with overgrowth of the epiphyses, maintenance of joint integrity with no narrowing, and no bone cysts. Stage 3. Joint disorganization is evident radiologically but with no significant narrowing of the cartilage space. Subchondral cysts, squaring of the patella, denser synovium (hemosiderin deposit), widening of the intercondylar notch of the distal femur, and ulnar trochlear notch widening are characteristic findings. Stage 4. Narrowing of the joint space with articular cartilage destruction. Stage 3 changes are magnified. Stage 5. Fibrous joint contracture, loss of joint space, extensive enlargement of the epiphyses and disorganization of the joint structures are seen.

Radiologic changes are illustrated in Fig. 4.17a–c.

The radiologic changes reflect the cumulative changes following both large and smaller subclinical hemorrhages. DePalma and Cotler noted irregular subperiosteal ossification following subperiosteal hemorrhages in some patients [309]. In addition to the other epiphyseal changes described frequently, they commented specifically on premature closure of part or all of the epiphyseal plate leading to shortening of the bone or angular deformities. They did not note discrepancy in bone length that could be attributed to overstimulation at the epiphyseal plate to the extent that it leads to an operable limb-length discrepancy. We have noted very few hemophilia patients in the growth study series, despite the fact that a large hemophilia program in the hospital has existed for some time.

Caffey and Schlesinger [318] outlined in detail the radiology of hemophilic joints when no effective treatment for the bleeding was available. Radiologically there was advanced maturation of the bony epiphyses, enlargement of the epiphyses, and irregular and asymmetrical ossification in particular in the hip joint. They described five children who also showed both advanced and abnormal epiphyseal development. Measurements indicated that all the epiphyses in the involved joints were larger than their counterparts on the opposite nonaffected side. The sizes of the secondary ossification centers in the various axes were measured.

There was early awareness of acceleration of epiphyseal maturation in those with hemophilic hemarthrosis including squaring and enlargement of the epiphyses [318]. There was also recognition of Perthes like changes in the femoral capital epiphysis with pronounced hip bleeds.

Radiologic evaluation of hemophilic arthropathy continues to be refined [323]. Kilcoyne and Nuss point out the inability of plain radiographs to detect the early changes of synovial hyperplasia and cartilage damage which are now detectable by MR imaging. Landin et al. have recently updated the MRI scale for assessment of hemophilic arthropathy [324].

(g) *Joint Evaluation Grading; Semiquantitative criteria established by World Federation of Hemophilia*: The World Federation of Hemophilia has established some semiquantitative standards for joint evaluation [325]. They consider four parameters involving pain, bleeding, physical examination, and the radiologic evaluation. The scoring system for pain goes from 0 to 3, bleeding 0–3, physical examination 0–12, and radiologic evaluation 0–13. Following the score, any patient requiring aids to ambulation is subcategorized as B for use of brace or orthosis, C—cane, CR—crutches, and WC—wheelchair.

Pain scores. A score of 0 is registered if there is no pain, no functional deficit, and no analgesic use except for acute hemarthrosis. A score of 1 indicates mild pain which does not interfere with occupation or activities of daily living (ADL) and may require occasional nonnarcotic analgesic. Moderate pain is given a score of 2 where there is partial or occasional interference with occupation or ADL, use of nonnarcotic medications, and occasional narcotic medication use. A score of 3 for severe pain involves discomfort which interferes with occupation or ADL and requires frequent use of nonnarcotic and narcotic medication.

Bleeding scores. A score of 0 is given if there is no bleeding; a score of 1 if there is no major or 1–3 minor criteria; a score of 2 if there is 1–2 major or 4–6 minor criteria; and a score of 3 is given if there are 3 or more major or 7 or more minor criteria. The guidelines for a minor grading are mild pain, minimal swelling, minimal restriction of motion, and resolution within 24 h of treatment. Guidelines for major criteria include pain, effusion, limitation of motion, and failure to respond within 24 h. The number of occurrences is registered in terms of hemarthroses per year.

Fig. 4.17 Radiographic joint changes in patients with hemophilic arthropathy are shown in **a**, **b**, and **c**. **a** Lateral views of affected right elbow (i) and nonaffected left elbow (ii) show decreased joint space and premature fusion of proximal radial physis on affected side. **b** Anteroposterior knee radiograph (i) shows widened intercondylar notch (*arrows*), joint space narrowing, and irregular subchondral bone. In a different patient, (ii) knee involvement at skeletal maturity shows markedly diminished medial and lateral femoral-tibial joint space and subchondral sclerosis due to cartilage destruction. (iii) to (vi): four views of the knee from patient who underwent the synovectomy whose tissue is illustrated in Figure 13 are shown. Marked cartilage degeneration (*joint space narrowing*), bone resorption, subchondral bone flattening and sclerosis, and osteophytic peripheral reactions are seen in (iii) anterior, (iv) lateral, (v) tunnel, and (vi) patello-femoral views. (vii) knee at skeletal maturity showing medial and lateral joint space narrowing, depression of the medial tibial plateau and radiolucent cyst formation of the medial femoral condyle. **c** Anteroposterior ankle radiographs show: (i) joint space narrowing with distal tibial epiphyseal and talar cysts (lytic areas); (ii) oblique radiograph with joint space narrowing and talar subchondral lysis; and (iii) characteristic talar flattening on the lateral projection. (iv) Magnetic resonance imaging is particularly useful to assess articular cartilage irregularity, the state of synovial vascularity, and the degree of cystic and inflammatory subchondral intraosseous involvement

Physical examination scores. Physical examination includes grading of swelling 0–2 or more with a subgradation for chronic persisting synovitis, muscle atrophy 0 or 1, axial deformity 0–2, crepitus on motion 0 or 1, range of motion 0–2, flexion contracture 0–2, and instability 0–2.

Radiographic scores. The specific criteria are listed in Table 4.6.

4.5.1.5 Intramuscular Hemorrhage Followed by Contractures, Ischemic Muscle Necrosis, Neuropathies

Ischemia of the calf muscles can occur following intramuscular bleeding in which a Volkmann-like compartment syndrome evolves. One of the occasional sequelae of such an occurrence is tightness of the gastro-soleus muscle and tendo Achilles shortening. This can be effectively repaired with tendo Achilles lengthening. The commonest area of muscle bleeding in some series is within the iliopsoas muscle mass. This can be recurrent and lead to difficulty because of the problems immobilizing the muscle. In one study of muscle bleeding in hemophilia, the sites included the quadriceps muscle (44 %), the posterior calf muscles (35 %), the hip adductors (7 %), and the anterior leg muscles (7 %) [326]. In the study by Houghton and Duthie, involving 170 episodes over a ten-year period, muscle hemorrhage was noted in the iliopsoas in 53 (31 %), thigh 40 (24 %), calf 34 (20 %), forearm 32 (19 %), shoulder girdle 7 (4 %), and buttock 4 (2 %) [305]. The complications of muscle hemorrhage involved limb contractures present in 20 % of severe calf and forearm bleeds. The other complication was nerve palsies. In the 170 patients with muscle bleeds, 43 (25 %) had an associated peripheral nerve lesion. This was usually a neuropraxia or axonotmesis, and with the exception of the sciatic nerve, full recovery invariably occurred. There were 30 femoral nerve palsies complicating 53 iliacus muscle hemorrhages and virtually all these recovered although full function often took 6 months before it returned. Katz et al. did a more detailed review of peripheral nerve lesions in hemophilia over a longer period of time from the Nuffield Orthopaedic Center in Oxford, England [327]. They identified 88 lesions in 54 patients over a 24-year period. The femoral nerve was most commonly involved. There were 61 lesions in which long-term followup was obtained. In 30 (49 %) of the lesions, the nerve had full motor and sensory recovery; in 21 (34 %), there was a residual sensory deficit; and in 10 (16 %), both a persistent motor and sensory deficit was noted. Patients with antibodies to factor VIII were significantly less likely to recover full motor or sensory function and the time to full recovery in these patients was significantly longer. The commonest nerve involved was the femoral which was affected in 31 of 61 instances (51 %). The next most common nerves involved were the median (10, 16 %), ulnar (7, 11 %), sciatic (4, 7 %), and radial (5 %). The most common cause of nerve palsy was intramuscular hemorrhage. Full motor recovery was more likely than full sensory recovery.

4.5.1.6 Fractures

Hemophiliacs are not considered to have an increased incidence of fractures and with appropriate treatment any fractures that occur unite without complications within the anticipated time. While their activity level is often diminished, the associated osteoporosis predisposes to injury. Skeletal traction is contraindicated but open reduction and internal fixation are often helpful. In the series of Houghton and Duthie, there were 23 fractures over a ten-year period [305]. The most common were those of the femoral and tibial shafts. Circumferential casts must not be used. Factor therapy is essential during the immediate postfracture period.

4.5.1.7 Hemophilic Pseudotumor

A hemophilic pseudotumor is a slowly progressive hemorrhage that increases in size in a confined space [328]. The most common site is the pelvis and proximal thigh and the lesions may originate within bone, in the periosteal region or occasionally in adjacent soft tissues. A pseutotumor is illustrated in Fig. 4.18. Since a pseudotumor is an expanding hematoma or hemorrhage it must not be biopsied or

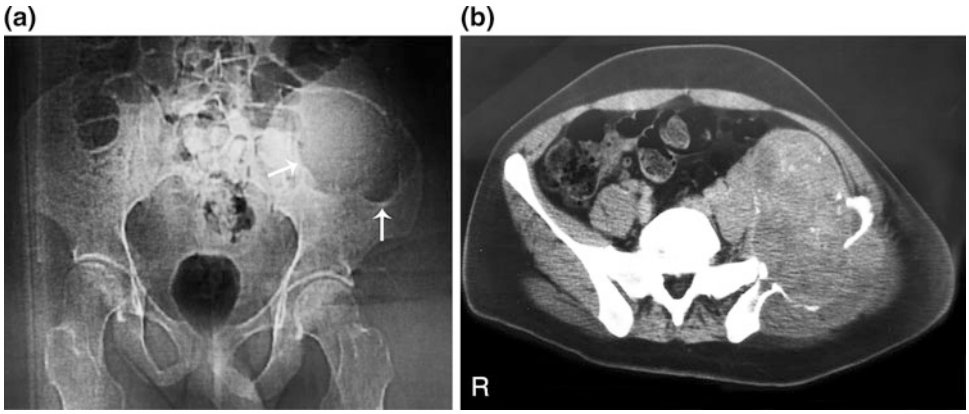

Fig. 4.18 The massive extent that can be reached by a pelvic hemophilic pseudotumor is shown. **a** Radiograph of pelvis shows extensive involvement of left iliac bone with arrows pointing to the inner bony edge of involvement. **b** Magnetic resonance image of the left sided lesion in (**a**) shows extensive bone lysis and soft tissue mass expanding both anterior and posterior to iliac the wing. Note the well-structured iliac bone on *right* [*R*]

aspirated for diagnosis. No malignant change of a pseudotumor has been documented although they can be confused with malignancy initially.

Pseudotumors have always been infrequent in hemophilia and with improvements in medical therapy they are becoming even less common. They are dramatic lesions, however, and have the potential to lead to disastrous results with inappropriate intervention so clear understanding of them is essential. Rodriguez-Merchan reported on 17 pseudotumors within bone [328]. Eight were in the femur, two in the pelvis, two in the radius, two in the hand, and one each in the tibia, humerus, and big toe. The pseudotumor is a progressive cystic swelling produced by recurrent bleeding involving muscle and accompanied by bone involvement. The commonest sites are the proximal long-tubular bones where repeated and unresolved intramuscular hematomas may lead to encapsulation and calcification with a progressive enlargement of the mass and erosion of the adjacent bone. The pseudotumor is an encapsulated hematoma. The hemorrhage is chiefly extraosseus with extensive subperiosteal bleeding and reactive new bone formation. The mass expands both externally and internally causing extensive destruction of the adjacent bone. They are most commonly proximal in particular around the femur and pelvis where they start in the soft tissues and erode bone secondarily. They tend to develop slowly over many years. They occur in adults and do not respond to conservative treatment. Calcification within the mass is common. Biopsy is absolutely contraindicated because of the danger of severe and perhaps lethal hemorrhage. Many of these are simply observed and appear to progress slowly over several years with minimal damage. In those where there is discomfort, unacceptable bone, and joint disruption, or associated neurologic problems treatment is mandatory. Extensive preoperative work up with multiple imaging techniques is essential. It is extremely important to outline the associated vascularity. The best approach if possible is to remove the entire mass "en bloc" with clear attention to its vascularity. Efforts to curette and pack the lesion are contraindicated.

4.5.1.8 Current Medical Treatment

(a) *Medical treatment*: The treatment of hemophilia became effective in 1940 when whole blood transfusions were utilized to replace the missing factor VIII and IX components [293–295, 297, 329, 330]. Treatment shortly evolved into the use of **fresh frozen plasma (FFP)**. In 1964, **cryoprecipitate** was developed; it represents the protein that precipitates in fresh frozen plasma when it is thawed at 4° C which is rich in factor VIII and fibrinogen are well as factor IX and VWF. In 1970, **specific factor concentrate** began to be used. Each of these methods, however, required the use of human blood, a situation which became devastating in terms of complications with transmission of the AIDS virus. Once the problem of the AIDS virus was recognized both factor VIII concentrates and cryoprecipitate were prepared from donors screened carefully for the human immunodeficiency virus (HIV). In addition, all factor VIII preparations were processed further to diminish the likelihood of any viral contaminants. Methods to destroy viruses are based on terminal heating of the lyophilized product at 80° C, heating in solution at 60 °C (pasteurization) in a suspension containing various organic solvents, or adding an organic solvent and a detergent during the manufacturing process. Heating serves to inactivate heat sensitive viruses such as HIV-1. Other preparations involving solvent-detergent extracted factor VIII remove coated viruses including HIV-I and hepatitis viruses. Since factor VIII concentrates are obtained from screened donors and have other antiviral steps performed their use became recommended replacing cryoprecipitate. During the 1970s and early 1980s, pooled plasma samples from 2000 or more donors were used to make clotting factor concentrates which explains the high number of hemophiliacs of that time period infected with hepatitis and AIDS. Other single-factor concentrates made from pooled donor plasma are fibrinogen, VWF, FVII, FXI, and FXIII. The risk of transmission of hepatitis B and C viruses has also diminished since use of virucidal methods but has not been abolished completely.

Many clinics turned increasingly to even safer factor VIII concentrates using either **monoclonal factor** VIII concentrates prepared using affinity chromatography or **recombinant factor** VIII which is a synthetic product prepared in Chinese hamster ovary cells or baby hamster kidney cells. Recombinant factor VIII products were initially approved for use in the United States in 1992 and recombinant-derived FIX was approved in 1997 [330]. In virtually, all North Americans and Western European clinics FFP and cryoprecipate have been completely abandoned for FVIII and FIX hemophilia. The monoclonal or recombinant forms of factor VIII have essentially no risk of hepatitis, AIDS or hemolysis. The first generation recombinant form still manufactured and in use is Recombinate (Baxter) in which bovine serum and human albumin are used in manufacturing. The advanced generation products made with no bovine serum and trace or no albumin are Helixate FS (ZLB Behring) and Kogenate FS (Bayer). Additional albumin-free recombinant agents for factor VIII deficiency are Advate (Baxter) and Xyntha (for IV

use only) (Pfizer). Replacement therapy in hemophilia B includes the infusion of factor IX concentrate recombinant BeneFIX (Wyeth) made with no animal or human proteins. It is produced by a genetically engineered Chinese hamster ovary cell line shown to be free of infectious agents. For FVIII 1, unit/kg of body weight produces a 2 % rise in plasma level with $T_{1/2}$ = 8–12 h while FIX infusion of 1 U/kg of body weight produces a 1 % rise in plasma level with $T_{1/2}$ = 24 h.

The hemophilia community was hit particularly hard during the time period when AIDS began to flourish and HIV within blood bank samples was either not recognized or not specifically looked for. AIDS was first identified in 1982 in a patient with hemophilia who had received transfusions. In some clinics, approximately 90 % of patients with hemophilia who had been multiply transfused with untreated products became HIV positive. One study showed 55 % of patients with hemophilia infected with HIV-I from 1979 through 1985, with even larger percentages of this population infected with hepatitis C. A study of mortality in patients with hemophilia between 1986 and 1992 showed that over one fourth of deaths (27 %) were related to HIV infection and only one fifth were related to hemorrhage. Prior to the AIDS epidemic, excess mortality among hemophiliacs had always been due to intracranial hemorrhage. The magnitude of the problem was also illustrated by Rodriquez-Merchan in a review from Spain [331]. Of the 435 hemophiliacs at one unit, 257 (59 %) had HIV infection caused by therapy with human plasma. Of these HIV-positive patients 95 (37 %) had already developed full blown AIDS. In Spain, roughly 70 % of hemophiliac patients who received pooled untreated factor VIII preparations became HIV positive with 90 % of severe hemophiliacs so affected. An estimated 9300 hemophiliacs in the USA, almost half the total number were infected with HIV and almost 80 % with hepatitis C. Greene et al. demonstrated that effective surgery could still be performed in hemophilic AIDS patients and listed preoperative evaluation criteria [332].

The number of affected patients diminished dramatically in new patients once the problem was recognized. All blood was screened for the HIV virus, and increasingly, manufactured monoclonal coagulation factors were used bypassing completely the need for human blood. Fresh frozen plasma (FFP) contains all coagulation factors, but is rarely used. Single donors with low risk of hepatitis or other viruses continue to provide blood products needed for some cases with pooled donor products eliminated. Cryoprecipitate contains factor VIII and fibrinogen and continued to be used in hemophilia A and von Willebrand's disease for a while but each bag was also manufactured from one donor with a low risk of hepatitis or other viruses.

The most commonly used treatment today is genetically engineered recombinant factor VIII or plasma derived, monoclonal antibody-purified factor VIII for hemophilia A. Other pharmacologic agents can be used in specific situations for some hemophilia patients. Desmopressin (1-deamino-8-D-arginine vasopressin) is a derivative of the antidiuretic hormone. Vasopressin was found to induce an increase in factor VIII but it also caused vasoconstriction, increased blood pressure and contraction of the uterus and gastrointestinal tract making it undesirable for clinical use. The synthetic analog of vasopressin, desmopressin, however, did not produce these effects and became valuable as a non-transfusional hemostatic agent. Desmopressin acetate (DDAVP) increases the plasma levels of factor VIII and von Willebrand factor and can be used for nontranfusional treatment of patients with mild or moderate hemophilia and von Willebrand's disease [297, 333–335]. Meanfactor increase of 2–4 times baseline can be seen with peak responses at 30–60 min after intravenous injection. Side effects include mild facial flushing and lightheadeness. DDAVP dosage is 0.3 mcg/Kg in 50 cc normal saline by IV infusion over 30 min. Desmopressin acetate nasal spray (Stimate) can be used for mild hemophilia A with FVIII greater than 5 %. For surgery, topical thrombin is of some value to control oozing or minor bleeding in difficult to access spots. Solutions of topical thrombin (Topical USP-bovine origin-thrombin, Jones Medical Industries, Inc) are reconstituted with sterile isotonic saline at a concentration of 1000–2000 US unit/ml. Thrombin in a drug form (Gen Trac, Jones Medical Industries, Inc) has been chromatographically purified. Antifibrinolytics such as Amicar and tranexamic acid are used for major surgical intervention. An outline of factor replacement in varying bleeding and operative situations is shown in Table 4.7.

An outline of product options for replacement therapy plus newer immune tolerance induction and gene therapy treatments provides a clear overview [336]. Kaufman and Powell have reviewed in detail the bioengineering of new products to further enhance the effectiveness, ease, and safety of factor replacement [330]. Current investigation focuses on conjugation at specific sites of the factor with polyethylene glycol (PEG) a hydrophilic polymer [330, 337]. The covalent attachment of PEG to a protein (referred to as PEGylation) can reduce its immunogenicity, an attractive feature in efforts to minimize formation of inhibitory alloantibodies.

Table 4.7 Brief outline of factor treatment for musculoskeletal bleeding in hemophilia A and B

Site/Situation	Hemophilia A		Hemophilia B		Desired range of factor levels
	Initial dose (U/kg)	Repeat dose (U/kg)	Initial dose (U/kg)	Repeat dose (U/kg)	
Acute hemarthrosis					
Early	15–30+	Rarely needed	20	Rarely needed	Early (<3 h from onset): raise factor level to 25–30 %, repeat if needed clinically
Late	25–50+	25 q12 h	40–80+	20–25 q24 h	Late: raise factor level to 50–100 %
Intramuscular hemorrhage	25–50+	25 q12 h, often for several days	Mild-moderate: 20–40	30 q24 h, often for several days	Major: calf, forearm, iliopsoas, hip; raise factor level to 100 %, maintain several days to several weeks, taper range to 30–50 % for additional periods
			Severe: 80		Minor: other areas, superficial bleeds, raise factor level to 50 %, usually for 2–3 days only
Major surgery	50	25 q8–12 h or 25 followed by continuous fusion IV 3–4 U/kg/hr	80	40 q24 h or loading dose plus continuous IV fusion	

Abstracted from Boston Hemophilia Center guidelines, 2/98, B. Ewenstein, E. Neufeld, J. Gorlin
See also DiMichele [293, 336]; + lower ranges represent "textbook" responses of 1 U/kg = 2 % factor increase

(b) *Early Intervention with Factor Replacement for Bleeding Episodes*: The commonest approach to medical management in North America has involved early intervention for bleeding episodes with increased factor given at onset of discomfort and if possible even prior to the observation of joint swelling. This approach is often referred to as on-demand or episodic treatment. This treatment involves the use of home infusion of factor VIII or IX without the need to be seen initially at a hospital or a clinic. Most clinics and families use this approach which is based on patient and parent awareness of the earliest symptoms of disorder and easy communication between families and comprehensive hemophilia clinic personnel. Immobilization of the affected joint with splints or bivalved casts is an integral part of the treatment program.

(c) *Prophylactic Factor VIII and IX Coverage*: Treatment involving continual prophylactic use of factor VIII has become more popular [338–340]. This approach seeks to maintain the factor VIII levels in a therapeutic range of 1–5 % at all times rather than reacting to the occurrence of joint bleeding. This level is chosen since moderate severity hemophiliacs rarely develop significant arthropathy. The prophylactic treatment converts severe patients to a moderate phenotype. The infusion of factor VIII is done three times weekly and of factor IX twice weekly. Trials in Europe extending as far back as four decades have been positive. A major Swedish study of prophylactic treatment for hemophilia A and B in 60 severe hemophiliacs (52 A, 8 B) has been reported [339]. Treatment was started when the boys were 1–2 years of age with a regimen of 24–40 IU factor VIII kg-1 three times weekly in hemophilia A (>2,000 IU kg-1 annually) and 25–40 IU factor IX kg-1 twice weekly in hemophilia B. Of those subjects aged 3–17 years 29 out of 35 individuals had joint scores of 0 (normal). Factor VIII and IX concentrations were designed not to fall below 1 % of normal. The study concluded that it appeared to be possible to prevent hemophilic arthropathy by giving effective continuous prophylaxis from an early age and preventing factor VIII and IX concentrations from falling below 1 % of normal. The treatment served to convert hemophilia from a severe to a moderate form thus preventing joint bleeds and hemophilic arthropathy. Best results were obtained when treatment began at the age of 1–2 years with factor VIII given in dosages of approximately 3,000 IU kg-1 annually.

A study has analyzed 70 patients treated actively when bleeding occurred and 17 receiving factor VIII regularly on a prophylactic regimen for a mean of 4.5 years [340]. Both pediatric and adult aged patients were included. The mean age of the prophylactic group was 18.9 years. The prophylactic group missed fewer days of work due to joint bleeding. There was less differential in relation to joint pain but the on-demand therapy patients experienced more pain with increasing age. The age of the patient was considered to be more important than treatment strategy in the development of joint symptoms. To be most effective prophylactic regimens should be started in the very young prior to any occurrence of joint pathology. Because of the

extremely high cost of prophylactic treatment, some feel that specific indications for its use should be developed rather than offering the treatment to all severe hemophiliac patients.

A longitudinal study for orthopedic outcomes for severe factor VIII deficient hemophilia was performed by Aledort et al. [338]. Twenty-one international hemophilia centers were included to assess patients over a 6-year period. Physical and radiologic examinations of ankle, knee, and elbow involvement were done. The study population involved those with severe factor VIII deficiency (<1 % factor) under the age of 24 years without inhibitors. Some patients were treated on a prophylactic regimen but most had an on-demand response for any joint bleeding. The authors concluded that year-long prophylaxis significantly reduced the rate at which joints deteriorated by both physical examination and radiographic criteria. Patients on prophylaxis had significantly fewer days loss from work or school and fewer days spent in hospital. They concluded that higher doses of factor in themselves did not produce improved orthopedic outcomes but that full-time prophylaxis was likely to produce the best orthopedic outcome. The most critical factor for a good orthopedic outcome was diminution in the number of joint bleeds. Full-time prophylaxis had been assessed in 66 of 477 patients with appropriate physical examination data and 53 of 323 patients with full radiographic data. These assessments led the authors to conclude that prophylaxis significantly reduced the rate at which joints deteriorated and that it did so by dramatically reducing the number of bleeds thus minimizing joint damage. The number of days lost from work or school was significantly lower in the entire population studied for those who received >2,000 units per kilogram per patient per year of factor VIII. Patients treated by on-demand therapy progressed significantly more than those on prophylaxis. Those on prophylaxis required significantly more factor than on-demand therapy. The findings strongly supported the above-mentioned Swedish experience that a high-dose regular prophylaxis starting at a very young age can maintain hemophilic joints in essentially a normal range for prolonged periods of time. Prophylaxis however could decrease the rate of deterioration of patients' joints if begun after some damage was already present. If prophylaxis was not performed doses of factor VIII from 25 to 40 units per kilogram per bleeding episode were best in reducing the progression of arthropathy. This approach is currently reserved for those in the severe category, partly because it is enormously expensive and the need to maintain comfortable, infection-free continuous intravenous access can be problematic.

Fischer et al. assessed the effects of postponing prophylactic treatment on long-term outcome in severe hemophiliac [341]. A cohort of 76 patients with severe hemophilia were assessed from childhood to young adult years. The median age at first joint bleed was 2.2 years (range 0.2–5.8 years). Ninety percent of patients had at least one bleed by age 4.4 years. There were three age groups at which time prophylaxis started: 16 patients started early (<4 years of age), 34 late (4–7 years of age), and 26 very late (>8 years of age. Clinical and radiographic scoring was done. The median followup was 16 years (range 11.2–20.5). At a median age of 19 years, arthropathy as measured by the Pettersson score was 7 points. After two decades followup, the Pettersson score was 8 % higher for every year prophylaxis was postponed after the first joint bleed. The effect was independent of the age at first joint bleed and the prophylactic dose used. The authors concluded that patients who start prophylaxis soon after the first joint bleed show little arthropathy in adulthood. Prophylaxis has always been more widely practiced in western Europe than elsewhere, including the United States. Initially prophylaxis was started in patients who had suffered several joint bleeds and often already showed synovitis. Hemophilic prophylaxis before the onset of arthropathy is now more commonly practiced and is referred to as primary prophylaxis. If started early enough, this treatment can prevent hemophilic arthropathy. In 1995, the World Health Organization recommended starting prophylaxis between the ages of 1 and 2 years and if possible continuing it throughout life. Some groups are now trying to determine the safety of discontinuation at 18 years of age.

A multicenter United States study recently assessed the value of recombinant factor VIII given as prophylaxis in one group (32 patients) and enhanced episodic treatment in another (33 patients) [342]. Assessment was only for mean of 49 months but use of magnetic resonance imaging (MRI) along with plain radiography allowed for more sensitive indications. The proportion of participants in whom all six index joints were normal at 6 years of age was 25 of 27 (93 %) in the prophylaxis group and 16 of 29 (55 %) in the enhanced episodic therapy group. The relative risk of damage to one or more joints was 6.1 in the episodic group versus 0.17 in the prophylaxis group, an 83 % reduction. Prophylaxs was initiated between 6 and 30 months of age; 18 of 32 (56 %) had 1–2 bleeds and the others up to 5 hemarthroses. Prophylaxis was beneficial in decreasing joint bleeding and damage after up to 5 hemarthroses. The study discussed the two major reasons for slowness in instituting widespread use of prophylaxis in the United States; these being the (i) AIDS epidemic beginning in

the mid 1980s, and once that was controlled regarding the source of factor, (ii) the enormous cost. The study estimated the annual cost of prophylactic therapy per patient per year at $300,000 (US).

(d) *Inhibitors*: Despite continuing improvement in the effectiveness of treatment for hemophilia A, the development of factor VIII inhibitors remains a serious problem. Factor VIII is a foreign protein for most patients with severe hemophilia. Since the antibody develops against the factor VIII itself the fact that monoclonal purified concentrates or recombinant factor are used increasingly does not change the development of the inhibitor effect. Hoyer has summarized the various strategies used for patients with inhibitors [295], and Hay et al. have updated these [343]. Possible reasons for high numbers of inhibitor patients include the increased use of factor VIII, for example, in prophylactic regimens, and perhaps stronger antigenicity of clotting factors. A study by Ehrenforth et al. clearly delineated the severity of the problem although they did not feel that antibody formation was greater using the monoclonal-recombinant factor VIII [303]. In a long-term study, they assessed 63 children with hemophilia A and 17 with hemophilia B. Only those with severe and moderate forms were analyzed since very few patients with mild hemophilia of either type ever develop inhibitors. Factor VIII inhibitors developed in 15 of 46 (33 %) hemophilia A patients. The percentage was greater in severe hemophilia with 14 of 27 (52 %) developing inhibitors compared with only 1 of 19 (5 %) with moderate hemophilia. If patients with mild hemophilia were also taken into account, the proportion affected was still 24 % in the entire group (15 of 63). Inhibitors developed quickly with the mean number of exposure days only 11.7. A review of several other studies also showed that the majority of inhibitors develop early after a median of 10 days (range 3–16) [343]. Inhibitors developed by age 1 in 33 % of the affected patients, by the age of two and half years in 73 %, and by the age of 5.2 years in all who were destined to develop them. In no patient did an inhibitor first develop after age 6 years.

Virtually all patients with factor VIII deficiency who developed inhibitors were those where factor VIII activity was <3 % [303]. Since previous studies tended to include all patients the number of patients affected with inhibitors was relatively lower. If one limits the study to severe and moderate patients the number increases. New inhibitor formation occurred in 24 % of all hemophiliac patients, in 33 % of those with factor VIII levels of 5 % or less, and in 52 % of severe hemophilic patients with factor levels <1 %. In larger studies inhibitors rarely develop after the age of 11 years and the greatest risk of inhibitor formation is before the age of 5 years. Data in this study are higher than those reported elsewhere. The general consensus is that in moderate and severe hemophilia A inhibitors develop to the infused product in 20–33 % of patients, while 3–4 % of hemophilia B patients develop inhibitors [344].

The risk of inhibitor development in hemophilia A and B is related to the underlying FVIII and FIX gene mutation and a positive family history of inhibitor development [343]. Inhibitors are much less common in factor IX deficiency. Previous reports indicated that inhibitors to factor IX developed in about 3 % of all patients with hemophilia B and in 7–10 % of those with severe disease. Treatment is with higher than normal doses of F IX or, if that is ineffective, Novo Seven or FEIBA can be used. Nongenetic factors also play a role in inhibitor development [344].

(e) *Bypassing agents for FVIII and FIX inhibitors*: Low titre inhibitors can be overcome by increased doses of FVIII. High-titre inhibitors of FVIII and FIX have led to the need to gain control of bleeding by bypassing the FVIII/FIX steps in coagulation. Prothrombin complex concentrates (PCCs) and activated prothrombin complex concentrates (aPCCs) have been used since the early 1980s. PCCs contain varying amounts of factors II, VII, IX, and X [343]. These are manipulated ex vivo to increase the concentration of activated clotting factors such as FVIIa. The current aPCC product available for this approach is FEIBA(factor eight inhibitor bypassing activity) which appears to act due to its content of prothrombin and activated FX. The dose is 50–75 units/kg q 8–12 h with a maximum daily dose of 200 units/kg. The initial effect with FEIBA at 6 h is about 50–60 % of what would be expected in a non-inhibitor case but increases to 85 % with repeat dosing. An additional approach is use of recombinant factor VIIa (rFVIIa, Novoseven, Novo Nordisk) which is identical to native FVIIa. Recombinant FVIIa is safe and effective and has not produced inhibitory antibodies in hemophilic patients since the patients have their own native FVIIa and do not recognize the infused rFVIIa as foreign. It is used effectively for FVII deficiency and for overcoming bleeding in FVIII and FIX with inhibitors. It activates FIX and X. Equivalence is found between a single FEIBA 80 n/kg dose and 2105 μg/kg doses of rFVIIa.

(f) *Immune tolerance induction*: It is usually recommended that when patients with hemophilia A develop inhibitors they are offered immune tolerance induction (ITI) therapy to eliminate the inhibitor and restore normal clinical responsiveness to FVIIII. This succeeds about 70 % of the time [330]. The dose and type of FVIII used for ITI

vary as do the use of associated immunosuppressive treatments such as rituximab. Prior to start ITI bleeding is controlled with rFVIIa (Novoseven).

(g) *Surgery in hemophiliacs with inhibitors*: Surgery in hemophiliacs with inhibitors is covered safely with either FEIBA or rFVIIa. They may be used interchangeably with effective hemostasis in 80–90 % of patients. [345]. The maximum dose of FEIBA is 200 U/kg/d and doses for rFVIIa were 240 ug/kg every 2 h for a total of 300 doses.

4.5.1.9 Orthopedic Management of Joint Bleeding

(a) *Overview*: The orthopedic management of hemophilia has been greatly modified and aided by the use of factors VIII and IX. Factor VIII and IX concentrates treated to inactivate viruses or produced by recombinant technology in viral-free environments prevent or control bleeding in most patients. Whether factor VIII is used as a prophylactic or immediately upon the onset of joint symptoms, the results have markedly improved the management profile from those described a few decades ago. The mainstays of orthopedic management for intraarticular, periarticular, or intramuscular bleeding are rest of the involved limb by decreased activity, ice, splinting, factor replacement, and gentle re-institution of motion and muscle strengthening once the bleeding symptoms are controlled. Joint aspiration plays virtually no role currently in the management of the hemophilic patient except for acute bleeds within the hip joint. The nature of the immobilization during the acute phase is dependent on the joint involved as well as the age and activity level of the patient. We never use solid circumferential casts to treat hemarthrosis or intramuscular bleeding in either the upper or lower extremity. A bivalved cast is slightly looser and can be easily removed in the home environment with any increased swelling or bleeding. Casts are often applied to the involved limb with the joint in a position of comfort but are immediately removed (bivalved), padded, and lined for re-application. Long arm (elbow), short arm (wrist), long leg or long leg cylinder (knee), or short-leg (ankle) bivalve casts are commonly used. In the upper extremity, the elbow is most commonly involved and we use either a sling alone in a particularly cooperative patient or a sling and bivalved long-arm cast in one who is younger or less cooperative. The initial cast is placed with the elbow in a position of comfort, even if flexion is less than a right angle (90°). In a few days when comfort and range of motion improve a new cast is made with the elbowed flexed at 90°. A sling or sling and swathe are used for immobilization of shoulder hemarthroses and a short-arm bivalved cast is used for wrist or hand hemarthrosis. Immobilization of the knee involves the use of a knee immobilizer or a bivalved long leg or long-leg cylinder cast and crutches. At the ankle either a bivalved short-leg fiberglass cast, a posterior short-leg splint, or a lightweight air-stirrup splint can be used along with crutches. Initially, the knee or ankle is immobilized by the bivalved cast in positions of comfort. At 7–10 days after partial resolution of the hemarthrosis, another bivalved cast is made with the knee in approximately 15° of flexion and the ankle at neutral to complete the immobilization part of the treatment. Immobilization is generally recommended for one to 2 weeks or until signs and symptoms resolve followed by active range of motion exercises and eventually by muscle strengthening as part of the rehabilitation process. The length of immobilization time has not been investigated but most of the hemophilia patients are reluctant to continue with full-time immobilization once discomfort has cleared. The ankle has proven to be the most difficult joint to maintain at a high-functioning level. Intraarticular hip joint hemarthrosis requires urgent management owing to the possible development of ischemic necrosis if intraarticular pressure is not relieved within hours. The child with an acute intraarticular hip bleed is in exquisite discomfort, cannot walk, and lies with the hip flexed, abducted and externally rotated. Hip ultrasound is effective in distinguishing between an intraarticular bleed and an adjacent iliopsoas hematoma. Once a hip a joint accumulation is diagnosed, then urgent joint aspiration is needed.

(b) *Recalcitrant Joints*: On occasion, return of normal function with full resolution of synovial thickening and joint effusion is difficult and more intensive or prolonged mechanical treatment measures are needed. It remains extremely important to quieten the synovitis and splints or bivalved casts should be used. It is not appropriate to rely completely on factor replacement to treat a hemophilic hemarthrosis. If there is a recurrence of bleeding at a joint after seemingly quietening the disorder, then further protection with function is needed. At the ankle, we use a solid ankle AFO followed by a hinged AFO for several months to limit joint motion while maintaining walking and then to allow for joint motion in a controlled plane. In situations where the synovitis and bleeding are recurrent, even with seemingly excellent control of factor VIII and use of immobilization, synovectomy has been used to control the synovitis.

(c) *Surgical Synovectomy*: Prior to the availability of factor VIII concentrate in the late 1960 s, major reconstructive surgery was simply not attempted for patients with hemophilia. Once factor replacement became feasible;

however, orthopedic surgical intervention was used to help alleviate some of the damage to involved joints. Synovectomy has played a major role in the surgical treatment of hemophilia ever since factor VIII and IX replacement became feasible. It is resorted to when recurrent joint hemarthroses prove to be difficult or impossible to control with factor replacement and non-operative orthopedic measures. In many instances, the synovitis reaches a degree of magnitude that appears manageable only by synovectomy. Removing the synovium from a hemophilic joint is a debulking procedure which removes a thickened, hypertrophic, hypervascular mass of tissue which is releasing toxic enzymes such as cathepsin D into the joint environment, serving as a source of repeat hemorrhage owing to its extreme friability and showing ineffectiveness in resorption. The procedure is not without its complications, however, and controversy continues in regard to indications for it. Some clinics resort to synovectomy after 2 or 3 episodes of poorly controlled hemarthrosis while others wait for several episodes until the synovium is so hypertrophied that resolution of a spontaneous nature would appear impossible.

The procedure itself can induce considerable bleeding and fibrosis and preoperative and postoperative factor management and rehabilitation must be extremely rigorous. There must be maximal hemophilic control and carefully regulated rehabilitation. The postoperative use of the continuous passive motion apparatus has been extremely helpful after synovectomy at the knee and can also be used at the elbow and for the rare hip procedures. With the increasing use of arthroscopic synovectomy, a further decision must be made between open and closed procedures. Much of the choice is dependent upon the experience and expertise of the surgeon. Some are more impressed with open synovectomy for the knee and ankle although elbow and hip arthroscopic synovectomy is generally recommended by all. A midline or medial parapatellar incision is used for open procedures at the knee. In some adolescent patients, a Baker's cyst is present which virtually mandates an additional posterior incision for removal. Use of the continuous passive motion apparatus for 10 days to 2 weeks, postsurgery has been extremely helpful in minimizing postoperative stiffness and eliminating the need for manipulations with all the risks they entail.

Synovectomy was first used widely for hemophilic arthropathy in the mid 1960s with early reports noting positive results [346]. Storti and Ascari reported that they had done 63 synovectomies for hemophilia A and B between 1966 and 1975 [347]. By removing the highly vascularized synovial tissue, they sought to prevent or at least minimize further bleeding. The synovectomy was thus viewed as a "hemostatic" procedure. The operation was performed when the synovial membrane had undergone a series of hypertrophic changes after repeated hemorrhage such that it was highly prone to further bleeding with minimal to no trauma. The increased vascularization was accompanied by proliferation of the synovial lining into innumerable villi each with a central vascular stem. A self-perpetuating cycle was established in which hemarthrosis led to synovial hypertrophy which itself was highly vascularized and led to recurrent hemorrhage with even more minimal trauma.

More recent overviews of the orthopedic/surgical management of hemophilia can be found in articles by Rodriguez-Merchan (1998) [331], Luck et al. (2004) [348], Branea et al. (2005) [349], Raffini and Manno (2007) [350], Caviglia and Solimene (2008) [351], and Pasta et al. (2008) discussing the ankle [352]. In the following sections, we refer to several articles (many from earlier periods when the treatment techniques were evolving) as well as more recent updates.

Knee. Review of results following knee synovectomy showed a significant diminution of recurrence of hemarthrosis episodes [347]. Of the synovectomies done, 51 were available for longer-term study. In 48 knee joints (94 %), a markedly reduced recurrence of hemarthrosis was observed. In 34 (66 %), the hemorrhage had been completely stopped, while in 14 (28 %) there were occasional episodes of mild knee swelling of short duration, these being much less severe than the preoperative episodes. They also noted increases in joint function with knee joint mobility improved in 28 cases (55 %), unchanged in 17 cases (33 %), and worsened in only 6 cases (12 %). In their discussion, they reviewed results from several European clinics during the same time period also showing good to excellent results from the procedure and the associated medical control.

Luck and Kasper reported on knee synovectomy and debridement, either open or arthroscopic, in 62 patients [310]. Results reported in open and closed arthroscopic synovectomy for the knee have been roughly comparable. In general, there is slightly increased range of motion maintained after the arthroscopic approach but most feel that open visualization allows for a more effective removal of synovial tissue. Rodriquez-Merchan et al. performed 18 open and 9 arthroscopic synovectomies and felt that the procedure by both methods significantly reduced bleeding episodes [353]. Arthroscopic synovectomy can lead to good short-term and long-term results [354]. It was recognized, however, that synovectomies were still essentially palliative procedures which appeared to slow but did not halt

deterioration of the joints. One of the problems following knee synovectomy has been stiffness. In a study by Montane et al. done before development of the concept of postoperative continuous passive motion, knee synovectomy in 10 of 13 patients was followed by a mean loss of 41 degrees of motion [355].

Rampal et al. reported good results in 23 patients followed long term (median followup 8.8 years) with median age at surgery 13.5 years. Their open procedure used 2 incisions, medial parapatellar and posterolateral [356]. Over half the patients had no additional hemarthroses, and range-of-motion limitation was moderate and not problematic.

Elbow. Favorable results were also reported in open synovectomy of the elbow by Balc'h et al. [357]. They reported on 23 elbow synovectomies in 18 patients 8–25 years of age. In those elbows operated after skeletal maturity, synovectomy frequently was accompanied by resection of the radial head. The authors noted a significant improvement in mobility for pronation–supination in 9 elbows and for flexion–extension in 14. Episodes of bleeding were markedly diminished. They recommended open synovectomy performed through a single lateral incision in those hemophiliacs in whom nonoperative treatment had failed.

Ankle. Greene reported on 5 ankle synovectomies in children with good results [358]. Arthroscopic intervention for the elbow have also been done (see below in "multiple joints"). He performed open synovectomy in 5 children at an average age of 9 years (range 4 years 7-months to 19 years). Postoperative results were favorable with no stiffness reported. He used three entry points: a 3 cm anteromedial incision just medial to the tibialis anterior tendon, a 3 cm anterolateral incision just lateral to the peroneus tertius tendon, and a 5–6 cm posteromedial incision between the medial malleolus and the tendo Achilles. With plantarflexion of the ankle, retraction of structures, and a transverse capsulotomy, the entire back of the joint could be visualized. The ankle range of motion in the (average 5 year) followup increased by 10° and the hemarthrosis episodes needing factor treatment decreased from 3.4 per month in the 6 months presurgery to 0.1 per month in the 12 months prior to the latest followup examination. He favored the open procedure as it most effectively allowed for the most complete synovectomy compared to arthroscopic views. Pantopoulos et al. reported 6 cases of open ankle synovectomy with favorable responses [359]. Arthroscopic synovectomy is favored by some groups [353, and see "multiple joints" section below].

Multiple Joints. De Gnore and Wilson reported on 34 synovectomies, 16 of the knee, 15 of the elbow with radial head excision, and 3 of the ankle [360]. The average number of bleeding episodes preoperatively was 26 per year in the target joint. With an average followup of 4.8 years, there was a marked diminution in the number of bleeding episodes after surgery to 4 per year. The continuous passive motion machine was utilized in the first week postsynovectomy.

Synovectomy relieves pain, decreases swelling, and diminishes the number of bleeding episodes per year. It is clearly not curative and one of the earlier complications was joint stiffness. Post et al. reported on a 5-year followup of 12 knee and 4 elbow synovectomies with the above-mentioned impressions [361]. In their small group of patients, elbow motion was reduced significantly. In a large arthroscopic synovectomy followup of 69 joints (39 ankles, 21 elbows, 7 knees, and 2 shoulders) the median age at surgery was 10 years with followup 79 months [362]. Bleeding frequency decreased 84 % with range of motion stable or improved in the year following surgery.

(d) *Radiation Synovectomy*: Radiation synovectomy has been used in many centers primarily in Europe but has not received governmental approval for unrestricted use in the pediatric age group in the United States. Radionuclide synovectomy (also called radioactive synoviorthesis) is designed to treat hypertrophic synovium in a hemophilic joint when recurrent articular bleeding is no longer being controlled by factor infusions and joint immobilization. It can be used in patients with inhibitors. It has been used for several decades to treat synovitis in rheumatoid arthritis [363] and was then adapted for use in hemophilia. Rodriguez-Merchan considered 90-Y(yttrium) or 32-P(phosphorus) to be the "gold standard" for treatment of chronic hemophilic synovitis [364] . He noted that after 30 years of usage there were no reports of articular or systemic damage or any neoplastic complication related to the treatment. He reported a mid-and long-term efficacy of 75–80 % by which was meant decrease in the number of hemarthroses by inducing a fibrosing effect on the synovium. "Up to three synoviorthesis are recommended, with a 3-month interval between them." When these fail, a surgical synovectomy is indicated. Radioactive substances are injected into the joint to damage and/or kill synovial cells once they are absorbed into them [363, 365, 366]. Radiation synovectomy (radiosynoviorthesis) has been reported using radionuclides such as Yttrium-90, Gold-198, and Phosphorus-32. Phosphorus 32 has been the agent most widely used in the United States. Merchan et al. reported on a long-term series of results with the use of Gold-198 in the treatment of hemophilic synovitis of the knee [366]. They described

treatments in 38 males with a minimum followup 13 years. One hundred affected joints in 64 patients were injected with a single dose of Gold-198. Followup was limited to those who had survived and had not had subsequent surgical synovectomy. The results based on the difference between the clinical joint score of the year before injection and the year of review were good in 8 (21 %), fair in 23 (60 %), and poor in 7 cases (19 %). There were more good results, 31 %, in those with a Stage I (milder) grading than in those with a stage II (more advanced) grading at time of intervention where only a 14 % good rating was achieved. Good and fair results were also more common in those whose symptoms were <1 year before injection compared with those >1 year. They concluded that there was a degree of effectiveness which might subsequently be improved with other radioactive agents or different protocols. Fernandez-Palazzi et al. have reviewed the use of radiation synovectomy for hemophilic hemarthrosis [365]. They reported on 50 procedures in 43 of their patients whose ages ranged from 6 to 43 years. They concluded that there was a significant reduction of hemarthroses, diminution in the amount of antihemophilic factor needed and a markedly diminished period of treatment needed for the patient since only an injection was required. They estimated that good results had been obtained in 80 % of patients, which were felt to be similar to the results with the more invasive surgical synovectomy. Radiation synovectomy has also been recommended for use in the ankle prior to consideration for surgical synovectomy [352].

Heim et al. reported good bleeding control with radiation synovectomy of the elbow with Yttrium but a higher than expected number of patients with a decreased range of motion subsequently [367].

Use of radionuclide synovectomy in the United States in particular slowed considerably after report of 2 cases of acute lymphocytic leukemia in pediatric hemophilia patients treated with intraarticular injection of P32 [368]. A possible problem with the technique is concern that the damaging effects of the radioactivity are not strictly limited to the synovium but could also affect the articular chondrocytes which are already abnormal because of the repeated episodes of hemarthrosis. Although this has not been studied in detail, it remains a theoretical concern.

Chemical synovectomy. Synoviorthesis has also been attempted chemically using rifampicin or osmic acid with some effectiveness reported [369]. The injections of rifampicin have been described as sometimes quite painful. These interventions did not reach the level of clinical effectiveness seen with radionuclides.

A series of several articles on radiation and chemical synovectomy was published in the journal Haemophilia in 2001, volume 7, supplement 2 from pages 1–58. Additional substances injected for symptomatic improvement of hemophilic joints include steroids and hyaluronic acid but no scientific studies have been done.

(e) *Soft Tissue Releases and Lengthenings*: Once a joint has been effectively quietened, either with medical and physical therapy alone or with synovectomy, persisting decreased range of motion can be improved in some cases with soft tissue releases and tendon lengthenings. Those areas most frequently approached by these techniques are the posterior knee with hamstring lengthening and the ankle where tendo Achilles lengthening with or without posterior ankle capsulotomy can be beneficial.

(f) *Osteotomy*: In some patients, angular deformity occurs due to relative overgrowth of one side of a physis in relation to the other which can cause valgus, varus, or flexion deformities in particular at the knee and ankle. Fibrous contractures also contribute to the malalignment. In those instances, where rehabilitation physical therapy is not effective, or where bony deformity is too great, osteotomy has been shown to improve alignment. The commonest joint deformity is a flexion contracture of the knee, often associated with a valgus, external rotation deformity. Partial epiphyseal arrest could be considered. Distal femoral supracondylar osteotomy may be required especially if 25° of flexion persists after nonoperative management. The hyperextension osteotomy should always be accompanied by some shortening to prevent neurovascular bundle stretching. Good results have been reported at distal femur, proximal tibia and fibula, and distal tibia and fibula in the supramalleolar region [370, 371].

(g) *Arthrodesis*: By the time, operative therapy became feasible with appropriate factor VIII and factor IX coverage, many joints had been so damaged that arthrodesis alone appeared to offer effective relief. This allowed for correction of angular deformity and elimination of pain. The joint most commonly and most effectively fused has been the ankle. With the increasing effectiveness of total hip and total knee arthroplasty, these two joints are now rarely if ever considered for fusion.

(h) *Wide range of treatments in ankle joint hemophilia including translesional drilling*: With recurrent ankle bleeding, there is a tendency for relatively rapid degeneration of the joint to occur with flattening of the talus, markedly diminished joint motion, overgrowth of the medial side of the distal tibial epiphysis, and a valgus alignment of the joint. Gamble et al. protected the ankle by casts and orthoses but compliance with treatment in this age group was poor [306]. In those joints not

responsive to medical treatment or synovectomy, degeneration of the joint was common and there was relatively early resort to arthrodesis. The results were good in terms of stabilizing the ankle, correcting equinus deformity, and eliminating discomfort and recurrent episodes of bleeding. The most common approach in adolescence where reasonable joint function persists is to perform a synovectomy and protect the joint with an articulated ankle-foot arthosis.

An international group of hemopilia physicians recently wrote a consensus review of orthopedic management of hemophilic arthropathy of the ankle [352]. Ankle bleeding involves not only the tibio-talar joint but also may involve the subtalar or talo-calcaneal joint. It may be difficult to determine which joint is primarily involved although clinically evident swelling, seen most clearly at the anterolateral and posterior parts of the joint, points to the tibio-talar joint. Recurrent episodes with less than full resolution can lead to tendo Achilles (equinus) contracture, flat foot deformity, a valgus hind-foot, and general decreased range of motion. Once treatment regimens of factor replacement, immobilization, and physical therapy fail to bring about complete clinical recovery, chemical or radioisotope synoviorthesis is attempted. Once those treatments fail (3 treatments 3 months apart), surgical synovectomy is recommended. Both open synovectomy and arthroscopic synovectomy have their advocates. They note that "even patients with severe radiographic changes can experience improved symptoms if the synovitis is controlled." Only small series of open procedures [Greene 5 cases in children and Panotopoulos et al. 6 cases mostly in adults] have been reported but results were good [358, 359], and this approach has been widely used. Arthroscopic synovectomy is less invasive and now preferred by many but published cases are not numerous [362]. An adjunct to pure synovectomy for the ankle is joint debridement. This can improve status by removing loose bodies and anterior osteophytes which decrease dorsiflexion. The osteophytes (more correctly osteocartilagenous collections) can emanate from either the talus or the anterior tibial lip. Collapse of the superior surface of the talus with osteochondral necrosis can be treated either by translesional drilling within the talus bringing new blood and reparative mesenchymal cells from normal bone below or by bone grafting. Osteochondral transplants done in other joints, might eventually be applicable to the hemophilic population. Supramalleolar tibial osteotomy can tilt the ankle axis back to the normal plane following valgus joint tilt due to medial distal tibial physeal overgrowth. Tendo Achilles lengthening can be done to improve the mechanics of gait and minimize abnormal stresses in the ankle and foot joints. When joint destruction is seemingly beyond effective relief with the above-mentioned procedures, ankle fusion in the adult years is performed. This almost always involves tibio-talar fusion with subtalar fusion included if indicated based on preoperative assessment. Clinical results are good, but at the expense of free mobility. In an effort to maintain function, there has been increasing use of total ankle replacement for adult hemophilia patients but success rates with the evolving implants have not approached those of hip and knee replacements.

(i) *Bone Density in Hemophilia*: The relative inactivity of patients with severe hemophilia would be expected to lead to decreased bone density and this has now been documented. A study of 19 patients with severe hemophilia A using lumbar bone mineral density (BMD) assessments by densitometry showed reduced values (0.102 g/cm^3) compared to 219 control subjects (0.113 g/cm^3) [372]. The mean areal BMD z score was −0.92, a significant reduction. When all factors were assessed, the authors felt that reduced physical activity was the most likely explanation. This parameter needs to be assessed in hemophilic children with calcium and vitamin D supplementation used as needed.

(j) *Adult Surgical Treatments*: Although treatment of the adult hemophiliac is beyond the scope of this book, it should be noted that total hip and total knee arthroplasty have been highly effective in adult patients with destroyed joints. The complication rate is higher than in otherwise uncomplicated joint arthroplasties but relief of discomfort and improvement of range of motion are most beneficial. Total knee arthoplasty has been done since the mid 1970s. A report on 90 primary knee replacement in 68 hemophilic patients done between 1975 and 2001 by the same surgeon showed the Knee Society clinical score to be excellent or good for 80 % of the knees with the functional score excellent or good for 97 % of the knees. Overall prevalence of infection was 16 % (in HIV positive 17 % and HIV-negative 13 %) [373]. A 2007 report of more recent cases (35 replacements in 30 patients done between 1996 and 2005 by the same surgeon) showed excellent outcome in 27 knees (77 %), good in 6 (17 %), and fair in 2 (6 %) [374]. There were no early wound infections and only 1 late deep infection. The survival rate at 7.5 years taking removal of the prosthesis for loosening or infection as the endpoint was 97 %. HIV positive and inhibitor patients could be safely operated. Antibiotic prophylaxis and antibiotic-loaded cement for all components was used. Other procedures in the adult with severe joint destruction have involved synovectomies, excision of the radial head at the elbow, fusion of the ankle and knee, and patellectomy, meniscectomy, and debridement

of the knee. An excellent review of 168 procedures over a 20-year period in end-stage adult hemophilia was presented by Luck and Kasper [310].

4.5.1.10 Pain Management in Hemophilia

The best form of pain management in hemophilia is the use of factor VIII or IX replacement plus splinting of the involved joint. Analgesics are often helpful. The use of aspirin is contraindicated because of its tendency to further limit platelet adhesiveness and in particular to predispose to gastrointestinal bleeding. The main nonnarcotic analgesic used is acetaminophen in particular in the childhood and adolescent age groups. Codeine or propoxyphene can be added. If chronic hemophilic arthropathy causes discomfort because of the arthritic component, Cox 2 inhibitors such as Vioxx or Celebrex were used. Once the existence of rare cardiac problems with these analgesics was recognized, they were banned in most United States jurisdictions for use in children although they are allowed with specific governmental approval. Nonsteroidal antiinflammatory drugs such as ibuprofen and naproxen should rarely be used and only with very close observation since both can potentiate bleeding. A considerable number of hemophilia patients, especially those with frequent bleeding due to inhibitors, cannot be controlled regarding pain with the above listed medications and require narcotic medications. While codeine is widely and safely used, some will require oxycodone or oxycodone/acetaminophen, morphine, or tramadol, a centrally acting synthetic opioid analgesic in an extended release formulation. The risk of addiction is high in this latter group, especially for a chronic disorder, and many physicians will not prescribe them. Many of these patients are helped by formal pain service consultations and the use of other modalities such as biofeedback, progressive relaxation, and psychotherapy.

4.5.1.11 Rare Variants of Hemophilia

Factor V hemophilia is rare and is usually inherited in autosomal recessive fashion. Factor V is a catalyst in the process where prothrombin is converted to thrombin. Hemarthroses occur but not as frequently as in those with factor VIII or IX hemophilia. Bruising, nose, and mouth bleeding are the usual presenting features. Fresh frozen plasma (FFP) is the only treatment available.

Factor VII hemophilia is infrequent. Unlike the main variants clinical bleeding is poorly correlated with FVII plasma levels. Recombinant FVIIa (NovoSeven) is the treatment of choice. The disorder is autosomal recessive. Clinical bleeding similar to FVIII hemophilia is seen including hemarthroses and chronic arthropathy.

Factor X deficiency is rare. It is autosomal recessive, has clinical symptoms similar to FVIII hemophilia, and is treated with FFP or PCCs (prothombin complex concentrates) that contain FX.

Factor XI deficiency is autosomal dominant with equal male and female occurrence, a high incidence in Ashkenazi Jews of Eastern European descent, and multisystem bleeding only occasionally including joints. Factor XI deficiency is a rare cause of postsurgery or posttrauma bleeding with no clear relationship between bleeding and FXI activity yet identified. Treatment is with FFP.

Factor XII deficiency occurs but has no hemorrhagic complications. Treatment is usually not necessary. It has autosomal recessive inheritance.

Factor XIII deficiency occurs in autosomal recessive fashion. Clinical symptoms are similar to FVIII hemophilia but intracranial bleeding is proportionately more frequent. Treatment is with recombinant FXIII.

4.5.2 Von Willebrand Disease

Von Willebrand disease (VWD) is a mild bleeding disorder which must be distinguished from hemophilia [375]. It is the most common autosomally inherited bleeding disorder affecting as many as 1 % of the population and resulting in significant bleeding symptoms in about 1 in 1000 subjects. Von Willebrand factor plays two major roles in normal hemostasis [302]. It is the cofactor for platelet adhesion and the carrier protein for factor VIII. When abnormal von Willebrand factor fails to bind to factor VIII the clinical picture resembles hemophilia. FVIII synthesis is not abnormal in VWD but its half-life is greatly decreased when VWF is deficient since VWF is bound to FVIII serving as both carrier and stabilizer in plasma. It is very rare, however, that the clinical bleeding disorder is anything more than mild. Most of the clinical manifestations of von Willebrand disease relate to postoperative bleeding or superficial bleeding such as epistaxis, menorrhagia, and cutaneous hemorrhage, sometimes referred to as mucocutaneous bleeding. Intraarticular and periarticular bleeding do occur, however, usually in association with mild to moderate trauma. Splinting of the affected area is helpful and joint degeneration changes like those seen in hemophilia are rarely if ever seen.

There are 3 major types of von Willebrand disease.

(i) Type 1 VWD. This is the most common type affecting 70–80 % of patients. It is caused by a partial quantitative deficiency of qualitatively normal VWF protein at levels that generally fall within 2–50 % of normal.
(ii) Type 2 VWD is characterized by a qualitative deficiency of VWF. There are 4 variants (2A, 2B, 2 M, and 2 N) affecting 20 % of people with VWD. (a) Type 2A VWD. This is caused by absence of an important part

of the VW factor protein, high molecular weight multimers which are needed to help form blood clots. Patients show decreases in both large and medium-sized VWF multimers. The VWF that binds at the site of injury is ineffective in recruiting platelets, the platelet-fibrin plug is poorly formed, and bleeding continues. (b) Type 2B VWD. There is an absence of high molecular weight multimers. The abnormal VW factor protein does not work properly and binds to platelets in the wrong way, leading to a shortage of VWD protein, a shortage of platelets, and the development of thrombocytopenia.

(iii) Type 3 VWD. This is the rarest form of VWD affecting only 1 person per million. The blood does not clot properly owing to an almost complete absence of VW factor protein. These patients also may have decreased levels of factor VIII which is synthesized normally but without the stabilizing VW protein its clearance is accelerated.

Treatment for VWD, in the milder variants, is by desmopressin (1-deamino-8-D-arginine vasopressin; DDAVP), available as a highly concentrated nasal spray although it is also available as an injection (DDAVP-desmopressinacetate). In many cases of type I VWD and in some cases of type 2 A disease, the use of desmopressin will provide adequate hemostatic coverage to treat mucocutaneous bleeding and to prevent bleeding at time of minimally invasive procedures. This agent is usually not effective in type 2 B, 2 N, and 3 disease. As many as 20 % of patients with type 1 VWD do not respond to DDAVP treatment, and a good response is uncommon in type 2 patients. Side effects include headache, facial flushing, tachycardia, and hyponatremia. In the more severe forms or where surgery is needed treatment is by replacement therapy with a VWF concentrate. These products represent plasma-derived VWF-FVIII concentrates with various VWF: FVIII ratios and multimer profiles with minor differences [335, 376]. The use of VWF concentrates with very low FVIII content should be accompanied by coinfusion of recombinant FVIII to enhance treatment of acute bleeding episodes and surgical hemostasis [335]. A recombinant VWF concentrate is also being tested. An early VW factor protein concentrate approved for use in the US is Humate-P (Aventis Behring) which is pd FVIII antihemophilic factor/Von Willebrand factor complex (human) [375].

4.5.3 Hemoglobinopathies: Sickle-Cell Anemia and Thalassemia

4.5.3.1 Terminology

Sickle-cell disease denotes all genotypes containing at least one sickle gene in which HbS makes up at least half the hemoglobin present. In addition to the homozygotic HbSS disease (sickle-cell anemia), five other major sickle genotypes are part of the disorder. These include HbS/ß^{o}- thalassemia major (almost phenotypically the same as sickle-cell anemia); HbSC disease-intermediate severity; HbS/ß$^{+}$ thalassemia minor; HbS/hereditary persistence fetal Hb- very mild or symptom-free; HbS/HbE- very rare and very mild; and rare combinations of HbS with HbD Los Angeles, HbO Arab and others.

4.5.3.2 Overview

The first scientific recognition of sickle-cell disease (5CD) was in 1910 by James Herrick of Chicago who published a case report titled "peculiar elongated and sickle-shaped red blood cells in a case of severe anemia" [377]. Linus Pauling showed the abnormal electrophoretic mobility of hemoglobin in an affected individual [378] and Vernon Ingram discovered that the defect was a single amino acid substitution in the hemoglobin molecule of sickle cells (HbS) [379]. The single amino acid substitution is at the sixth position of the ß-globin chain of hemoglobin A. The adult hemoglobin is a tetramer of 2 α-globin and 2 ß-globin polypeptides. A single nucleotide substitution (GTC for GAG) in the sixth codon of the ß-globin gene results in the substitution of valine for glutamic acid on the surface of the chain [380]. The substitution predisposes hemoglobin molecules with the defect to link together, deforming the red blood cells into inflexible sickle-shaped cells which clog small blood vessels causing occlusion with microinfarcts leading to pain, tissue damage, and anemia, often referred to as "sickle crises." All individuals with SCD have the same mutation in the ß-globin gene, causing amino acid substitution, but other factors lead to considerable phenotypic variability [381]. Watson identified the fact that symptoms did not appear in infants until concentrations of fetal hemoglobin (HbF) had fallen, establishing the recognition of the beneficial effect of HbF on the disorder [382]. Fetal hemoglobin is a tetramer similar to the adult form with 2 γ-globin subunits in place of the 2 ß-globin subunits. When the switch from γ-to ß-globin occurs after birth those with mutations in the ß-globin gene develop symptoms of SCD. Most adults have about 1 % HbF but those with SCD with higher levels of HbF have a milder course since HbF inhibits polymerization of sickle hemoglobin.

The hemoglobinopathies can lead to bone growth problems primarily due to osteonecrosis which is characteristic of sickle-cell anemia and premature fusion of physes which is characteristic of thalassemia. In these diseases, autosomal dominant mutations of the hemoglobin gene lead to disorders of hemoglobin structure and a tendency to premature breakdown and change of cell shape from a round concave disk to a pointed ellipse or sickle-shaped cell [383–385]. The three most important abnormal hemoglobin genes are the

sickle gene hemoglobin S, hemoglobin C, and the thalassemia gene. When an abnormal hemoglobin gene is inherited from both parents the patient will show the clinical features of a hemoglobinopathy. When an abnormal hemoglobin gene is inherited from only one parent, there are usually no clinical manifestations and the involved patient is said to have the sickle trait. Hemoglobin C abnormalities tend to be mild.

Sickle-cell disease is a hemoglobinopathy which causes sickling of the red cells leading to thromboembolic infarcts in bone. There is increased hemolytic destruction of inefficient sickle red cells and subsequent erythroblastic activity increases the volume of the marrow cavity leading to appearance of osteolysis radiographically. The normal fetal hemoglobin (HbAF) is gradually replaced by sickle-cell hemoglobin (HbSS) within the first year of life. The normal hemoglobin genotype is HbAA. When sickle hemoglobin (hemoglobin S) is deoxygenated, the replacement of beta 6-glutamic acid with valine results in a hydrophobic interaction with another hemoglobin molecule triggering an aggregation into large polymers [383]. The polymerization of deoxygenated hemoglobin S is the primary event in the pathogenesis of sickle-cell disease resulting in distortion of the shape of the red cell and rigidity of the cell with a marked decrease in its deformability. These rigid cells are then responsible for the vaso-occlusive phenomena that characterize the disease. An excellent overview of sickle-cell disease especially regarding the physiology and molecular biology underlying the disorder, systemic effects, and medical management has been provided by Stuart and Nagel [381].

4.5.3.3 Clinical Characteristics

(a) *Sickle-Cell Disease*: Those with severe sickle-cell disease generally referred to as sickle-cell anemia are affected by multiple episodes of pain and by sickling crises which lead to vaso-occlusive disorders. These in turn can lead to stroke, acute chest syndromes, impaired neuropsychological function, and premature death. The vaso-occlusive crisis is the hallmark of symptomatic disease. Microvessel occlusion at single or multiple sites induces pain, inflammation and often considerable disability. Microvascular occlusion arises primarily in bone marrow leading to necrosis. Common areas are long bones, ribs, sternum, spine, and pelvis. Cortical and subperiosteal involvement can be extremely painful. Occlusion in mesenteric vessels can mimic acute abdomen.

The acute chest syndrome is the leading cause of mortality in young adults. Pulmonary infiltrate, fever, and respiratory symptoms occur. It can be difficult to separate primary and secondary causes but various factors include marrow pain (ribs, sternum), decreased depth of respiration (due to pain or narcotic agents), pulmonic infection, fat embolism, and hypoxia (which further constricts the pulmonary vasculature).

Stroke is usually due to infarcts in children. It is commonest in young children 2–5 years of age. Sickle-cell disease is present when the abnormal hemoglobin gene is inherited from both parents (HbSS). When the gene is inherited from only one parent, there are usually no clinical manifestations and the patient is said to carry the sickle trait only (HbAS) which has no clinical significance in relation to the skeleton. The disorder is far more problematic in homozygous HbSS than in heterozygous HbAS or HbSC. Acute osteomyelitis is common and often the early stages cannot be distinguished clinically from the vaso-occlusive crises of bone infarcts. Chronic osteomyelitis can occur. Salmonella is the major organism involved with osteomyelitis in this disorder, accounting for from 65–80 % of cases. Other problems involve leg ulcers and growth retardation in particular in the early years of life in those with active crises. This rarely leads to short stature since in many skeletal maturation is delayed allowing normal height to be reached.

A large study of 3,578 patients with sickle-cell disease found the number of pain episodes per year to correlate well, in patients >20 years of age, with frequency of death with those with high rates of pain episodes tending to die earlier than those with low rates [386]. High rates were associated with a high hematocrit and low fetal hemoglobin levels. Mortality was greatest in sickle-cell anemia (HbSS disease) and sickle-beta (o) (HbS/ß^{o}) thalassemia, referred to as thalassemia major, and lower in hemoglobin SC (HbSC) disease and sickle-beta (+) (HbS/ß$^{o+}$ thalassemia). The fetal hemoglobin level had a strong influence on the pain rate without a threshold effect. Increments in the fetal hemoglobin level were beneficial even when the level was low. The presence of fetal hemoglobin in effect converted the severity of the sickle-cell disorder to those with the milder hemoglobin SC disease. Mild or symptom-free phenotypes include HbS/hereditary persistence of fetalHb and HbS/HbE syndrome, with other even more rare combinations identified.

Other medical disorders in sickle-cell anemia include pulmonary hypertension and renal disease (nephropathy).

(i) *Prediction of adverse outcomes in children with sickle-cell disease*: Guidelines have been determined to identify infants with sickle-cell anemia likely to have severe complications later in life based on findings in the first 2 years of life [387]. The clinical course in 392 children was carefully followed from infancy to 10 years of age. Diagnoses were homozygous sickle-cell anemia or sickle-cell-ß^{o}-thalassemia. Of the 392, 70 (18 %) subsequently had an adverse outcome including death (18 patients, 26 %), stroke (25, 36 %), frequent pain (17, 24 %), or recurrent acute chest

syndrome (10, 14 %). Three statistically significant predictors under 2 years of age for an adverse outcome were: hemoglobin level <7 g/dl, an episode of dactylitis before the age of 1 year, and leukocytosis in the absence of infection [387].

(b) *Thalassemia*: Thalassemia is a form of hemolytic anemia and sickle-cell disease common in those of Italian and Greek descent and previously referred to as Mediterranean anemia [388, 389]. The severe variant referred to as sickle-beta thalassemia (S β-thalassemia) results from inheritance of a sickle (S) gene from one parent and a beta thalassemia gene from the other. In the "+" type some normal beta chain is produced and in the "o" type no normal beta globin is produced. Even in the severe forms, bony changes are only slight during the first year of life. Bony abnormalities frequently affect the femurs and vertebral bodies. The vertebral bodies are osteopenic and may be flattened with prominent cupping owing to displacement of the adjacent intervertebral disks. The cortices are thin and the trabeculae are markedly reduced in number. On occasion, there is shortening of the spine without deformity but instances of scoliosis or kyphosis also occur. The cortex of the long bones tends to be thinned and the marrow cavities widened and prominent. Angular bone deformities occur owing to the structural weakness. Premature fusion of the epiphyses of long-tubular bones has been noted in severe cases of thalassemia. When this is asymmetric in relation to left and right femurs or tibias, length discrepancies occur. When asymmetric involvement occurs within the same epiphysis, angular deformity is seen. The head of the humerus is often found to be tilted into varus.

4.5.3.4 Therapy

Initial treatment of pain in acute vaso-occlusive episodes is essential. Pain severe enough to require hospitalization is best controlled by intravenous opioids with morphine the drug of choice. Gradual tapering to oral nonsteroidal antiinflammatory drugs (NSAIDs) is done. Hydration and antibiotics are also part of acute management owing to increased susceptibility to gram-positive and gram-negative organisms. Antibiotics are given empirically until cultures indicate the absence of infection. Fluid replacement, preferably oral but intravenous if necessary is done and blood transfusion might be needed [390]. Most cases in patients followed closely can be managed on an out-patient basis with antiinflammatory agents, nonopioid analgesics, or lesser strength opioids.

Treatment of sickle-cell disease includes blood transfusions (to correct anemia), antibiotics (to treat associated osteomyelitis), hydroxyurea to increase the levels of fetal hemoglobin (HbF) in the blood, and myeloablative allogeneic hematopoietic stem cell transplantation (to completely replace the hematopoietic cells of the affected recipient).

Blood transfusion and antibiotics are needed for acute crises. In surgical settings, simple blood transfusions to increase hemoglobin (Hb) levels to 10 g/dl are as good as or safer than aggressive transfusions to reduce sickle hemoglobin (HbS) levels to below 30 %. Transfusion therapy keeping the proportion of HbS below 30 % is also standard care for primary and secondary stroke prevention in children with SCD.

The stroke prevention in sickle-cell anemia showed that regular blood transfusions produced a 90 % reduction in first stroke in asymptomatic high risk children who had 2 abnormal transcranial Doppler studies with velocities of 200 cm/s or greater [391]. Long-term treatment beginning in the symptomatic child for sickle-cell anemia is designed to increase fetal hemoglobin (HbF) levels which serve as a protective effect minimizing sickling crises and associated symptoms. This is currently most effectively accomplished by the antineoplastic drug hydroxyurea which tends to sustain HbF levels in the 20 % range, lowers the painful crises, ischemic events, and needs for transfusions significantly [392, 393]. Hydroxyurea is safe, given orally once daily, and has done well in clinical trials even though its mechanism of action is uncertain. The dose rate is 20–30 mg/kg per day. A review of several studies showed increase in fetal hemoglobin from 5–10 % to 15–20 % on hydroxyurea [393]. Extensive work is being done to understand the postnatal switch from γ-globin to ß-globin and inhibit it to maintain the fetal form postnatally.

Pneumococcal vaccine is recommended to prevent pneumococcal pneumonia in children.

It was felt that therapy with drugs such as hydroxyurea and 5-azacytidine, which increased the production of fetal hemoglobin, could reduce the pain rate and by implication improve survival [386, 394]. Hydroxyurea has been used widely to enhance hemoglobin F production in patients with sickle-cell anemia but less frequently in thalassemia. Molecular approaches to therapy currently being investigated include chemical inhibition of hemoglobin S polymerization, reduction of the intracellular hemoglobin concentration, and pharmacologic induction of hemoglobin F since F is a very potent inhibitor of the polymerization of deoxyhemoglobin S [383, 395]. Hemoglobin F therefore inhibits sickling and drugs that could increase its synthesis would be expected to benefit patients with sickle-cell disease. Bone marrow transplantation has been used effectively to cure sickle-cell anemia and thalassemia but the complications of this treatment can be devastating and considerable concern exists as to its advisability for this disorder, [394, 396]. The initial approaches involved myeloablative allogeneic hematopoietic stem cell transplantation but more

recently the less toxic approach of nonmyeloablative stem cell transplants is being investigated [380, 381]. At present, only severely symptomatic cases of sickle-cell disease are considered for transplantation in most centers (sickle-cell anemia, HbSS; sickle-cell hemoglobin C disease, HbSC; and sickle cell—β—thalassemia). Current treatment for thalassemia major is supportive involving regular transfusion therapy to maintain hemoglobin levels of 9–10 g per deciliter and iron-chelation therapy for minimizing iron overload. The main iron-chelating agents are deferoxamine (which is administered parenterally) and the newer orally active chelator deferiprone [397]. Hematopoietic stem cell transplantation is the only curative treatment for thalassemia.

4.5.3.5 Survival of Children with Sickle-Cell Disease

Studies have updated survival data to reflect improvements in management. Quinn et al. followed 711 patients identified as newborns as having sickle-cell anemia (SS), sickle-ßº-thalassemia, sickle hemoglobin C (SC), or sickle-ß+-thalassemia [398]. Followup was to 18 years of age. Death occurred in 25 at a mean age of 5.6 years but only 5 died of infection. At least one stroke occurred in 30. Survival analysis of SS and Sßº subjects (n = 4 8) predicted the cumulative overall, SCD-related, and stroke-free survival to be 85.6, 93.6, and 88.5 % by 18 years of age. This is a death rate of 0.21/100 patient–years. A large longitudinal study from Los Angeles including observations for the 25 years preceding 1990 reported a death rate of 3/100 patient-years. No deaths or strokes occurred in SC or Sß+ subjects (n = 263).

4.5.3.6 Pathophysiology of Bone Disease in Hemoglobinopathies

Jaffe noted that changes in the bone result from (1) hyperplasia of the erythroblastic elements of the bone marrow; (2) plugging or thrombosis of local blood vessels by masses of sickle cells; and (3) a complicating infection usually salmonella involving bones at the site of infarcts [1]. In a patient with sickle crisis, there may be an anemia but it is the thrombotic episode with fever and leucocytosis along with pain which simulates an acute bone or joint infection. When bone is the main site of thrombosis acute osteomyelitis is suspected and if a joint is involved acute arthritis may be suspected. Two pathologic processes are involved: (1) sickling of the red cells results in thrombotic infarcts in bone which cause pain, crises, and in some cases, osteomyelitis; and (2) increased destruction of inefficient sickle red cells produces hemolysis. Pathologic occurrences in bones in sickle-cell disease are due to blockage of the microcirculation which causes infarction of the bone marrow and adjacent bony trabeculae. The marrow infarcts occur during generalized vaso-occlusive crises and are the main cause of pain. Bone marrow aspirated from areas of infarct during crises actually shows necrotic hemopoietic cells. The earliest skeletal symptoms in crises often occur in the digits and are referred to as dactylitis or the hand and foot syndrome. This occurs in approximately 60 % of patients presenting between the ages of 9 months and 4 years with painful tender swelling of the hands and feet along with fever and leucocytosis. The discomfort is caused by expansion of the bone at the metaphyseal regions. Bone and joint pains then occur between 3 years of age and skeletal maturity.

Diggs has pointed out that the bone marrow in sickle-cell anemia is hypercellular and contains little fat [384]. Even in infants the red marrow fills all of the marrow spaces including the small bones of the hands and feet. In older children and adults, the marrow recedes from the tubular bones of the hands and feet but persists in the carpal and tarsal bones and the shafts of the long bones. The cellular marrow extends into the widened Haversian and Volkmann canals within the cortices. There is widening of the medullary cavities and intertrabecular spaces and thinning of both trabecular and cortical bone. Avascular necrosis is most common in the femoral head and to a lesser extent in the humeral head. It is the femoral lesion that is most disabling. Owing to the necrosis of the bone and the poor ability at repair an involved femoral head almost invariably proceeds to complete degeneration with need for early arthroplasty. Necrosis also tends to occur in the vertebral bodies which not only causes considerable back pain but also owing to the osteoporosis flattening of the vertebrae.

The pathoanatomy is characterized by a hypercellular marrow, superimposed on which is vascular occlusion due to sickled erythrocytes and increased viscosity of the blood, chronic stasis, and hypoxia. Focal areas of ischemia thus occur. Chung and Ralston have reviewed the stages of femoral head necrosis in sickle-cell anemia [399]. The bone changes, as noted by Diggs, fall into two categories: (1) those due to erythroid hyperplasia and (2) those due to thrombosis and infarction. “Hyperplastic changes involve the following: the vertebral bodies (osteoporosis with biconcave cupping and bulging of the discs); the skull (loss of trabecular definition, thinning of the outer table, hair-on-end appearance, localized osteoporosis, lamellated new bone); the flat bones (osteoporosis, widening of the trabecular pattern, cortical thinning); and the long bones (osteoporosis, widening of the medullary canal, thinning of the cortex, and widening of the diaphyseal trabeculae). The changes associated with thrombosis and infarction are seen in the vertebra (massive infarction with collapse); the small tubular bones (periostosis, cortical destruction); the flat bones (patchy sclerosis); the shafts of long bones (cortex thickened and sclerosed, patchy and irregular segmental

necrosis); and the epiphyses (retardation of growth, acceleration of growth, and necrosis and collapse)."

(a) *Femoral head osteonecrosis*: The major problem referable to the epiphyses is avascular necrosis with the disorder becoming apparent clinically between the ages of 10–15 years [384, 400–402]. The head of the femur is affected most commonly after puberty. Milner et al. studied a large group of 2,590 sickle disease patients who were over 5 years of age at entry [403, 404]. Hip radiographs were taken at least twice several years apart in the large group followed for an average of 5.6 years. The overall prevalence of osteonecrosis of the femoral head in sickle-cell disease is about 10 %. Patients with the hemoglobin SS genotype + alpha thalassemia were at the greatest risk for osteonecrosis. The patients with hemoglobin SS genotype alone had approximately the same extent of involvement as those with the hemoglobin SC genotype. Intermediate rates of osteonecrosis were seen in those with hemoglobin S beta thalassemia of either type. Osteonecrosis was occasionally found in patients as young as 5-year old. It was further noted that 3 % of the patients under 15 years of age had osteonecrosis. Virtually none of these, however, were of the thalassemia or hemoglobin SC variants. For the entire series, the prevalence of osteonecrosis of the hip was 9.7 %. This was 10 % in SS, 11.9 % in Sßº, 9.1 % in SC, and 6.9 % in Sß+. There was progressive involvement the older the patient. In those from 5 to 9 years of age, involvement was only 1.3 % and in those from 10 to 14 years of age it was 4.6 %. At each decade following 15 years of age, the rate of involvement increased. When disease was present, it was bilateral in 54.2 %. The estimated median age at diagnosis was 28 years for the most severe hemoglobin SS/alpha thalassemia group, 36 years for those with hemoglobin SS alone and 40 years for those with hemoglobin SC. In approximately half of the patients in whom osteonecrosis developed during the time of the study, no pain or limitation or motion was initially noted. A high percentage of patients went on to hip arthroplasty. A study of risk factors for developing femoral head osteonecrosis in sickle-cell disease found that the avascular necrosis group had a significantly higher rate of painful crises, hospitalizations per year and euglobin clot lysis time than those sex/age matched patients with sickle-cell disease without avascular necrosis [405].

In more recent studies from orthopedic centers specializing in hip disorders and following patients into adulthood, the incidence of femoral head avascular necrosis in patients with sickle-cell disease (SS and SC) increases with age and approaches 50 % [406, 407]. The lesions appear like Legg–Perthes disease although those affected are somewhat older than those with Perthes. The disorder begins with subchondral sclerosis progressing to a Perthes-like necrosis and finally totally collapse of the femoral head with degenerative changes of osteoarthritis occurring 5–10 years later regardless of the age of the patient. Early management appears to have no beneficial effect. Avascular necrosis of the hip generally leads to a disabling disorder necessitating relatively early intervention with hip arthroplasty. When osteonecrosis occurs in the femoral capital epiphysis prior to skeletal maturity, healing can occur but distortion of the head similar to the Legg–Perthes disorder is seen almost invariably. This is particularly true since the osteonecrosis occurs later than in patients with Perthes disease and generally is not seen until just before skeletal maturity. The patients tend not to do well. In a study by Hernigou et al. assessing 95 affected hips in 52 patients with sickle-cell disease, whose osteonecrosis of the femoral head occurred between the ages of 7 and 15 years, 80 % of the hips were painful and showed permanent damage with decreased mobility, limb-length discrepancy and an abnormal gait at a mean followup of 19 years [401]. When patients were evaluated at an average age of 31 years, 15 hips (16 %) had already undergone surgery and 60 (63 %) had major problems due to pain. Premature closure of the physis was seen frequently. The premature closure, however, was either across the entire physis leading to a short femoral neck with no major change in the head–neck/shaft angle or premature closure involving only the medial portion of the physis leading to broadening of the femoral neck and development of a varus deformity. Lateral physeal arrest leading to valgus angulation of the femoral neck was never noted. The closure also occurred sufficiently late that it did not appear to have any effect on development of the acetabulum.

Hernigou et al. updated their previous study assessing orthopedic management in 121 patients [406]. They followed 121 patients with sickle-cell disease and asymptomatic osteonecrosis of the femoral head (that was contralateral to a hip with symptomatic avascular necrosis). Identification was by MRI. At a mean followup of 14 years (mean age 26 years) pain had developed in 110 (91 %) and collapse of the femoral head occurred in 93 (77 %). Pain always preceded collapse over a time frame of a mean interval of 11 months. Surgical intervention occurred in 91 (75 %) involving injection of cement to support the femoral head sphericity (26), valgus femoral osteotomy (23), and total hip arthroplasty (42).

In a study by Neumayr et al. from several US centers [407] with patients of comparable age, but only followed 3 years reconstructive surgery of total hip replacement was done in 8 %. Several of their patients had core decompression and physical therapy but a similar group having physical therapy only had the same clinical score as the core group at 3 years. These studies further support the progressive nature of the avascular necrosis with time as well as the need for improved biologic treatment both for the sickle-cell disease and the avascular necrosis of bone.

(b) *Humeral head osteonecrosis*: The head of the humerus can also be affected by osteonecrosis [408]. Osteonecrosis was studied in a large group of 2,524 patients in a multicenter study. The patients had HbSS (1,737), HbSC (510), sickle-cell ß (+) thalassemia (139), and sickle-cell ß (0) thalassemia (138). The overall prevalence of humeral head necrosis was 5.6 %. It was bilateral in 2/3 of those involved. Osteonecrosis was seen in each of the variants in approximately the same amounts. There was a gradual increase in osteonecrosis the older the patient. The prevalence was 1.2 % of those between 5 and 9 years of age at initial assessment, 2.6 % in those between 10 and 14 years of age, and 3.8 % in those between 15 and 24 years of age. The prevalence increased with each advancing age of adult assessment. Those slowest to develop the disorder were in the sickle-cell ß (+) thalassemia group none of whom had the disorder under the age of 25 years. The disorder, however, was much less debilitating than that which occurred in the femoral head. At the time of diagnosis, 80 % of the patients were completely asymptomatic. Pain and limitation of motion developed in most at a later date but this was mild to moderate only and only one patient in the entire study had undergone shoulder arthroplasty for severe symptoms.

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Epiphyseal Growth Plate Fracture-Separations

5

5.1 Introduction

Preradiographic era, pathoanatomic approaches, pathophysiological approaches: Epiphyseal growth plate fracture-separations have been recognized and studied for over 250 years. Early comments on their occurrence were made in the 1500s and 1600s but it was not until the early 1700s that meaningful work on the subject appeared. They were considered first in specific detail by Reichel in 1759 in a thesis published in Leipzig in which he distinguished between traumatic and spontaneous (pathologic) separations and indicated that following separation the growth plate remained adherent to the epiphysis [1] (Fig. 5.1). Many articles on these injuries were published in the nineteenth century in the preradiographic era of growth plate fracture assessments. With the discovery and widespread clinical use of radiographs 100 years ago, each fracture could be assessed more easily prior to, during, and after treatment. From the 1930s to 1990s, several classifications of epiphyseal fracture-separations were proposed. These are referred to as pathoanatomic since they are based on the pattern of fracture as determined on plain radiographs. One of the therapeutic benefits of the pathoanatomic approach was the recognition that anatomic open reduction and rigid internal fixation were helpful in minimizing growth problems in certain fracture-separations. Dynamic assessment of these injuries and utilization of pathophysiologic approaches at time of diagnosis during the healing phase, and in the months following healing should further improve management. We present the pathophysiologic approach to growth plate fracture-separations and review its development as an extension of the work from the preradiographic and pathoanatomic eras. Projected therapeutic benefits of the pathophysiologic approach involve earlier detection and more biological treatment of negative growth plate sequelae.

5.2 Clinical and Experimental Investigations of Growth Plate Fracture-Separations in the Preradiographic Era

5.2.1 Early Clinical Descriptions

Case descriptions establishing the reality of the entity were published in the early 1800s. Prior to this time and for several decades afterwards, many surgeons did not recognize the existence of epiphyseal fracture-separations or considered them to be very rare and to occur only in the very young. Laurent in 1818 referred to three cases of Dr. Champion: a proximal humeral fracture-separation in an 11-year old confirmed at postmortem examination, a distal humeral injury in a 13-year old, and a distal tibial fracture-separation caused by a complicated delivery in a newborn [2]. Laurent also discussed a case of multiple epiphyseal separations noted at autopsy in a 7-month-old fetus with hydrocephalus. Roux in his 1822 thesis "Dissertation on Separation of the Epiphysis" reported epiphyseal fracture-separations of the distal femur in one patient and multiple separations of the distal radius, distal ulna, and three proximal phalanges studied by gross inspection following amputation [3]. Roux, as quoted by Poland, commented upon the following: "(1) the danger of ignoring epiphyseal separation when its reduction ought to be possible; (2) the progress of the phenomena which result from an error of judgment; (3) the possibility of separation of the epiphyses occurring up to the 18th year; and (4) the possibility of such separation taking place on the largest cylindrical bones as well as on the medium sized and smallest" [4]. In a later article, he added additional cases (some of questionable validity) and noted that in his thesis he had discussed the differentiation between internal (pathologic)

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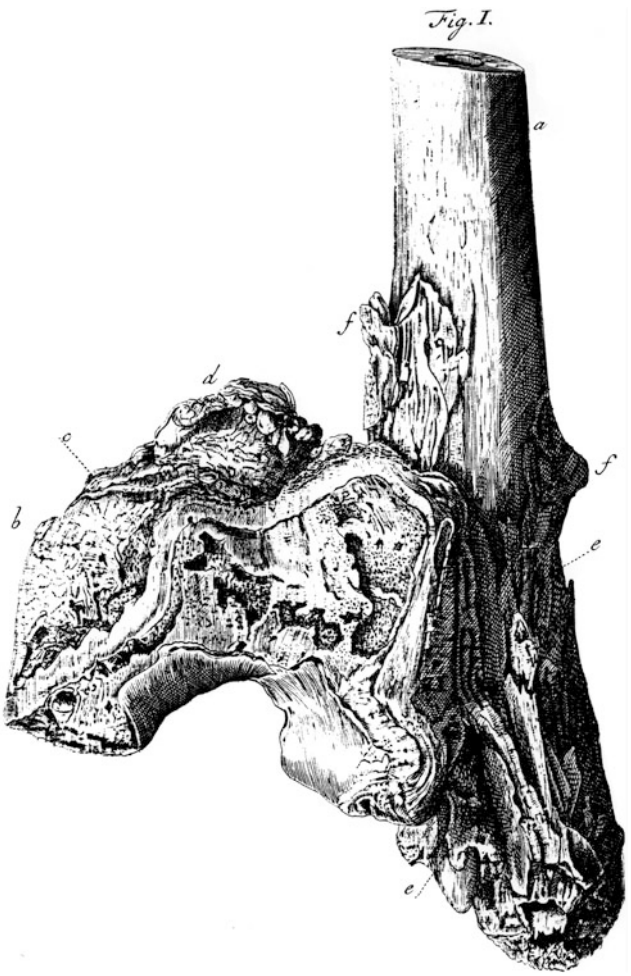


Fig. 5.1 Illustration from Reichel's thesis [1] published in 1759 shows a characteristic type II fracture-separation of the distal femoral epiphysis. The epiphysis, physis, and metaphyseal fragment are shown at left. Reichel recognized that the physis remained with the epiphyseal segment after most fractures and that adjacent segments of metaphyseal bone were frequently separated as well

and external (traumatic) causes of epiphyseal separations; the differential diagnosis between epiphyseal separations, joint dislocations, and fractures; and the relative brevity of treatment time needed for traumatic separations [3].

Fontenelle reported on a distal femoral epiphyseal fracture-separation in an 11-year old based on the anatomic specimen obtained at time of amputation [5]. Goyrand in 1836 discussed a distal radial injury in an 11-year old which he saw shortly after injury prior to the onset of severe swelling [6]. Clinical examination indicated displacement near the wrist joint but the normal relationship of the radial styloid to the wrist ruled out dislocation. Other clinical features such as the ease of reduction, a sensation on reduction similar to cartilage surfaces of a joint relocating rather than the rubbing of fracture fragments, and the occurrence of healing after only 20 days of immobilization led him to distinguish a distal radial epiphyseal separation from a metaphyseal fracture.

5.2.2 Important Studies Establishing the Validity of the Entity of Epiphyseal Growth Plate Fracture-Separations

Two extensive multipart papers on epiphyseal fractures by Rognetta and Gueretin were published in France in the 1830s [7, 8]. They are summarized in detail as they demonstrate the then current conceptions of the entity and the early development of a coherent body of investigational and clinical information.

5.2.2.1 Rognetta

Rognetta (1834) wrote a 4-part article in which he stressed that epiphyseal fracture-separations represented a definite entity. He provided an excellent summary of the earliest examples of recognition of epiphyseal injuries from the sixteenth, seventeenth, and eighteenth centuries [7]. Many, including Pare, Severin, Eysson, Platner, Albinus, Haller, Kerkeringius, Spingeler, Coyter, Reichel, van Swieten, Morgagni, Weiss, Duverney, Petit, Verduc, Palletta, Ruysch, Bertrand, and Monteggia, had commented on the entity and presented isolated case reports of traumatic or spontaneous (pathologic) epiphyseal separations. Ruysch commented in 1713, according to Rognetta, that it was possible to separate the epiphysis in the living as soon as the perichondrium surrounding the growth cartilage was torn. Rognetta pointed out the importance and high degree of organization of the growth cartilage and stressed the observations of Howship which were aided by early microscopic assessment. These observations included the fact that: (1) the growth cartilage formed an integral part of the bone itself; (2) the cartilage was continuous both with the epiphysis and the body of the entire bone rather than being merely placed between them; (3) the growth cartilage had within its interior and adjacent to it a specific organization with arteries, veins, circulatory canals, and a mucus substance; (4) the epiphyseal bed far from just being resorbed with time formed an outline at its base upon which bone was deposited; and (5) the perichondrium which surrounded the growth cartilage exteriorly was closely adherent to it. The initial articles were devoted to description of the differences between the various epiphyses in terms of their structure, ossification, and fusion times to the adjacent diaphyses. He noted that the epiphyseal cartilage was strongly adherent to the perichondrium which covered it and that this membrane actually formed the principal bond between the epiphysis and the diaphysis. The joint capsules and ligaments were stronger than the periosteum in children which explained why traumatic dislocations in the young were very difficult if not impossible to produce experimentally and why separation of the epiphysis invariably resulted. In a study of two fetuses at term he was not

able to dislocate any of the joints since the epiphyses separated first. In the clinical state, cases of traumatic dislocation were rarely described before the ages of 5 or 6 years, while many examples of epiphyseal detachment were reported. He also pointed out the work of Wilson who in his book "On the Bones and Joints" published in London in 1820 reported that when longitudinal traction alone was applied, it took a force of 550 pounds when the periosteum was intact to detach the distal femoral epiphysis in a childhood specimen, whereas when the periosteum was removed a force of only 119 pounds was required [9]. Rognetta felt that far less force was needed to produce epiphyseal separation in the newborn. The point was made, however, that when the surrounding periosteal–perichondrial sheath was removed, the only intrinsic support that the growth plate provided was from the mammillary processes from the cartilage plate which interdigitated for a short distance into the diaphysis. Rognetta, quoting Portal, observed that ossification of the distal femoral epiphysis always began during the final 15 days of fetal life, an observation which is valuable in determining the age of the newborn concerning whether or not it was fully at term. He reviewed the importance of the growth cartilages in long bone growth based on the work of Hunter, Duhamel, and others and the differing mechanisms of bone formation from the periosteum and via the epiphyseal cartilage plate and the bony nucleus of the epiphyseal cartilage (our secondary ossification center). Rognetta pointed out how epiphyseal separation of the proximal femur was produced by trauma from the newborn period and for several years into childhood (and even beyond) rather than traumatic dislocation or femoral neck fracture. He stressed that there was a clear pathologic difference between an epiphyseal separation and fractures in infants of very young age adjacent to the growth plate. In the epiphyseal separation, there was a clean division of the cartilage line without marrow involvement; whereas, many childhood fractures up to the age of three or four involved a crushing of one side of the metaphyseal–diaphyseal bone with partial tearing of the periosteum, partial cracking of the cortical bone, and damage to the marrow contents. Separation of the epiphysis and bone fractures in infants formed "two distinct disorders."

Epiphyseal separations were recognized as complications of difficult deliveries, frequently detected at postmortem examination. Rognetta referred to several clinical mechanisms by which proximal humeral epiphyseal separations occurred both in the newborn period and through the growing years. The frequency of distal radial epiphyseal separations was recognized as was the fact that proximal radial or ulnar separations were rare. Two distal radial separations were described, one in a 15-year-old male seen at autopsy and another in a 10-year-old girl based on clinical assessment. Fracture-separations were also identified at the distal femur, proximal tibia, and distal tibia. Sibley of London had even diagnosed a separation of the tibial tubercle following a strong muscular action [10]. Valgus deformation was noticed to follow fracture-separations of the distal tibial epiphysis.

5.2.2.2 Gueretin

Gueretin (1837) wrote a rigorous three-part comprehensive review of growth plate fractures [8]. He detailed: the age at growth plate fusion; the relative growth rates of the various ends of the long bones; his human cadaveric experiments on reproducing dislocations, growth plate separations, and metaphyseal-diaphyseal fractures; the distinction between spontaneous (pathologic) and traumatic separations; a discussion of injuries at each major long bone epiphysis; treatments; and results including complications. The growth in length of bones at their diaphyseal ends through the functions of the cartilage growth plates was well recognized as was the fact that if healing following a growth plate fracture was associated with a bony callus ("un cal osseux") the bone would remain much shorter than that on the opposite side—an early reference to transphyseal bone bridge formation. The surrounding periosteum and perichondrium were recognized as having a major supporting role for the epiphysis. Experimental studies showed that in the newborn, epiphyseal separations invariably occurred rather than joint dislocations and that proximal humeral separations were readily produced. In the newborn, the entire epiphysis separated from the diaphysis. Separation in the newborn and for several months thereafter tended to be completely through the cartilage plate with no bone attached. After 2–3 years of age, the structure of the epiphyses changed somewhat and the growth plate fractures were less uniform in appearance; some occurred slightly away from the epiphyseal plate, while those involving the epiphyses often dragged with them fragments of "the extremity of the diaphysis." (The term metaphysis was seldom used in the nineteenth and early twentieth centuries' orthopedic and anatomic literature). Different patterns were also seen after 10 years of age, not associated with pure structural separations but rather with less regular snapping or bursting patterns. Distinction was made between external or traumatic separations and internal or spontaneous separations caused by pathologic conditions such as rickets, infection, scurvy, congenital syphilis, and tuberculosis. A review was made of epiphyseal separations of each long bone. The most common epiphyseal fractures were those of the proximal humerus especially in association with difficult births. At the distal humerus, complete transverse separations were noted as were separations which passed between the separate ossification centers to involve internal or external condylar fractures. It was recognized early that the distal radial epiphysis was very commonly separated in childhood but that the proximal radial separation was rare. Proximal femoral

separations were difficult to produce in experimental postmortem studies and were only rarely verified in clinical situations. The distal femur and proximal tibia were known sites of epiphyseal separation. The distal tibia and fibula were readily separated experimentally in the newborn but infrequently recognized clinically. Gueretin made the interesting observation that in his experimental approaches to the distal tibia, he sometimes noted the periosteum to be intact while the epiphysis itself separated. Others subsequently noted this sequence of events, with cartilage separation, occurring first and displacement occurring only with secondary rupture of the periosteum. The end results of epiphyseal fractures were characterized by uneventful healing; by healing with deformity and shortening; by nonunion; or by amputation or death.

Malunions were commonly reported and shortening of the involved limb was often apparent. There was a recognition that growth deformities could occur even after healing of the epiphyseal fracture. Gueretin reported his interpretation of a case shown by Reichel that epiphyseal healing after separation occurred "by means of a bony bridge (cal)." He went on to indicate that "in the humerus illustrated by Reichel in addition to the shortening caused by the collapse of the humeral head and its faulty position one still could establish or ascertain a perceptible difference in length for the rest of the bone." He thought that the bone had lost its growth in length since it no longer had at one of its extremities the epiphyseal cartilage plate where this growth occurred. These cases proved the need to observe for shortening in any limb which had suffered a growth plate separation previously whether or not union had occurred. Treatment of spontaneous (pathologic) separations was directed primarily at the underlying cause. In the straightforward traumatic separations, treatment involved (i) reduction, (ii) maintenance of reduction for 8–30 days in the group from newborns to 4 years of age and for 15 days to 3 months in those >4 years of age, and (iii) prevention of complications of an infectious or vascular nature.

One can appreciate the high degree of awareness of epiphyseal injuries shown by Gueretin in his three papers written in 1837 [8]. Sixty years later, Poland in 1897 [10], another major figure in outlining the epiphyseal fracture-separation entity was describing in detail the clinical diagnostic features of these injuries in children and adolescents differentiating them from fractures since the epiphyseal injuries were still not appreciated well by surgeons of his time.

5.2.2.3 Smith

Smith presented a very clear description of epiphyseal separation of the distal end of the humerus demonstrating not only its existence, but also the way of differentiating it from what are now recognized as supracondylar fractures of the distal humerus and from elbow dislocations [11]. He pointed out the basic anatomical fact "that the lower epiphysis of the humerus does not include the condyles which belong entirely to the shaft of the bone."

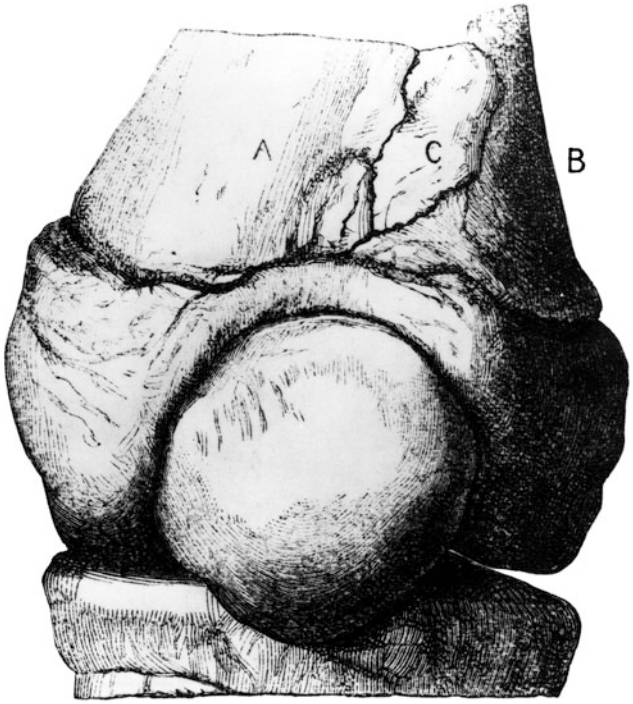


Fig. 5.2 A distal femoral epiphyseal fracture-separation is shown from an article by Canton [12] published in 1861. The fracture line passes along the physis of the distal femur at left and then into the metaphysis demonstrating the type II pattern. Pathoanatomic studies of gross specimens during that era also allowed for demonstration of multiple and divergent fracture patterns subsequently not appreciated on plain radiographs. In this specimen the metaphyseal segment C is clearly shown and was described as a separate fragment

Canton illustrated two cases of fracture-separation of the distal femoral epiphysis, both of which came to amputation [12]. The first example is what we would identify today as a Type II fracture-separation and a second appears as a Type I (Fig. 5.2).

5.2.3 Relatively Slow Acceptance by Many of the Existence of Epiphyseal Fractures

For the next several decades, debate continued over the existence of epiphyseal fracture-separations with acceptance slowed by failure of many of the leading surgeons to recognize them or to consider them only as rare and not particularly important. Salmon performed extensive experimental work inducing fracture-separations in human bones and was credited by Poland as being the first to prove that tearing of the periosteum around the growth plates was

accompanied by separation [4]. Much awareness of the occurrence of growth plate fracture-separations came from the studies on stillborn or neonatal infants with extensive limb trauma accompanying difficult deliveries. Poland well documented the fact that widespread acceptance and accurate description of these fractures dated only from the 1870s. Many surgeons and investigators focused on the fracture fragments associated with these injuries and on the fact that the transverse lines of separation were often in the spongieux layer (or within the outermost parts of the metaphysis "below" the hypertrophic zone in our terminology). They thus felt comfortable considering these injuries as fractures since pure epiphyseal fractures, with the line of injury totally within the cartilage, were felt to be rare or nonexistent. The treatments were also the same. Although there was still widespread uncertainty as to the nature and extent of the injuries, acceptance of their existence increased. Poland quotes Holmes as saying in 1869, "the conclusion to which my experiments of this injury would lead me is that fracture occurs not very rarely at or in the immediate neighborhood of the epiphyseal line; that the line of fracture coincides in these cases partially with that of the epiphyseal cartilage but seldom completely, that the general symptoms are therefore the same as those of fracture, while the special symptoms must be sought from the anatomy of each joint."

In a special discussion group of the Surgical Society of Paris in 1865, many prominent surgeons of the day spoke about the entity [13]. Marjolin, in a review of 600 fractures in children from his hospital over a 7 year span, reported that no diagnoses of separation of the epiphyses had been made. He commented that others also considered complete epiphyseal separations to be rare. Others focused on the associated fractures of the diaphysis which adhered to the epiphyseal fragment and thus lead to their interpretation as fractures rather than growth plate injuries. Richet described a case of a separation of the distal radial epiphysis in a 15-year-old male which was irreducible by closed manipulation and was reduced following resection of the distal radial diaphyseal (metaphyseal) segment. The diaphyseal part of the radius jutting out had "a smooth surface with rounded processes (mammillary projections) that obviously represented the diaphyseal portion of the radius separated from the epiphysis." Subsequent examination of the resected segment clearly established the reality that epiphyseal separation and not a bone fracture had occurred. Lefort described another resected fragment of the proximal tibia showing partial epiphyseal separation with passage of the fracture line into the adjacent diaphyseal bone. Broca mentioned elsewhere that epiphyseal separation could be produced in the postmortem state which leads to his belief that it was also common clinically.

Smith further expanded upon the reality of the entity noting the existence of epiphyseal fracture-separations, which he referred to as "epiphysary disjunction," at either end of the humerus, lower epiphysis of the tibia, and lower epiphysis of the radius. He commented (in 1867) that epiphyseal fracture-separations were "either but slightly noticed or all together omitted in our systematic works on surgery" and that there continued to be considerable ignorance about them by the profession [14]. He felt that they were a clear class of injuries which could be readily diagnosed and should be considered in any child with injury around a joint. As well as discussing the distal humeral epiphyseal fracture-separation, he pointed to the occurrence of such injuries at the distal tibia in which the internal malleolus preserved its relationship to the foot and ankle joint but not to the leg or proximal tibia above. The proximal humerus was also the site of growth plate fracture-separation. Smith again stressed knowledge of the anatomy, in that the epiphysis comprised not only the head of the bone, but also both of the tuberosities. He felt that fracture at this region was quite common. Separation of the lower epiphysis of the radius was also a frequent occurrence. He felt that it could be distinguished quite readily from a both bones fracture of the distal radius and ulna, in the sense that the radial epiphyseal separation was usually isolated and displaced in a dorsal direction with no tendency to supination.

5.2.4 Pathoanatomic Studies of Epiphyseal Growth Plate Fracture-Separations

The morbidity and mortality rate from trauma in the nineteenth century was so high that there were many pathoanatomic studies of human amputation or autopsy specimens. The authors were able to assess bone, cartilage, and soft tissue damage directly; whereas, with the onset of radiography there was reliance almost exclusively on radiographs since the large majority of growth plate injuries were treated by closed means. Even when open reduction and internal fixation was used, exposure of the physis was kept to a minimum. Their reports can be studied with interest today, especially in view of the crucial importance to the eventual outcome of the path of fracture lines within the radiolucent growth plates. These are undetectable by plain radiographs but help determine in a major way which fractures will heal uneventfully and which will predispose to focal transphyseal bone bridge deformity.

5.2.4.1 Broca

Broca had further described the structure of the growth region demonstrating that between the cartilage of the epiphysis itself and the spongy tissue of the diaphysis, there were two layers of variable thickness one of which was no longer plain cartilage and the other not yet fully spongy tissue; layers referred to as the chondroide and spongoide, respectively [5]. The thickness of these two layers varied

according to the age and particular bone. Broca, as well as providing macroscopic terminology for the epiphyseal region, also pointed out that the epiphyseal growth plate cartilage remained with the epiphysis after fracture.

5.2.4.2 Foucher

Foucher focused more attention on epiphyseal growth plate fracture-separations in 1860 [16, 17]. Foucher felt that he had established a direct relation between the thickness of the chondroid layer and ease of the epiphyseal separation and between the appearance of bony tissue in the epiphysis and the type of separation. He felt that with trauma there was a true interruption in continuity through the plate and not a simple separation of adjacent or contiguous parts. The layer of union between the diaphysis and epiphysis was not level but often alternatively concave and convex especially the older the patient. At birth, each of the growth plates was relatively level with the deviations more apparent after the age of 1 to 2 years. The shape of the growth plate varied from bone-to-bone and had no relationship to that of the adjacent articular surface. Foucher presented the first detailed pathoanatomic classification of these injuries in 1860 based on the extensive examination of specimens at the macroscopic level. Between the cartilage of the epiphysis and the bony tissue of the diaphysis which was referred to as the spongy ("tissue spongieux") there were two distinct layers of the growth plate, as defined initially by Broca, referred to as the chondroid layer ("couch chondroide") and the spongioid layer ("couche spongoide"). These can be seen by examining a growth plate macroscopically (or with a magnifying glass) with the chondroid layer essentially referring to the germinal, proliferating, and upper hypertrophic layers and the spongioid layer to the lower part of the hypertrophic layer and the zone of provisional calcification including the upper reaches of bone deposition on the calcified cartilage cores. Foucher defined three types of fracture depending on the transverse level of injury (Table 5.1). Type I was a pure epiphyseal separation (divulsion or decollement epiphysaire) in which the transverse line of injury was completely within the growth plate cartilage at the point of union of the chondroid and spongioid layers; Type II was a fracture-separation (fracture epiphysaire) with some fragments of bone present on the epiphyseal side separation surface and separation through the point of union of the spongioid and spongieux layers; and Type III was a fracture-separation within metaphyseal bone or the tissue spongieux layer just below the growth cartilage, referred to as a juxta-epiphyseal fracture (fracture pre-epiphysaire). He never noted transverse separation solely within the cartilage tissue (although subsequently others have noted such pathways). The presence of a secondary fracture angling through metaphyseal or epiphyseal bone was not the important consideration, it was the physeal separation that was paramount. He indicated that the line of separation could be variable in any single injury involving each of chondroid, spongioid, and spongy layers partially because the growth plate was often not a straight line but increasingly concave with age. This observation concerning a wandering line of separation was also made by Bret and Curtillet [18] and by Poland [4]. Most separations from 1 month to 1 year of age were Type I, those between 1 and 4 or 5 years Type II, and those from 5 to 10 plus years Type III.

Table 5.1 Foucher 1860 classification

First detailed pathoanatomic classification of these injuries	
Macroscopic examination	
Type I	Divulsion epiphysaire
	Pure epiphyseal separatio within couche chondroide
Type II	Fracture epiphysaire
	Fracture between spongoide and spongieux layers
Type III	Fracture pre-epiphysaire
	In metaphyseal bone

Foucher pointed out the importance of associated lesions with epiphyseal separation, namely the separation of the periosteum. It was widely recognized that the periosteum was only minimally adherent to the underlying bone in children. Epiphyseal separations caused by direct traction were not accompanied by a separation of periosteum but tearing of the periosteum was an invariable occurrence with displaced epiphyseal fracture-separations. The age of the subject was not the only factor which influenced the frequency and ease of epiphyseal separation; there were diverse results in different epiphyses. He then referred to the mechanisms which produced these lesions, a feature that was felt to be extremely important. He had never been able to displace an epiphysis regardless of age by a force directly applied on the epiphysis. Traction along the axis of the limb sometimes produced epiphyseal separation in the very young but he felt that massive force greater than would be seen in the human was needed. Very rarely did direct traction alone prove to be sufficient in the living to produce an epiphyseal separation. It was with the flexion, abduction, and rotation and extension movements that the displacements occurred. Extension at the knee was able to produce epiphyseal separation usually of the distal femur but occasionally of the proximal tibia. At the elbow this produced separation of the lower humeral epiphysis and very rarely that of the olecranon. At the proximal humerus and proximal femur yet another mechanism was involved, namely with abduction forces and with rotation. He summarized by indicating that it was torsion which favored epiphyseal separation in each bone. The abnormal positions of extension and abduction

combined always with torsion or rotation predisposed to epiphyseal separation. The effect of severe muscular contraction on the separation was also felt to be important.

Foucher summarized with seven conclusions: (1) the epiphysis could be separated from the diaphysis either by trauma or spontaneously in association with other disorders. In the latter case separation was only an epiphenomenon following after other affections in particular those of the periosteum which was swollen and weakened, for example, by subperiosteal abscesses; (2) the traumatic epiphyseal separation was easiest to produce when the infant was youngest; (3) the level of epiphyseal and diaphyseal separation varied according to age and cause with three specific levels of separation noted; (a) the level where the chondroid layer met the spongioid layer; (b) the level where the spongioid layer met the spongy (spongieux) layer; (c) within the spongy bone tissue itself; (4) regardless of the level of the lesion they involve complete loss of cartilage continuity, with associated fractures dependent on the mechanisms of production; (5) exaggerated motion is the most common cause of epiphyseal separations with muscular action having secondary influence; (6) the surface of the separated fragments is alternatively convex and concave and the periosteum is largely separated from the diaphysis; and (7) an important prognostic point is whether the separations are intra-articular or extra-articular.

5.2.4.3 Vogt and Bruns

In Germany, Vogt and Bruns wrote detailed articles concerning epiphyseal separations [19, 20]. Bruns described a similar macroscopic classification to that of Foucher differing mainly in his feeling that on occasion transverse separations occurred higher within the cartilage plate such that both fragments (epiphyseal and diaphyseal) clearly showed a cartilage covering. He summarized in detail and completely referenced 81 epiphyseal separations (78 from the literature and 3 of his own), which had been authenticated by gross inspection of open wounds or by pathology examination either at autopsy or following amputation. His work was done to assess the nature of growth plate damage following these injuries. A cardinal question in terms of outcome was the specific tissue layer in which the separation occurred. Bruns distinguished between two common patterns of fracture, that within the lower part of the growth cartilage although 5 of 81 cases were within the higher levels of cartilage, and that within the bony substance of the adjacent diaphysis.

Vogt, performing animal experimentation, observed pure epiphyseal separations only in very young animals with injuries of the growth cartilage in older animals usually being mixtures of cartilage separations and bony fractures. The developmental state of the epiphysis was felt to contribute to the pattern of fracture. In chondro-epiphyses, before appearance of the secondary ossification center, pure cartilage separation was more common while in osteoepiphyses where bone had replaced cartilage, the cartilage separations were usually associated with bone fractures.

Experiments in goats and lambs injuring the epiphyseal growth plate and adjacent regions were done to assess where the greatest growth disturbances occurred. He found that the greatest disturbance took place after injury to the epiphyseal cartilage plate. His work indicated that after subperiosteal resection of the physeal cartilage in growing bones, regeneration of bone itself took place but the growth in length ceased. Diaphyseal resection caused no growth disturbance, but removal of the cartilage between the diaphysis and the epiphysis caused a growth disturbance. Separation of the epiphyseal cartilage from the adjacent diaphysis caused growth disturbance if there was damage to the cartilage substance.

5.2.4.4 Ollier

In an effort to assess limb shortening, Ollier produced several lesions in the area of the growth plate and demonstrated that considerable growth arrest occurred not because of premature growth plate fusion but rather due to diminished growth over a prolonged period with trouble due to diminished nutrition slowing growth not by premature ossification but rather by arrest of proliferation of the cartilage cells [21]. When he produced major direct growth plate injuries, however, by excising growth cartilage either of the distal femur or of the proximal tibia, he noted a massive stoppage of growth which was asymmetric if he had made the excision of the growth plate cartilage focally and complete if the lesion had extended across the entire transverse diameter of the bone. He showed clear examples of growth arrest in lesions made in the 1-month-old rabbit. Destruction of the lateral region of the distal femoral growth plate led to considerable shortening and extensive valgus deformation with continued growth of the medial and central parts of the plate. Considerable shortening and varus deformity of the proximal tibia was demonstrated with incision of the medial part of the growth cartilage also in the 1-month-old rabbit. Ollier studied the influences of diaphyseal fractures and periosteal irritation on long bone growth and clearly demonstrated that both led to increased growth on the involved side. He specifically studied growth plate fracture-separations in terms of subsequent growth. His experiments illustrated that growth plate separations influenced subsequent growth in a variable fashion. There was no cessation of growth if reduction had been made immediately and inflammation avoided but growth arrest was considerable where the reduction had not been performed. The latter point was soon recognized as inaccurate; nonreduced fractures did not invariably proceed to growth arrests.

Ollier also wrote a detailed work on traumatic lesions in the juxta-epiphyseal region of diaphyseal bone which he

referred to as l'entorse juxta-epiphysaire (juxta-epiphyseal sprains) [22]. Injuries in the area of a joint in the adult led either to ligamentous tears, intra-articular fractures, or dislocations; whereas in the young child, the weakest areas were either the epiphyseal growth plate or the region at the extreme end of the diaphysis immediately adjacent to the plate. It was often this latter juxta-epiphyseal region which suffered the effects of trauma. The lesions Ollier was describing were generally nondisplaced and thus poorly understood clinically. He referred to a case in which a fall had caused a seemingly mild shoulder injury in a 7- or 8-year-old girl which subsequently presented as a growth arrest with shortening of the proximal humerus of 7 cm, years later. This and other clinical examples were used as evidence to confirm his previous experimental findings of the possibility of growth arrest in a clinical setting. Occult trauma might in some instances lead to subsequent growth arrest even though the initial injury appeared benign and any evidence of infection had been excluded. The juxta-epiphyseal sprain was considered to represent the first degree of what would become an epiphyseal separation if greater force was applied. They were particularly common where the bone was osteopenic with systemic involvement. Those most clinically significant occurred in the 1st years of life up to about 6 or 7 years. The bending of bone, incomplete infractions, and subperiosteal fractures were not seen at later ages. He defined a variety of these lesions based on the changing consistency of the metaphyseal tissue. An example is with an abduction injury. The fracture was within the diaphysis only 8–10 mm from the lowest part of the growth plate. The cortex on the concave side cracks and bends first, and the adjacent spongy bone and its associated trabeculae has cracks, the marrow is disturbed, but there is no lesion of the growth cartilage and the intact periosteum hides the view of the cracked bone. A benign form of this is the metaphyseal buckle fracture. If the traumatic force continued, there was more pronounced squeezing of the juxta-epiphyseal cortical and trabecular bone on the concave side; separation of segments of spongy bone and perhaps separation of a part of the growth cartilage on the convex side with the periosteum remain intact. The final stage involved further force, a trans-diaphyseal spongy bone fracture. He concluded that the juxta-epiphyseal sprain was a group of lesions produced in the juxta-epiphyseal region of the diaphysis of long bones.

Poncet, from the same school as Ollier, demonstrated how damage to radial or ulnar epiphyses had a negative growth effect on the other nonaffected bone [23].

5.2.4.5 Bidder

Bidder produced focal growth plate defects in the rabbit by several methods leading to a bone bridge between epiphysis and metaphysis and causing growth retardation [24].

5.2.4.6 Nove-Josserand

Nove-Josserand performed experiments to study the mechanisms of growth arrest histologically following small partial cartilage growth plate injuries and to disprove the then widespread belief that growth cartilage irritated by trauma underwent a generalized acceleration of its development to fuse prematurely [25]. The studies were done in 2-week and 1-month-old rabbits using aseptic technique with no infections (which had compromised previous studies) seen. He created variably sized focal vertical lesions through the growth plate cartilage and elicited transphyseal bone bridge formation between epiphysis and diaphysis, well shown histologically (Fig. 5.3). In 8 of 10 instances, he induced a localized transphyseal ossification between the epiphysis and the diaphysis. He concluded that it was this bony communication between epiphyseal and diaphyseal bone that led to growth arrest and deformity. The "bony wedge" between epiphysis and diaphysis established a "true synostosis fixing one to the other like a solid and inextensible nail." He also felt that the bony bridge formation could be rapid or slow.

5.2.4.7 Bret and Curtillet

Bret and Curtillet examined human specimens microscopically to assess histologic structure using the Foucher classification as a reference point [18]. This represents one of the earliest microscopic studies; the work of Foucher and Broca was macroscopic even though microscopic techniques were

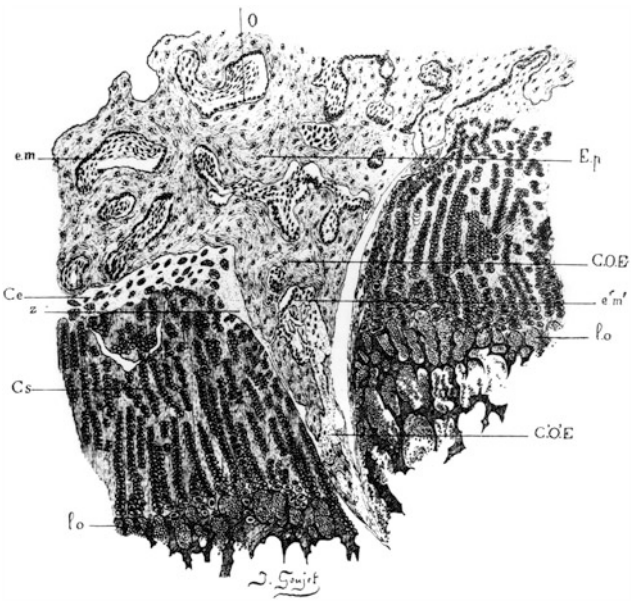


Fig. 5.3 The fact that some epiphyseal growth plate fracture-separations had physeal damage followed by transphyseal bone bridge formation was studied by several French investigators in the late nineteenth century. This illustration in a rabbit model from the work of Nove-Josserand [25] shows epiphyseal bone above, a break in the physeal cartilage centrally, and passage of bone into the gap

available. (Broca did correlate his macroscopic finding of normal growth plates at a microscopic level.) In newborn specimens, the line of fracture was not felt to be within the chondroid layers of the growth plate as microscopically small fragments of bone were seen attached to the cartilage side thus representing a "fracture epiphysaire" and not a true separation (divulsion epiphysaire). The separation had thus occurred in what was referred to as the lower part of the spongioid layer. In a 3-year-old child, the fracture lines were even further from the epiphyseal cartilage totally within spongy bone and in two teenage specimens the fractures were even further away from the growth cartilage (fracture pre-epiphysaire). They concluded that the small spicules of bone adherent to the epiphyseal fragments indicated that pure epiphyseal separations did not exist and that the Foucher classification at the macroscopic level was inaccurate to assessments at the microscopic level. They continued to recognize the value of a separate definition of juxta-epiphyseal fractures, however, and termed traumatic separation to exist for any fracture produced between the growth cartilage and the bulbar region of the diaphysis. This article while interesting from the point of view of the questions being asked about the precise histologic level of injury involved epiphyses only from four patients in whom the fractures were created manually at time of autopsy.

5.2.4.8 Cornil and Coudray

Cornil and Coudray performed particularly noteworthy studies in demonstrating at the histologic level the varying types of epiphyseal fracture-separation patterns producible in immature rabbits [26, 27]. The initial studies involved angular and rotational forces applied to 54-day-old rabbits immediately post-sacrifice with assessment histologically of fracture patterns at the distal radius and ulna, distal femur, and distal tibia and fibula. They noted the similarity of patterns produced in humans and rabbits to the extent that they reproduced all varieties of lesions seen. Epiphyseal separations were produced along with mixed lesions involving partial epiphyseal separation and associated diaphyseal or epiphyseal fractures. The term metaphyseal was not widely used in that era and the authors are referring to what we now call the juxta-epiphyseal or metaphyseal regions. The diaphyseal fractures were either continuous with the epiphyseal cartilage fractures (as in the Salter–Harris II terminology), at right angles to the growth plate passing into the diaphysis (metaphysis) as longitudinal clefts, or transverse in the diaphysis seemingly separate from the physeal separation. Many more fractures were then created in the living with sacrifice and histologic studies done after several days or weeks to determine the sequelae of injury, particularly in relation to growth problems. They defined multiple fracture patterns including (i) pure transverse epiphyseal separations; (ii) complete transverse fractures through the spongioid and diaphyseal spongy bone layers; (iii) mixed lesions involving partial epiphyseal separations with deviation of the line of injury causing a diaphyseal fracture; (iv) complex fractures involving oblique planes from the diaphysis through growth plate, epiphysis, and articular cartilage, and (v) longitudinal fractures of the growth plate cartilage. The longitudinal fractures of the growth plate in particular warranted close attention as they were frequently demonstrated histologically in isolation or coexisting with each of the type ii, iii, and iv injuries described above even without displacement (Fig. 5.4a). The cartilage was often broken by one or several longitudinal tears opening a communication between epiphyseal and

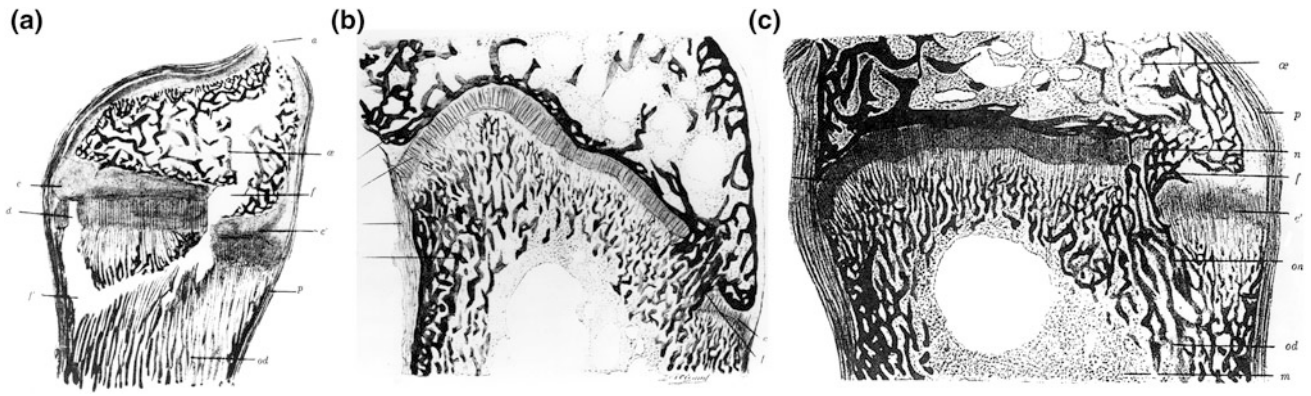


Fig. 5.4 Experimental studies by Cornil and Coudray [27] using the rabbit model identified each of the pathoanatomic patterns of epiphyseal fracture-separation which later came to characterize classifications throughout the twentieth century. **a** A type IV pattern is shown involving passage of the fracture pathway from the articular cartilage (a) through the epiphyseal secondary ossification center bone and then through the physis and metaphyseal bone. **b** Following application of an angular and rotational force, a transphyseal bone bridge links epiphyseal and metaphyseal bone with the rest of the physis remaining open. The fracture model frequently caused longitudinal tears within the fractured physeal cartilage opening communication between epiphyseal and metaphyseal bone. **c** Another fracture leading to transphyseal bone bridge is shown

diaphyseal bones. The loss or separation of cartilage was filled in by solid bony spans directly continuous with bone of the epiphysis and diaphysis (Fig. 5.4b, c). Multiple histological preparations were shown demonstrating "un cal osseux" or bony callus replacing growth plate cartilage. The authors summarized by indicating that longitudinal fractures of growth cartilage always repaired themselves by "un cal osseux" quickly developed and thrown out like a bridge between the epiphysis and the diaphysis. They felt that the longitudinal fractures were frequent and that they often led to shortening of the involved bone since shortening could be seen even in those cases without displacement. The general conclusion of the work was somewhat flawed in that they felt that virtually all growth plate fractures led to growth inhibition. While this is inaccurate, it should not cloud the central importance of the concept of the longitudinal growth plate cartilage cleft allowing epiphyseal and metaphyseal vessel and bone communication followed by bone bridge formation. The detailed drawings of the histologic sections and the descriptions in the text illustrate other important features of growth plate fractures: (i) the line of injury within the physis tends to wander through the various physeal layers; (ii) the cartilage can be fragmented at focal points into several pieces; and (iii) the adjacent bone on the diaphyseal and occasionally epiphyseal side is often fractured in various planes such that mixed or complex lesions are prominent. Studies also demonstrated displacement of cartilage plate fragments into the diaphysis and repair of segments of damaged physeal cartilage by fibrous tissue rather than bone.

5.2.5 The Level of Transphyseal Fracture

The level of fracture came to dominate discussion of these injuries. Most studies of this era, where many clinical samples were studied, considered the transverse injury generally to be a fracture of the outermost reaches of the diaphysis (metaphysis) since a thin layer of ossifying tissue (spongioid) clung to the cartilage. The level of injury is of prognostic significance since fractures through the lower parts of the hypertrophic zone or the metaphysis have little likelihood of producing growth arrest, while those through the germinal, proliferating, and upper hypertrophic zones can be problematic. Pure cartilage separation was conceded to exist but was felt to be concentrated in the very young (<1year) and rather rare. Bruns considered lesions within the cartilage to be common, however [20]. Most studies defined some bone fragments with the cartilage fracture with involvement of the spongioid and spongy diaphyseal bone layers most common. The work of Bret and Curtillet spurred this view; Ollier pointed out the common juxta-epiphyseal lesion; and Rollet opted for a "juxta-epiphyseal detachment" terminology. Coulon focused on the rarity of the pure trans-cartilage pathway of separation commenting that "we have found in most of those in which the accident was recent that the fracture if it traversed the epiphyseal line at one part of the bone generally left it at another part." Ollier felt that epiphyseal separations never occurred within the cartilage, but rather within or at the level of spongioid bone [21].

5.2.6 Mechanisms of Injury

Many studies were done to assess the mechanism of injury that led to epiphyseal fracture-separations. Enormous amounts of traction applied along the longitudinal axis of the bone were needed to bring about epiphyseal displacement in particular when the periosteum remained intact. Virtually, all studies from Rognetta and Gueretin in the 1830s onward showed that torsional and rotational movements were far more effective with less force in bringing about separation [7, 8]. Tapret and Chevet described a distal femoral epiphyseal fracture-separation assessed post-amputation from a 9½-year-old male. The fracture pattern was along the physis and then into the diaphysis. The ligaments were intact and they postulated an extension-rotation mechanism [28]. Many experiments had shown the extreme importance of the periosteum in supporting the attachment of the epiphysis to the diaphysis. Internal support was relatively weak and was due to the interdigitation of the epiphyseal cartilage columns with diaphyseal bone from below. These tissues are in continuity, and thus no specific anatomic structure is defined by them, although when the physis is ruptured away from the metaphysis/diaphysis, examination of the undersurface of the cartilage shows small cartilage processes protruding from the surfaces and these have been referred to as mammillary processes.

5.2.7 Epiphyseal Fracture-Separations Accompanying Traumatic Births

The occurrence of epiphyseal separations accompanying difficult deliveries was well documented. Extreme manual traction and rotation on the limb during difficult deliveries led to epiphyseal separations rather than to ligamentous injuries as had been suspected previously. Simpson documented one case in which the child died during birth and subsequent analysis showed epiphyseal separation at the upper end of the femur, the lower end of the tibia, the lower end of the fibula, and a partial separation of the epiphysis of the distal femur [29]. His review of the literature also showed increasing awareness of this injury which had previously been unsuspected. Experimental work also showed that epiphyseal separation could be produced with extremes of traction.

He reports the work of Hofmakl who indicated that attempts to produce dislocations in fetal cadavers at hip, elbow, and shoulder joints always failed and ended only in epiphyseal separations. He also quotes Kuestner indicating that his experiments showed that in the lower extremities, the epiphyses that yielded most easily were those at the lower end of the tibia and fibula. The observation was also made, consistent with many reports including those at the present time, that the epiphysis gives way initially from within after which displacement passes outwards with further pressure.

5.2.8 Understanding of Growth Plate Fracture-Separations at the End of the Preradiographic Era

5.2.8.1 Hutchinson

Hutchinson presented a general overview of epiphyseal injuries including a review of fractures at each anatomic area in 1893–1894 [30–32]. In his introduction, he referred the possibility of growth arrest with these injuries and the fact that intra-articular joint involvement of the fractures often worsened prognosis. He pointed out that epiphyseal separations were associated with significant amounts of periosteal elevation and stripping which led to subsequent hematoma formation and abundant newbone repair along the adjacent shaft. He pointed out that fractures led to a separation of the lowermost parts of the epiphyseal growth plate such that most of the plate remained with the epiphysis. The presence of epiphyseal separations, however, in many instances showed elevation but no tearing of the periosteum which confirmed the belief that the strongest means of union between the shaft and the epiphyses was via the periosteal and perichondrial sleeve. Although epiphyseal fractures were relatively common, they showed "a remarkable power of resistance" by which he meant that following healing, they continued to function rather than being obliterated. Hutchinson referred to six separations of the lower epiphysis of the radius which he followed for a considerable period of time, only one of which showed some shortening (Fig. 5.5). His feeling, however, consistent with that of Ollier, was that displaced epiphyses had a higher incidence of growth arrest. Hutchinson was one of the earliest to note the importance of prompt and accurate reposition of the displaced bone in particular with "careful avoidance of rough manipulation in so doing."

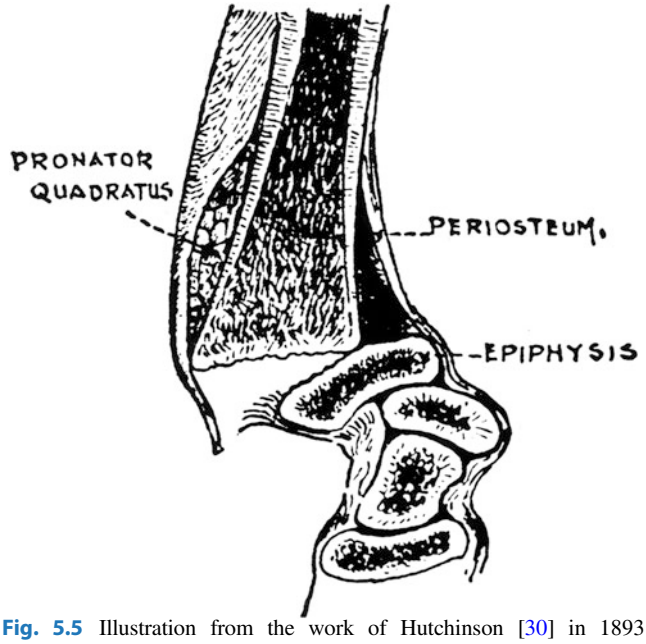


Fig. 5.5 Illustration from the work of Hutchinson [30] in 1893 demonstrates a type I distal radial fracture-separation. This was recognized as one of the commonest of injuries. Note the continuity of the periosteum on the dorsal or concave surface and the rupturing of the periosteum on the volar surface. The physeal tissue is noted to be displaced with the epiphyseal fragment

5.2.8.2 Jouon

Jouon presented a clear view of all aspects of growth plate fracture-separations in 1902 [33–36]. He stated that traumatic separation of the epiphyses constituted a loss of continuity in bones that was very different from fractures in all viewpoints including causes, symptoms, treatment, and prognosis. The three most common fractures were those of the proximal humerus, distal radius, and distal femur. His focus, as with many preceding works from the nineteenth century, was on understanding of the pathologic anatomy of the fractures, their mechanisms of occurrence (generally forceful movement beyond the normal range combined with torsion), and the methods of treatment required in general and in reference to each specific epiphysis. General treatment approaches involved approximately 3 weeks of plaster cast immobilization for nondisplaced injuries. Displaced fracture-separations required reduction under general anesthesia and maintenance of reduction or by continuous traction in a plaster cast for 1 month. Irreducible fractures were treated by open reduction and removal (resection) of the diaphyseal segments of bone. As early as 1878, Ollier recommended and practiced cuneiform osteotomy, segmental bone resection, and growth plate cartilage removal (chondrectomy) in cases where deformity followed growth plate arrest.

5.2.8.3 Poland

John Poland in 1898 published a classic treatise close to 1,000 pages long, "Traumatic Separation of the Epiphysis," reviewing a vast number of articles pertaining to growth plate fracture-separations [4]. The work summarized the extensive knowledge on growth plate injuries which had accumulated during the preradiographic era. Chapters dealt with history, anatomy, etiology, age and sex, frequency of the various separations, experiments in pathological anatomy, mechanism, prognosis, and results, and a discussion of

fractures at each specific epiphysis. He listed and clearly illustrated a classification of epiphyseal fracture-separation patterns which included five types, although a numbering system was not applied (Fig. 5.6a, b). These included pure and complete transverse separation, partial transverse separation with fracture of the diaphysis, partial transverse separation with fracture of the epiphysis, complete transverse separation with fracture of the epiphysis, and fracture passing from diaphysis through the growth plate to epiphysis and articular cartilage. Poland thus indicated the great frequency with which the transverse epiphyseal separation deviated obliquely into the diaphysis carrying with it a variable-sized diaphyseal fragment. He also defined the much less-frequent association of the epiphyseal separation with an epiphyseal fracture passing into the joint itself. These patterns were seen most at the distal femoral and distal humeral areas.

Additional pathoanatomic findings remain valid today: (i) the periosteum is widely detached from the diaphysis in displaced fractures but remains attached to the epiphysis on the concave side of the injury. The periosteum has its strongest attachment to the developing bone beyond the growth plate into the epiphysis. (ii) In many instances, there can be a separation of the epiphysis but no displacement of the fragments owing to the stability provided by the intact periosteum. The absence of displacement with epiphyseal separations due to maintenance of the periosteum was noted by Salmon in studies on newborn human cadavers. The periosteum can be lifted or separated from the diaphyseal bone but not torn. These separations without displacement were considered to be common and were often felt to be ligamentous sprains.

Poland recognized that "the history of many examples of arrest of growth of bones is that the injury had been considered as that of a sprain." Poland clarified that the age of greatest occurrence of these injuries was after 11 or 12 years, rather than early in childhood. He presented detailed preradiographic era tables on the ages of appearance of the epiphyseal ossification centers and of their time of union to the diaphyses. In summary of major series of cases, the frequency of long bone epiphyseal injuries was (1) lower epiphysis of femur; (2) lower epiphysis of radius; (3) upper epiphysis of humerus; and (4) lower epiphysis of tibia. Of his personal series of 693 separations, the upper extremity/lower extremity ratio was 1.6:1 (426/267), respectively, including: distal femoral (125–18 %); proximal humeral (120–17 %); distal radial (112–16 %); distal

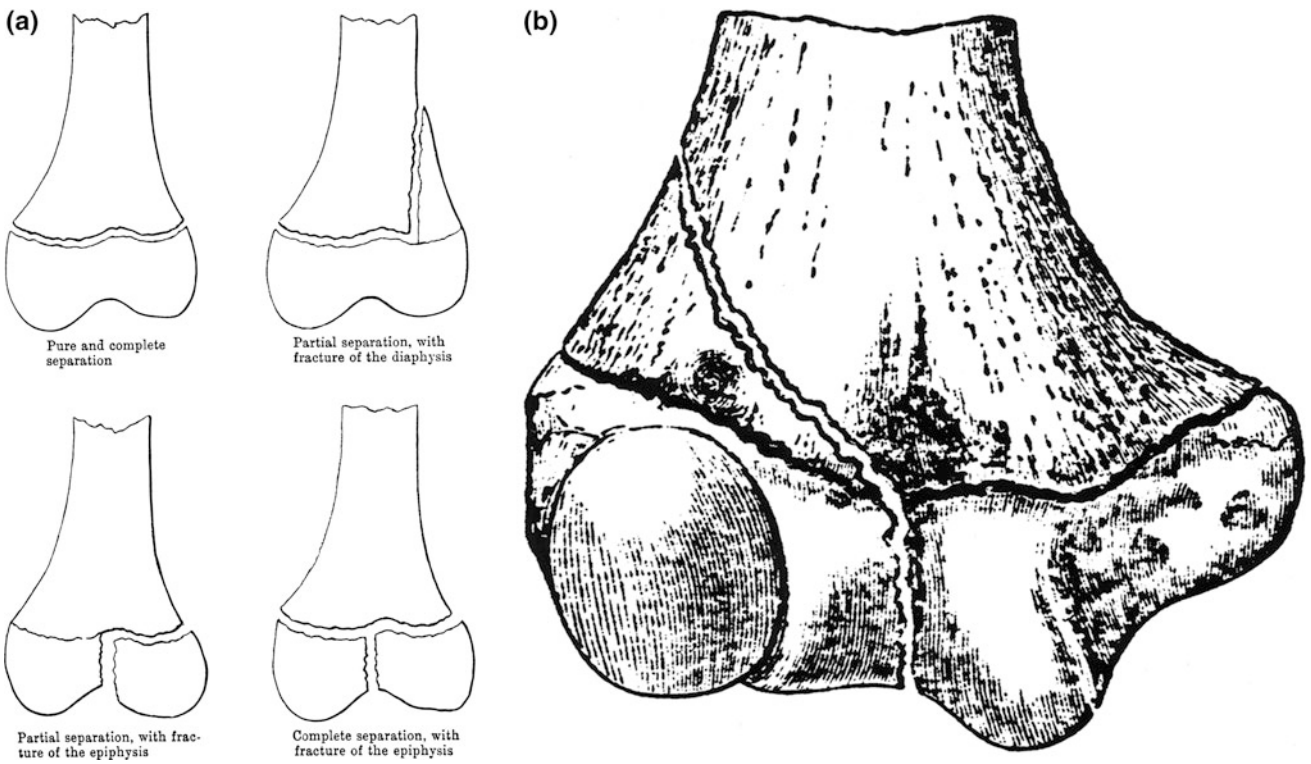


Fig. 5.6 **a** and **b** from the work of Poland [4] published in 1898 show his representations of epiphyseal fracture-separations. In (**a**) at *upper left* he demonstrates a pure and complete separation (listed as a type I injury now); *upper right* partial separation with a fracture of the diaphysis (now type II); *lower left* partial separation with fracture of the epiphysis (type III); and *lower right* complete separation with fracture of the epiphysis (not currently classified but occasional examples identified). In (**b**) Poland illustrates the current type IV fracture-separation of the distal lateral humeral epiphysis

humeral (81–12 %); and distal tibial (46–7 %). (The internal epicondyle of the distal humerus was 61–9 %).

Systematic clinical reviews of traumatic epiphyseal separations were also written by Wolff in Germany in 1900 and by Kirmisson in France in 1904 [37, 38].

5.2.9 Early Surgical Efforts in Relation to Growth Plate Injuries

Surgical intervention in relation to growth plate fracture-separations was increasingly bold as problems referable to certain types of fracture became apparent clinically. Diaphyseal resection was done to allow reduction in otherwise nonreducible fracture-separations [13]. Delens reported on an open reduction and a surgical resection of the diaphyseal (our metaphyseal) fragment of what we would now refer to as a displaced Salter–Harris Type II distal femoral growth plate fracture [39]. This allowed removal of interposed periosteum and muscle, easy reduction, and relief of vessel constriction, and did not compromise subsequent growth. Open reduction and diaphyseal resection were done increasingly to achieve reduction without excess pressure on the swollen adjacent tissues and skin. Jetter operated frequently on proximal humeral fracture-separations observing clean intra-cartilage separations, intra-cartilage separations with associated longitudinal fractures, partial epiphyseal separations with diaphyseal fractures (S–H II), and juxta-epiphyseal fractures (within the metaphysis close to the growth plate) [40]. As early as 1873, there were clinical reports of growth plate excision and stimulation by periosteal irritation in the treatment of leg and forearm problems caused by growth damage to one of the paired bones.

By the end of the nineteenth century, which coincided with the end of the preradiographic era, there was good experimental and clinical awareness of the epiphyseal growth plate fracture-separation entity and of the general range of treatments needed. Shortening and angular deformity were recognized as potential negative sequelae. The problems were also understood to be due to the mode of repair post-injury as well as to the initial degree of displacement.

5.3 Clinical Approaches to Growth Plate Fracture-Separations in the Radiographic Era

5.3.1 Pathoanatomic Classifications

The advent of radiography immediately removed any lingering doubts about the existence of epiphyseal fracture-separations and allowed vastly more accurate diagnosis and treatment. Classifications were formulated on the basis of plain radiographic assessments and these classifications came to dominate the perception and management of growth plate fracture-separations. We refer to these classifications as pathoanatomic since they are based on the pattern of fracture as determined by plain radiographs. Several of these classifications are illustrated in Fig. 5.7 and described in more detail below.

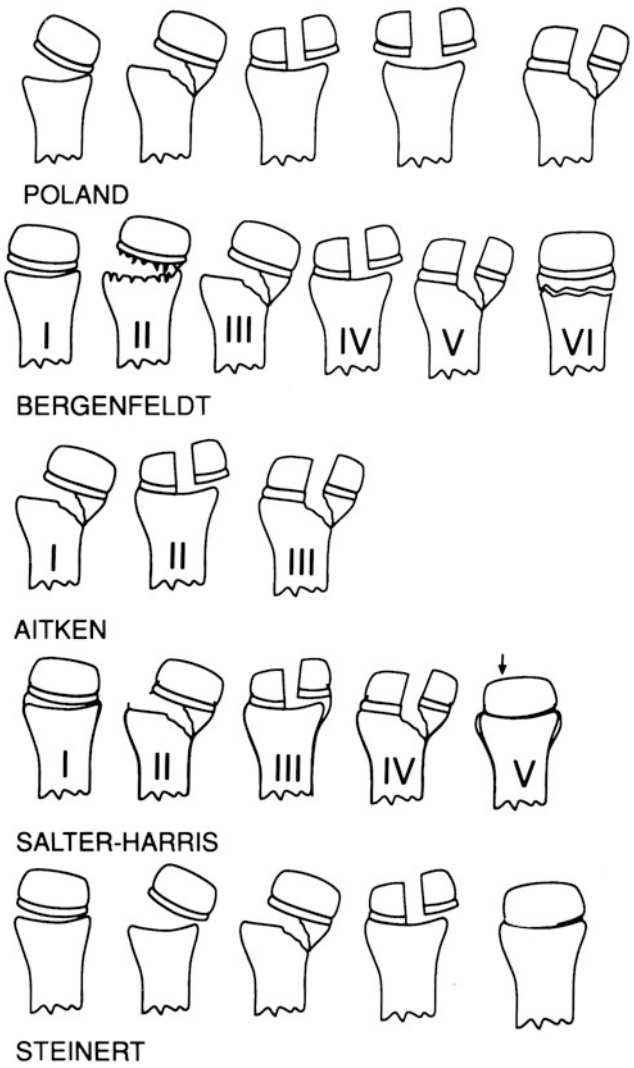


Fig. 5.7 Several pathoanatomic classifications of epiphyseal growth plate fracture-separations are shown: Poland, 1898; Bergenfeldt, 1933; Aitken, 1936; Salter and Harris, 1963; and Steinert, 1965. The similarity in categorization is evident

5.3.1.1 Bergenfeldt

In 1933, Bergenfeldt presented a large study involving 310 patients from Stockholm, Sweden between 1919 and 1928 [41]. His work represents the first definitive study from the radiographic era. His pathoanatomic classification defined six

types of epiphyseal fracture-separation based on the radiographic appearance as follows: Group I, epiphyseal separation with no demonstrable bone involvement; Group II, epiphyseal separation with traces of thin bone fragments accompanying the epiphysis on its diaphyseal side; Group III, epiphyseal separation combined with a diaphyseal fracture; Group IV, epiphyseal separation combined with an epiphyseal fracture; Group V, epiphyseal separation combined with epiphyseal and diaphyseal fracture; and Group VI, juxta-epiphyseal fracture. The epidemiologic patterns were documented for such factors as the number of fractures at each epiphysis, the group distribution at each epiphysis and the age/group relationship. The frequency distribution was similar to that seen now with distal radial separations commonest, followed by those at distal humerus and distal tibia. Group I fractures accounted for 7.4 % of all injuries, group II 31 %, group III 50 %, group IV 6.1 %, group V 4.2 %, and group VI 1.3 %. In one case, he felt that fracture occurred between the epiphysis and the upper part of the growth plate. The incidence of growth inhibition problems overall was quite small and was attributed to a direct lesion of the proliferating cartilage or, in completely intra-articular epiphyses, to marked damage to vessels with loss of nutrition to the growth plate cartilage. There were no instances of increased growth following epiphyseal separation. He concluded that growth damage was significantly less in man than in animals subjected to experimental growth plate injury, an impression which must be borne in mind in interpreting animal work. The epiphyseal separation in many of the injuries was localized to the zone of ossification and did not interfere with the growth cartilage itself. Even when damage was direct to the growth cartilage, it infrequently led to growth damage. He recognized that negative growth sequelae resulted especially from group V injuries where both epiphyseal and diaphyseal fractures occurred with 33 % of cases in this group developing shortening.

5.3.1.2 Aitken

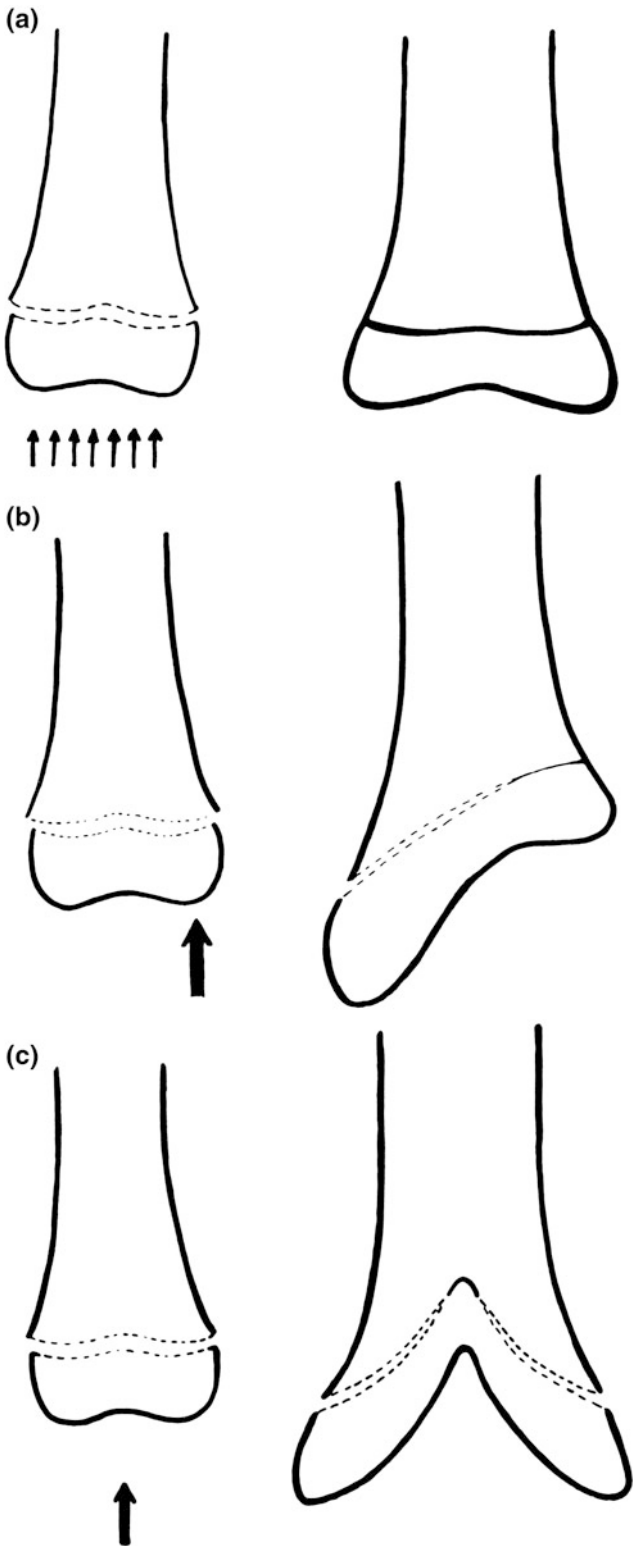
Aitken wrote extensively on epiphyseal growth plate fracture-separations with articles on injuries at the distal radius, proximal humerus, distal femur, and proximal and distal tibias [42–47]. He indicated that "in discussing the end results of epiphyseal fractures, each epiphysis must be considered individually" as they varied greatly in anatomical structure and physiological function. Such factors as size, shape, and position of each epiphysis as well as the amount of growth contribution had to be considered. Each epiphysis was subject to different types of fractures, the end results of which differed considerably. He first defined his classification of three types in relation to distal tibial epiphyseal fractures (1936) and then related it to distal femoral and proximal tibial fractures.

Type I: The fracture line runs parallel to the cartilage plate and just within the newly formed bone on the diaphyseal side prior to passing obliquely outwards through a diaphyseal segment. The epiphysis is displaced en masse with little or no damage to the cartilage plate since the fracture line appears to pass through the zone of degenerating cartilage cells and newly formed osteoid tissue and bone.

Type II: The fracture line crosses the bony epiphysis from the joint surface to the cartilage plate, crushing the plate in just under half the cases. In his initial work, Aitken described the fracture line as passing only to the growth plate; in later work, he showed it continuing along the growth plate. If the fracture line emerged between the bony epiphysis and the cartilage plate, no growth damage would occur; but if it passed through the plate and emerged between the plate and the diaphysis growth damage would occur.

Type III: The fracture line runs from the joint surface through the bony epiphysis crossing the growth cartilage and passing out the metaphysis. Types II and III were seen particularly at the distal femur and proximal and distal tibia. Mechanism was also implicit in his approach. The more favorable prognosis in Type I fractures was due to the fact that they were avulsion injuries, with a less favorable prognosis in Type II and Type III injuries due to the fact that they were compression injuries with the fracture line crossing and crushing the growth plate. He recognized, however, that even Type I avulsion injuries of the distal femoral epiphysis led on occasion to serious growth deformity.

Over the next 30 years, large numbers of studies were performed assessing the results of epiphyseal fracture-separations in relation to the radiographic and clinical findings at specific epiphyses. The pathoanatomical classifications pointed out by Bergenfeldt and Aitken were commonly referred to. Fractures of the distal tibia were commonly assessed because they were frequent and had a variable prognosis with the differing fracture patterns. Works by Buttner (1956), Bartl (1957), and Ehalt (1958) were notable [29, 48–50]. Bartl reviewed in excellent detail 235 cases of epiphyseal fracture-separations of the distal tibia in a study between the years 1928 and 1953. Rehbein and Hofmann pointed out the negative effects of axial injuries to the growth plates in 1963 (Fig. 5.8) [51]. They commented on a complete fusion of the functioning growth plate with longitudinal forces affecting the complete physis; unilateral



asymmetric growth plate arrests with axial forces concentrated on one part of the periphery of the physis; and central arrests where the axial force was limited to the central part of the physis.

5.3.1.3 Salter and Harris

Since its description in 1963, the classification of Salter and Harris, has been used extensively to define growth plate injuries [52, 53]. Their work defined five types.

Type I: There is a complete separation of the epiphysis from the metaphysis with no bone fracture and with the growing cells of the epiphyseal plate remaining with the epiphysis.

Type II: The line of separation extends along the growth plate then exits through a portion of the metaphysis. The periosteum is torn on the convex side of any angular deformity but intact on the concave side where the metaphyseal fragment is present.

Type III: An intra-articular fracture extends from the joint surface through the secondary ossification center to the hypertrophic zone of the growth plate and then along the growth plate to the periphery.

Type IV: An intra-articular fracture extends from the joint surface through the secondary ossification center, across the growth plate, and exits through the metaphysis.

Type V: A severe crushing force is "applied through the epiphysis to one area of the epiphyseal plate."

Rang has added a Type VI to the Salter–Harris classification encompassing injury to the periphery of the growth plate region with removal of the overlying periosteal–perichondrial tissues of the groove of Ranvier [54, 55]. Removal of this tissue component allows bony bridging between epiphysis and metaphysis.

The article referred briefly to the earlier works of Bergenfeldt and Aitken but no indication was made to the similarity of viewpoints. Salter and Harris added the Type V

◀**Fig. 5.8** Illustration from the work of Rehbein and Hofmann [51] shows their concept of growth plate damage in association with axial forces. In part **a**, the small arrows at left indicate damage over the entire extent of the epiphysis leading to a complete premature growth plate closure. Forces in part **b**, concentrated at one side of the physis lead to focal growth plate closure and subsequent angular deformity with persisting growth of the rest of the physis. Part **c** illustrates axial pressure centrally leading to a focal bone bridge formation and a tethering effect allowing for the characteristic fishtail appearance with medial and lateral physeal growth continuing. (Reprinted with permission from Rehbein and Hofmann, Knochenverletzungen im Kindesalter. Langenbeck's Archiv fur Chirurgie. 1963;304:539–562. Copyright 1963 Springer Science+Business Media)

injury to their classification. The occurrence of growth plate arrests after seemingly benign injury, where no fracture was diagnosed, had been known or suspected since the works of Ollier. This injury can be diagnosed by plain radiographs only retrospectively after a growth plate premature fusion has occurred; whereas the other types, excepting some undisplaced Type I injuries, are seen on the initial postinjury film. Rehbein and Hofmann also drew attention to growth plate damage following axial force [51]. They illustrated in Fig. 5.8 that axial force across the entire width of a physis could lead to a complete destruction of the growth cartilage; asymmetric forces could produce partial growth damage and angular deformity, and local centralized axial damage could produce a central focal physeal arrest and a funnel-shaped withdrawal of the physis. The Type V injury has been documented infrequently in other series and the proposed mechanism of occurrence, a compression force along the long axis of the bone, has been doubted by some while others postulate varus, valgus, and shear forces as causative factors [56–59].

Salter and Harris in their paper described the applied anatomy and histology referable to growth plate injuries, reviewed their own experimental work and cautioned that prognosis depended not only on the type classification of the injury but also on age, blood supply, method of reduction, and open injury contamination. General principles of treatment and treatment at each specific growth region were detailed. Subsequent works have pointed out some limitations of the Salter and Harris approach in that it serves poorly at certain epiphyses as a prognostic indicator. The numerical grading scheme, in particular types I to IV, has been almost universally adopted and has served as a baseline for describing and reporting cases of fracture-separation for the past several decades.

5.3.1.4 Steinert

Steinert assessed growth plate injuries in 1965 in an article entitled "Epiphyseal separations and epiphyseal fractures" [60]. He differentiated five forms of epiphyseal damage: (1) epiphyseal separation without displacement (epiphyseal loosening); (2) chondro-epiphyseal separation with displacement; (3) osteochondroepiphyseal separation (the "osteo" referring to the metaphyseal fragment); (4) epiphyseal fracture; and (5) crush fracture of the diaphysis (metaphysis) with contusion of the epiphyseal junction. The combined epiphyseal, transphyseal, and diaphyseal fractures are illustrated elsewhere in the article. He indicated that prognosis in types 1 and 2 was good, in 3 relatively good and in 4 and 5 often unfavorable.

5.3.1.5 Weber

Weber (1980) attempted to provide a prognostic focus based on the pattern of fracture and mechanism of injury [61]. The various mechanisms of injury had been discussed extensively in the preradiographic era but were much less frequently mentioned when the radiographic appearance of the fracture pattern became the focus of categorization and management. Weber referred to the work of both Steinert and Aitken for his approach. He also subdivided the injuries as (i) epiphyseal separations: occurring in the layer of hypertrophic cells, associated with shear forces, leaving the germinal and proliferating cell layers of the plate intact and having a good prognosis and (ii) epiphyseal fractures: occurring through the articular surface, secondary ossification center, and germinal proliferating cell layers before exiting through the hypertrophic zone or metaphysis, produced by axial compression and bending and having a worse prognosis. Among the epiphyseal separations, Weber included (a) loosening of the epiphyseal plate with or without dislocation and (b) partial separation of the epiphysis together with a metaphyseal fracture fragment. Among the epiphyseal fractures, he included fracture of the epiphysis with extension of the fracture line through the epiphyseal plate and then along the interface between the growth plate and the metaphysis and fracture of the epiphysis with extension of the fracture line through the epiphyseal plate and then through the metaphysis. The lesions associated with epiphyseal separation had a relatively benign fate since the injury was through the layer of hypertrophic or degenerating cartilage cells or within the outer reaches of the zone of primary ossification such that the germinal and proliferating layers of the physis, which were responsible for longitudinal growth, remained intact. Even if a metaphyseal bone segment was displaced with the epiphyseal fragment, there was no growth arrest phenomenon since the physis immediately adjacent to the metaphyseal fragment was not fractured and retained its blood supply. Epiphyseal fracture, however, whether the Aitken Type II or III or the Salter–Harris Type III or IV category had a poorer prognosis since the germinal and proliferating zones of the epiphyseal growth plate cartilage were of necessity damaged. Weber thus felt that "abnormal growth can be predicted on the day of the accident if the injury is sufficiently severe." The mechanism of injury could be deduced from consideration of the pathological anatomy as seen in the radiograph. Separation of the epiphysis was felt to be relatively benign since it was caused by an avulsion or shear force which was relatively harmless in comparison with the compression fracture which crossed the epiphyseal bone and the epiphyseal plate, damaging the crucial cell proliferation region in the process. While there was no ability for the damaged physis to correct itself, many of the sequelae of epiphyseal fractures could subsequently be considered due to transphyseal bone through gaps in the normal epiphyseal growth plate anatomy. Anatomic reduction and rigid internal fixation served to minimize the gap and allow the best opportunity for

normal growth to occur. The purpose of operative treatment was to return the anatomical segments of metaphysis, growth plate cartilage, and epiphyseal bone to their normal relationships with each other.

His classification defined prognosis as being either good, type A, or doubtful, type B, depending on the line of fracture. The good prognosis type A injuries were Aitken Type I or Salter–Harris types I and II and the doubtful prognosis type B injuries were Aitken Type II or III or Salter–Harris types III and IV. Accurate reduction and rigid internal fixation in the type B group were felt to be essential to minimize negative sequelae.

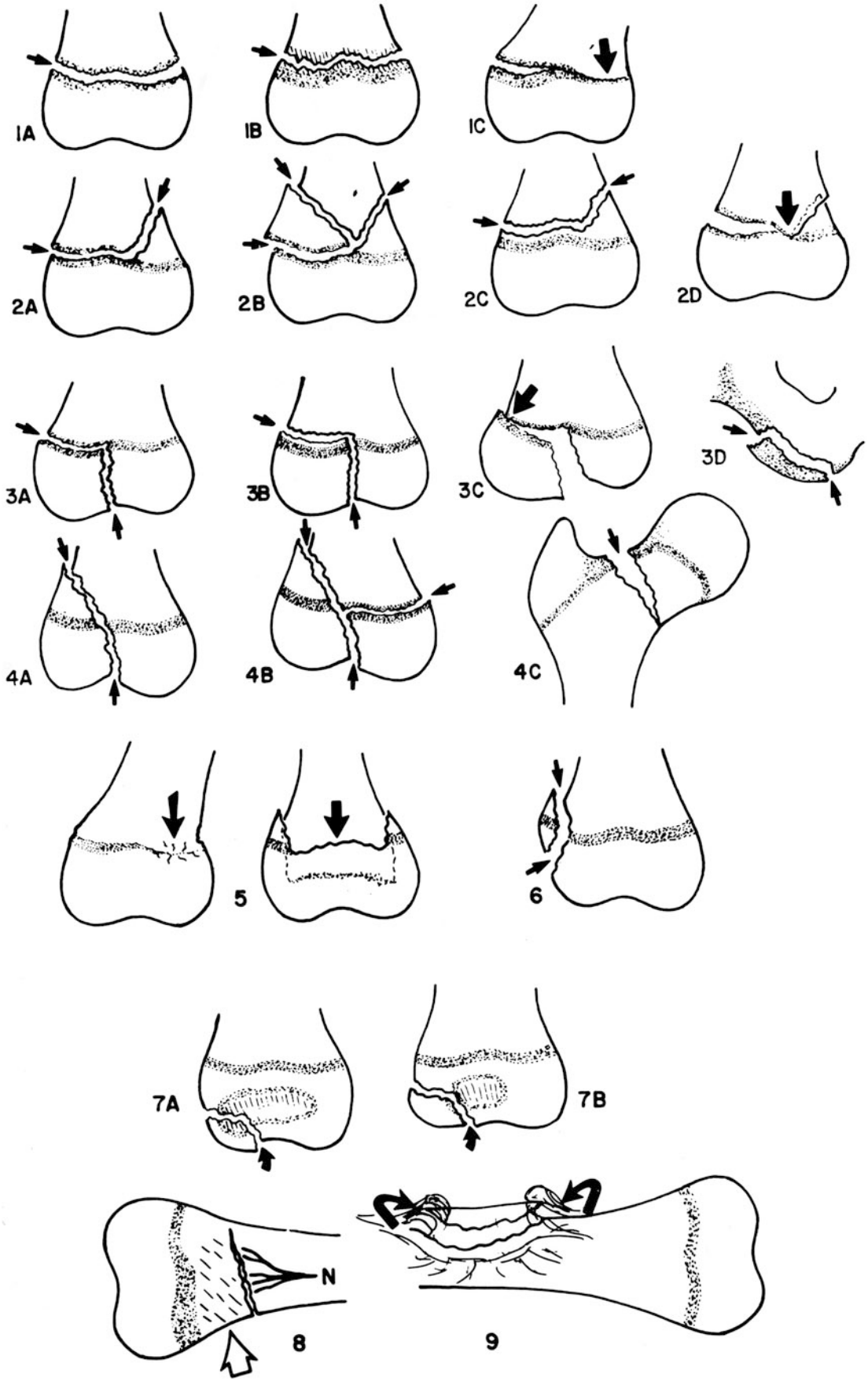
5.3.1.6 Morscher

Morscher also approached the injuries from a mechanistic viewpoint. He made the point that the hallmarks of a good classification are simple, complete and generally applicable [62]. A classification should help to determine the appropriate form of treatment. He felt that neither the Aitken or the Salter–Harris approaches fully satisfied these criteria. Both classifications were felt to be incomplete. The Salter–Harris classification, even though somewhat more extensive than Aitken, was felt to concentrate too much on the distal tibial epiphysis and to leave out other important categories. He included among these types a crush injury of the distal femoral growth plate region with disruption of the femoral origin of the lateral collateral ligament which lead to premature fusion laterally and a resultant genu valgum. He also pointed to the triplane injury of the distal tibia. Morscher also pointed out that neither Aitken nor Salter–Harris paid attention to the mechanism of injury although Aitken did use the mechanistic terms avulsion and compression. He felt that it should be possible to determine the type of lesion and prognosis of an epiphyseal injury from the mechanism causing it. Four factors were felt to be determinants including (1) the direction of the force producing the injury; (2) the size of the force; (3) the mechanical resistance of the epiphyseal cartilage plate; and (4) the mechanical resistance of the adjacent epiphyseal and metaphyseal bone.

Morscher indicated that compression type growth plate injuries were associated with fractures that passed through the bony epiphysis and produced mechanical growth plate damage in particular to the germinal and proliferating cell layers predisposing to growth disturbance. Traction and shear forces on the other hand led to epiphyseal separation tending to the metaphyseal side of the plate in the already degenerating hypertrophic zone and often associated with prognostically unimportant metaphyseal fractures such that only rare growth disturbances occurred. More recent studies, however, have shown that the fracture line in these injuries can deviate into the germinal and proliferating cell layers, thus damaging the active growing cells. He thus divided injuries into epiphyseal fractures (compression mechanism) and epiphyseal separations (traction–shear mechanism) which included the prognostically unimportant metaphyseal fractures. The epiphyseal fractures were always associated with injuries of the germinal zone of the growth plate, whereas epiphyseal separations were concentrated in the nongrowing or hypertrophic parts of the plate. This classification, attributed originally to Steinert, was helpful in terms of management in that "every epiphyseal fracture is "an absolute indication for operative reduction" with "absolute anatomical reduction of the fragments with compression" needed to prevent bony bridge formation between epiphysis and metaphysis and a resultant deformity. The simple epiphyseal fracture—epiphyseal separation distinction allowed a prognostic approach from which treatment could be inferred.

5.3.1.7 Ogden

In the early 1980s, Ogden defined several patterns of fracture presenting nine basic types with 21 subtypes in an effort to relate specific injury patterns to the risk of growth disturbance (Fig. 5.9) [63, 64]. This classification pointed out the greater variability of fracture patterns than described by the more basic Salter–Harris scheme. Types I to VI are the Salter–Harris plus Rang groups with subtypes defining either the transverse level of injury as Foucher described in the 1860s or additional lines of fracture associated with the basic pattern. Type I injury patterns involve three variants. Type Ia has the fracture line propagating across the physeal cartilage; Type Ib across the primary spongiosa with the physeal interface invariably involved; and Type Ic disruption of a localized segment of the physis. Ogden indicates that a large majority of the Type Ib injuries occur in children with systemic disorders affecting the endochondral calcification patterns within the metaphysis such as leukemia and thalassemia. Type II injury patterns involve foursubtypes. Type IIa involves a partial propagation of the injury transversely across the physis with passage of the fracture path into the metaphysis; Type IIb is the same pattern except that the metaphyseal fragment adjacent to the area of physeal fracture is also fractured and free; Type IIc propagation travels transversely across the primary spongiosa and then exit the bone through the metaphysis; and Type IId involves a pattern similar to IIa except that there is localized disruption of the physis at the point of propagation into the metaphysis. Type III is also comprised of four patterns. Type IIIa involves propagation through the physis with subsequent deviation of the fracture line through the ossification center of the epiphysis and out through the articular cartilage; Type IIIb, involves transverse fracture through the primary spongiosa with passage through the physis, secondary ossification center and articular cartilage; Type IIIc involves a crushing injury through the peripheral cartilage followed by exit of the fracture through the epiphysis; and Type IIId is a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nonarticular cartilage fracture, for example, of the ischial tuberosity. Type IV injuries are subdivided into three categories. The Type IVa pattern involves a combined epiphyseal–physeal–metaphyseal fragment; Type IVb involves an epiphyseal–physeal–metaphyseal fragment combined with a Type IIIa or IIIb transverse lesion of the physis; and the Type IVc fracture involves propagation through a nonarticular epiphyseal region, which is the most common intraepiphyseal cartilage of the developing femoral neck. Type V injury patterns involve two variants which are either eccentric disruption of the physis or a telescoping, comminution of the metaphysis into the epiphysis. The Type VI injury involves avulsion or crushing of the periphery of the physis at the groove of Ranvier area. Type VII fractures are intraepiphyseal involving the articular surface analogous to osteochondral fractures but not involving the main physis. The Type VII injuries have two variants. The VIIa pattern involves an osteochondral fragment of the secondary ossification center physis and trabecular bone and the VIIb pattern involves a chondral fragment only passing as deep as the hypertrophic cell layer of the physis of the secondary ossification center. The Type VIII injury is a metaphyseal fracture adjacent to the growth plate (and analogous to Ollier's juxta-epiphyseal lesion) which impacts negatively on the physis by temporarily cutting off the nutrient artery causing ischemia to the metaphyseal segment between the fracture and the physis. Type IX injury involves damage to the periosteum of the diaphysis and adjacent metaphysis with or without bony injury which serves to disrupt the normal periosteal intramembranous ossification growth mechanism. The Ogden classification represents the most extensive presentation of the pathoanatomic approach to categorization.

5.3.1.8 Peterson

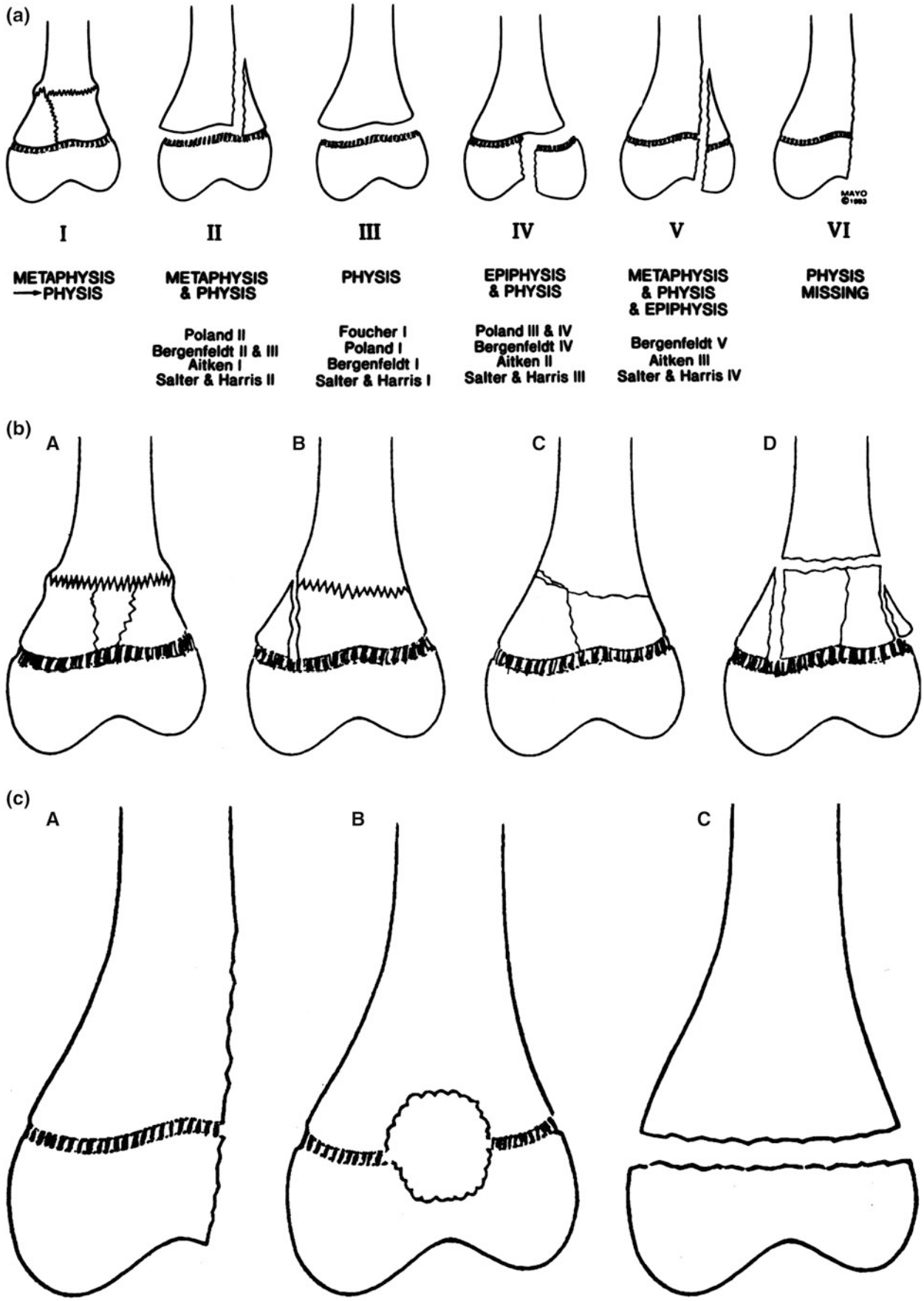
Peterson reviewed physeal fractures and developed a classification encompassing 6 types (Fig. 5.10a–c) [65, 66]. He assessed 951 physeal fractures over a 10-year period from one county in Minnesota. Based on his study, he found that approximately 16 % of the fractures did not fit comfortably into the Salter–Harris classification. Two new fracture types were defined [65]. In his review of fractures, he found no Salter–Harris Type V injuries and therefore did not include them in his classification. Peterson's numerical classification from types I through VI is based on the increasing degree of subsequent physeal damage found such that Type I has the least amount and Type VI the most. Type I fracture refers to transverse metaphyseal fractures which have linear fracture extensions from the metaphysis into the physeal cartilage but do not either pass along or through the physis. He subdivided these into four types (A–D) depending on the number, position, and displacement of the linear fractures passing from the transverse metaphyseal fracture to the physis. Essentially, all of the 16 % of cases which did not fit into the Salter–Harris classification are defined as Peterson Type I injuries. These injuries were concentrated in the distal radius, metacarpals, and finger phalanges which comprised almost 80 % of those found. All were treated nonoperatively with uniformly good result. Type VI physeal fracture refers to major trauma in which part of the physis is missing. These injuries are extremely rare, require an open or compound injury, and are almost always followed by development of transphyseal bars. Peterson's Type II, III, IV, and V patterns are well-recognized components of all the other pathoanatomic classifications. His classification concentrates on physeal injuries but he does point out that some epiphyseal fractures do not involve the physis such as those of the ulnar styloid, distal tibial medial malleolus distal to the physis, tibial spine, osteochondral fractures involving the articular surface and secondary ossification center in several bones and the distal tip of the fibula. Ogden classified some of these injuries in his type VII group.

5.3.2 Mechanistic Considerations

5.3.2.1 Broca

Broca was one of the first to try to relate epiphyseal growth plate fracture-separations to the mechanism of injury and the anatomic structure of the periphyseal ligaments [67, 68]. He defined two possible mechanisms: direct, where the force was applied directly onto the physis; and indirect, where the physis was ruptured by ligamentous traction. When the mechanism of injury was by a direct force, it was irrelevant whether the physeal ligamentous insertions were above or below the physis since physeal separation was not caused by ligamentous traction. The majority of injuries were felt to be caused by the indirect mechanism. An essential anatomic

◀ **Fig. 5.9** Ogden's [63, 64] pathoanatomic classification of growth plate fracture-separations is shown. Types I–V are essentially modifications of the Salter–Harris approach with anatomic variations added showing differences in the level of physeal or periphyseal fracture or the presence of additional fragments making the injuries more complex. The precise level of fracture can have meaningful effects as to whether or not negative growth sequelae occur. The type VI pattern was that described by Rang. The type VII fracture does not involve the physis itself but does involve the epiphysis and is frequently referred to as an osteochondral fracture. The type VIII fracture is metaphyseal and similar to that described by Ollier. This injury too can have negative physeal sequelae. The type IX fracture does not involve either the physis or the epiphysis but is included in growth injuries as it involves the periosteum and subperiosteal cortex. (Reprinted with permission from Ogden J, Skeletal growth mechanism injury patterns. J Pediatr Orthop. 1982;2:371–377. Copyright 1982 Wolters Kluwer Health)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feature of epiphyseal separations caused by the ligamentous traction mechanism was the need for the ligament to insert onto the epiphysis between the articular cartilage and the physis [68]. In other words, the growth plate had to be extracapsular since all intracapsular growth plates had ligamentous attachments beyond the physis at the metaphyseal level. The tearing away of the physis, or the physeal separation, began at the side where the traction force made the ligament tight since the same force tended to relax the ligament on the other side of the bone. A series of anatomic drawings at each major physis accompanied one of his reports [69]. In those regions where ligamentous insertions were exclusively onto the epiphysis, a high number of primary and complete separations occurred with the distal radius, and distal tibia are good examples. Separations caused by ligamentous traction were also common at the distal femur, where the most (although not all) insertions were onto the epiphysis, but relatively rare at the proximal tibia and fibula where most insertions were below the physis. The proximal femoral capital epiphysis was rarely the site of fracture-separation and was characterized anatomically by having no major ligamentous or muscle attachments. Broca also pointed out that in growth plate separations caused by ligamentous traction the periosteum was elevated from the shaft of the bone often for a considerable distance on the side to which the epiphysis was displaced while it was torn on the opposite side.

5.3.2.2 Aitken, Steinert, Weber, and Morscher

Each of the pathoanatomic classifications of Aitken, Steinert, Weber, and Morscher listed in the previous section attempted to incorporate mechanistic features with the implication being that compression injuries had a far greater negative effect on physeal tissue than traction or shear injuries. It is of course difficult to work such dynamic considerations into static radiographic categorizations but efforts to consider and document such mechanisms in some way should ultimately prove beneficial.

5.3.2.3 Carothers and Crenshaw

Carothers and Crenshaw attempted to derive clinical significance from a classification of epiphyseal injuries and concentrated on those at the ankle owing to their frequency and fairly marked differences in outcome [70]. In assessing fractures at the ankle, they recognized that anatomically similar fractures and/or growth plate separations had been caused by predictably similar injuries. They felt that the causative mechanism was crucial for a determination of the end result. For this reason, they categorized their ankle fractures into groups dependent on the mechanism of injury and the position of displacement. Lateral displacement of the distal tibial and fibular epiphyses involved abduction type injuries; posterior displacement of the tibial epiphysis was caused by an external rotation type, a forcible plantar flexion type, axial compression, or direct violence; and medial displacement was seen with adduction injuries. Each of their lateral displacement or abduction injuries involved the entire epiphysis moving as an intact unit with an accompanying lateral metaphyseal fragment (Aitken type I, or S–H type II). There were 20 of these injuries in their series. The results were almost uniformly good with few negative sequelae. External rotation epiphyseal fracture-separations were recognized by a tendency toward a posterior displacement of the tibial epiphysis accompanied by a fracture of the fibula. Deformity was not noted in any of the five patients in this group at long-term follow-up. Even in those cases with imperfect reduction in these groups remodeling occurred well. In those with forced plantar flexion there was posterior displacement of the tibia with a posterior metaphyseal triangular fragment. Long-term growth was good. In the group with posterior displacement due to axial compression and direct violence, there were a few cases but no negative sequelae seen. It was the group with adduction injuries who had the major negative long-term sequelae. There was a marked tendency toward medial displacement of the distal fragments. Second and third degree injuries involved fractures through the tibial epiphysis with first degree injuries having only minimal medial displacement. In those with second and third degree adduction injuries, three of six cases had major negative growth sequelae with deformity due to medial physeal closure and varus ankle tilting and shortening. They concluded that all of the clinically significant deformities resulting from the injuries of the ankle epiphyses were due to the second and third degree adduction fractures. First degree injuries had no negative sequelae. They then invoked mechanistic reasons to explain the long-term prognosis. In external rotation or abduction injuries at the ankle, the deforming force was by a shear mechanism which involved transverse fracture through the relatively weakened hypertrophic region of the physis and into the metaphysis.

◀**Fig. 5.10** The most recent pathoanatomic fracture classification is by Peterson [66]. **a** Categories *I–VI* are illustrated along with regional involvement and corresponding patterns from previous pathoanatomic categorizations. (Reprinted with permission from Peterson H, Physeal fractures: Part 3. Classification. J Pediatr Orthop. 1994;14:431–439. Copyright 1994 Wolters Kluwer Health). **b** Variants of Peterson's type I pattern are shown each of which involves metaphyseal fractures which pass into the physis. **c** The type VI categorization is illustrated in which variable segments of the physeal tissue are missing owing to the severity of the trauma

With the adduction injuries, the medial border of the talus exerted a compressive force through the articular surface and through the tibial epiphysis. They referred to their experimental studies in which the force exerted through a bone in compression is many times greater and thus presumably more destructive than that which can be exerted through shear.

5.3.3 Negative Sequelae of a Growth Plate Fracture-Separation

There are three negative sequelae which can follow a growth plate fracture-separation: (i) shortening of a long bone which occurs due to premature fusion of the growth plate across its entire extent; (ii) angular deformity and some shortening, which occurs due to a localized transphyseal bone bridge which prevents growth in a part of the physis while continuing growth of the rest of the physis leads to angular deformity; and (iii) joint surface irregularity, which occurs with failure of anatomic reduction of fractures involving the articular surface or with central transphyseal bone bridges with continuing growth of the physis peripherally. These are illustrated in Fig. 5.11. The optimal treatment of any growth plate fracture-separation relieves the patient's pain and allows for continuation of normal growth. Treatment is designed to prevent the complications listed, or if they occur, to diagnose them early and minimize their effects by various interventions.

5.4 Pathophysiologic Approaches to Growth Plate Fracture-Separations

5.4.1 Pathophysiologic Classification—Shapiro

5.4.1.1 Conceptual Considerations

A common thread runs through each of the pathoanatomic classifications since the patterns of separation and fracture are defined on the basis of plain radiographic appearances. The articles concerning traumatic separation of the epiphyses show that the various categorizations describe the fracture patterns and provide, in some instances, prognostic indications based on the pathoanatomic pattern of injury [71, 72]. There appeared, however, to have been little conceptual progress made. If one considered the clinical and experimental preradiographic era work of Foucher (1860), Cornil and Coudray (1904), and Poland (1898), and the radiographic era study by Bergenfeldt (1933), all subsequent categorizations were either repetitive or showed differences that were not substantial in nature [4, 16, 26, 27, 73]. This is not surprising since the same method of assessment, the plain radiograph, was being used. An extensive literature review of papers reporting fracture-separations from each of the major epiphyses showed that the pathoanatomic classifications were often lacking in prognostic significance [71]. For example, many Salter–Harris Type II fractures of the distal femur had extremely negative sequelae, whereas the large majority of Type II fractures of the distal radius and proximal humerus had a benign outcome. It was thus evident that several factors other than the pathoanatomic pattern as revealed by plain radiographs played a role in determining the outcome.

This led us to consider a different conceptual approach to growth plate fracture-separations, focusing on events at the cell and tissue levels that are the ultimate determinants of whether growth post-injury will continue normally or be compromised (Tables 5.2 and 5.3). A pathophysiologic approach to growth plate fracture-separations has been outlined that seeks to better define the specific factors leading either to full recovery or growth plate damage [71, 72]. It is important to assess each epiphysis specifically and also to take into consideration such factors as the shape of the epiphysis, the age of the patient, and the force and mechanism of the injury. The approach is designed to superimpose determination of physiologic conditions onto the pathoanatomic categorizations to provide a better prognostic index. The pathophysiologic approach seeks to define whether a growth plate arrest will or will not occur using physiologic indicators as well as relying on inferences from the radiologic patterns and reported results. While the various pathoanatomic systems are valuable in describing the fracture patterns within the limits of resolution of plain radiographs, they do not relate to this specific point. Based on extensive experimental and clinical evidence, there are three basic ways in which a growth plate fracture-separation can lead to negative growth sequelae. These involve: (i) damage to the blood supply on the epiphyseal side, which prevents appropriate chondrocyte proliferation and growth of the plate from occurring; (ii) intermixture of the epiphyseal and metaphyseal circulations, each with their associated osteoprogenitor cells, thus allowing a focal or extensive transphyseal bone bridge to form; and (iii) nonfunctioning or non-physeal soft tissue interposition within the physis blocking the normal endochondral growth progression from the upper reserve zone to the lower hypertrophic zone.

5.4.1.2 Pathophysiologic Classification

A pathophysiologic classification with types A, B_1, B_2, C or D_1, D_2 is described to be used in association with the pathoanatomic classifications (Fig. 5.12) [71, 72]. (Type A) The epiphyseal circulation remains intact and there is no communication between the epiphyseal and metaphyseal circulations such that after healing growth proceeds normally. (Type B) The epiphyseal circulation remains intact,

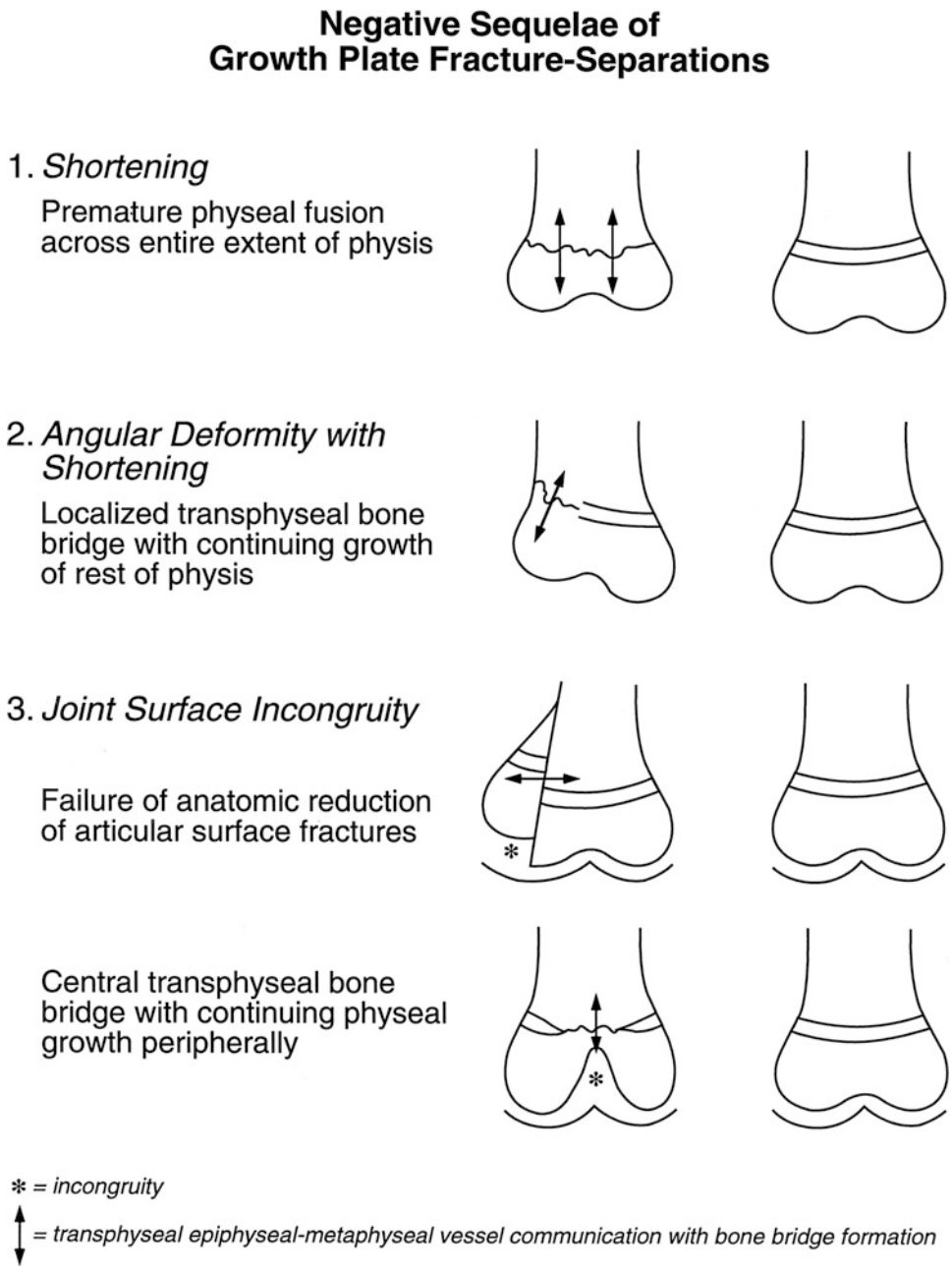


Fig. 5.11 The three types of negative sequelae following a growth plate fracture-separation are illustrated

but there is a communication between the epiphyseal and metaphyseal circulations, with their associated osteoprogenitor cells, allowing a bone bridge to form. This communication can occur on the basis of gross displacement (B_1) or microscopic crushing, fissuring, and longitudinal fracture causing transverse separation of the cartilage plate (B_2). (Type C) The epiphyseal circulation is damaged and the adjacent growth plate cartilage dies. (Type D) There is soft tissue interposition within the physis blocking normal growth even though epiphyseal and metaphyseal circulations are intact and separate. This tissue is either interposed periosteum (D_1) or crushed nonfunctioning physeal cartilage which tends to become fibrous (D_2). Descriptions of these basic types are amplified in Fig. 5.13. By superimposing pathophysiologic considerations on the pathoanatomic type it is felt that better prognostic indices can be obtained that will be helpful in terms of treatment of the initial fracture and appropriate follow-up. The experimental and clinical considerations underlying the pathophysiologic approach are described in Sects. 5.4.2–5.4.5.

Table 5.2 The Salter–Harris (S–H) classification of growth plate fracture-separations and its relation to prognosis

• Proposed in 1963 and still widely used 50 years later; defined types I–V based on the pattern of fracture as seen on plain radiographs; *pathoanatomic approach*
• Types I–IV were widely recognized and described previously by Poland (1898), Bergenfeldt (1933), and Aitken (1936); also referred to as pathoanatomic approaches
• S–H proposed type V caused by longitudinal compressive forces with radiographs noninformative at time of injury but premature physeal fusion subsequently noted. Studies by others found that type V occurred very rarely or was not seen. Rang (1969) modified the S–H classification adding a type VI for peripheral displacement of the perichondrial ring, also referred to separately by Ogden (1981) and Peterson (1994) (both of whom used the I–IV types and expanded upon them in the pathoanatomic mode)
• Weber (1980) and Morscher (1981) stressed the pattern of fracture and the mechanism of injury; *pathomechanical approach;* (i) shear forces—relatively benign and (ii) axial compression forces—poorer prognosis; considerations included: direction of force, size of force, mechanical resistance of growth plate, and mechanical resistance of adjacent epiphyseal and metaphyseal bone
• Shapiro (1982) proposed a *pathophysiologic approach* to growth plate fracture-separations to consider and study injuries at the cell and tissue levels which are the main determinants of the eventual result. The pathophysiologic approach is superimposed on a pathoanatomic or pathomechanical categorization
• As a general rule, the S–H types I and II fractures are considered to have a good/very good prognosis while types III and IV have a much higher likelihood of a fair/poor result and might often need an operative repair to improve prognosis. Type V invariably has a poor result (growth arrest) but is not prognostic, being diagnosed several months–years post-injury only after a growth problem has occurred. Weber and Morscher defined shear fractures as relatively benign and compression fractures which involved epiphyseal–metaphyseal bone as more damaging

Table 5.3 Concepts underlying the pathophysiologic approach to epiphyseal growth plate fracture-separations

1. Negative sequelae following growth plate fracture-separations occur due to (i) damage to the blood supply on the epiphyseal side, and (ii) communication between the normally separate epiphyseal vessels with their associated osteoprogenitor cells and the metaphyseal vessels with their associated osteoprogenitor cells allowing a transphyseal bone bridge to form	
2. Pathoanatomic classifications are based on the pathway of breakage as determined radiologically. The pathophysiologic classification is based on the state of the epiphyseal blood supply and the presence or absence of epiphyseal–metaphyseal vessel communication	
3. By superimposing the pathophysiologic classification on the pathoanatomic classifications, such injuries can be considered on the basis of the cellular and tissue events that are the main determinants of the end results	
4. Use of the pathophysiologic approach	
(i) Knowledge of growth plate anatomy, blood supply leads to expectation of which\injuries might produce problems	
(ii) Knowledge of reported results of injuries at each epiphysis provides a good awareness of possible problem situations	
(iii) Demonstration at time of injury and/or after reduction of epiphyseal vascularity, epiphyseal–metaphyseal vessel communication in those lesions with a likelihood of growth arrest problems	
5. Pathophysiologic classification	
Type A	The epiphyseal circulation remains intact and there is no communication between the epiphyseal and metaphyseal circulations
Type B	The epiphyseal circulation remains intact, but there is communication between the epiphyseal and metaphyseal circulations, with their associated osteoprogenitor cells, allowing a bone bridge to form. This communication can occur on the basis of gross displacement (B1) or gross microscopic crushing, fissuring, and transverse separation of the cartilage plate (B2)
Type C	The epiphyseal circulation is destroyed and the growth plate cartilage dies
Type D	The epiphyseal circulation remains intact, but there is an abnormal presence of fibrous tissue within the physis. There is either interposition of a periosteal fibrous tissue flap between the physeal fragments (D_1) or localized damage to growth plate chondrocytes in germinal and proliferating zones by mechanical crushing with replacement by fibrous tissue formation between epiphyseal and metaphyseal regions (D_2)

5.4.2 Experimental Approaches to Growth Plate Structure, Blood Supply, and Function in Relation to Growth Plate Fracture-Separations

The anatomy of the growth plate including its surrounding periosteal–perichondrial sheath and blood supply have been described extensively in Chap. 1. Important features in relation to growth plate fracture-separations are reviewed here.

5.4.2.1 Growth Plate Relation to Capsule

The position of the epiphyseal growth plate in relation to the joint capsule, and the associated variations in blood supply that occur due to such positions, have long been considered to have prognostic significance following injury. Those epiphyses that are entirely intracapsular and completely covered by articular cartilage (proximal femoral capital and proximal radial) are more likely to suffer damage in association with fracture-separation because of their vulnerable blood supply. The articular cartilage covers the epiphysis completely passing almost to the level of the physeal cartilage such that vessels enter the epiphysis through a narrow rim of space between the articular and physeal cartilage. Completely extracapsular epiphyses are less vulnerable to complete devascularization following injury, since they obtain their blood supply via vessels that penetrate the side walls of the epiphyses at numerous sites

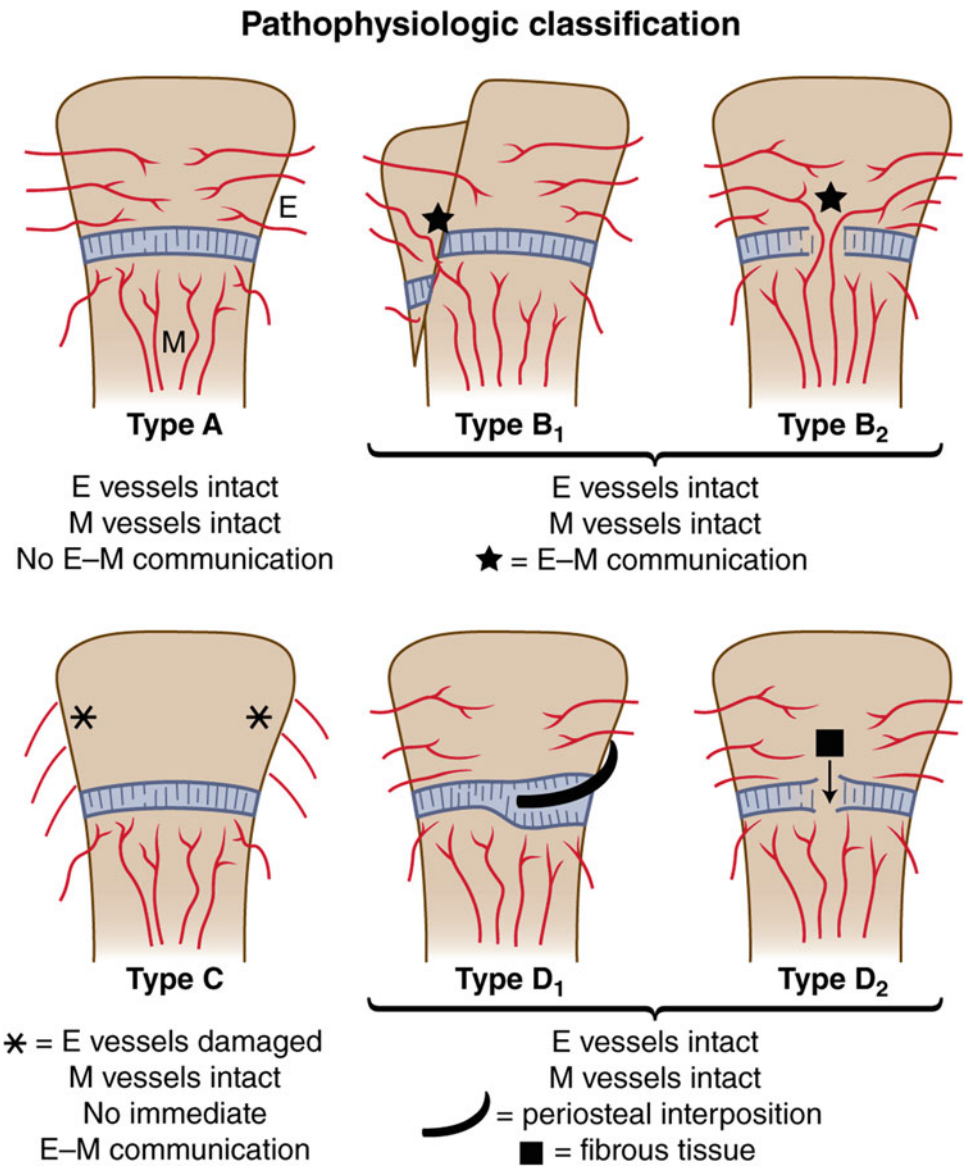


Fig. 5.12 The pathophysiologic approach is defined here. The original description was published using types *A*, B_1, B_2, and *C* [71, 72]. This categorization has now been expanded to include types D_1 and D_2 for greater accuracy. In *type A*, there are no negative growth sequelae as the epiphyseal vascular supply remains intact and there is no communication between epiphyseal and metaphyseal vessels. In *type B*, epiphyseal and metaphyseal vessel communication in association with their osteoprogenitor cells occurs allowing a transphyseal bone bridge to form. In the B_1 *type* with gross displacement, epiphyseal bone rests adjacent to metaphyseal bone. In the B_2 *type*, the growth plate suffers crushing and fissuring allowing longitudinal fractures to occur that lead to transphyseal vessel interaction between epiphyseal bone and metaphyseal bone. This occurrence is not evident by plain radiographs and accounts for many growth arrest problems after seemingly benign separations. *Type C* injuries significantly disturb the epiphyseal blood supply thus rendering all or part of the growth plate nonviable. Bone bridge formation occurs secondarily with vascular invasion of the nonfunctioning growth plate cartilage from the metaphyseal side and eventual linkage of epiphyseal and metaphyseal vessels. *Type D* injuries involve additional soft tissue damage. *Type* D_1 is present when there is interposition of a periosteal flap at the fracture site. This should be removed to allow the physeal cartilage to heal either with adjacent physeal cartilage or metaphyseal bone (depending on the level of the physeal fracture). *Type* D_2 describes transphyseal fibrous tissue repair rather than repair with cartilage or (more commonly) transphyseal bone. Even a fibrous interposition can limit growth and subsequently turn into bone

around the entire circumference. There is considerable space between the articular and physeal cartilage through which abundant numbers of vessels can pass. The extracapsular growth plates are at the distal radius, the proximal and distal ulna, the proximal and distal tibia, the proximal and distal fibula and all epiphyses of the metacarpals, metatarsals and phalanges. The proximal humeral epiphysis is partially intracapsular (medial part) and partially extracapsular. Those of the distal humerus and distal femur are also partially intracapsular, but primarily extracapsular. The distal femoral

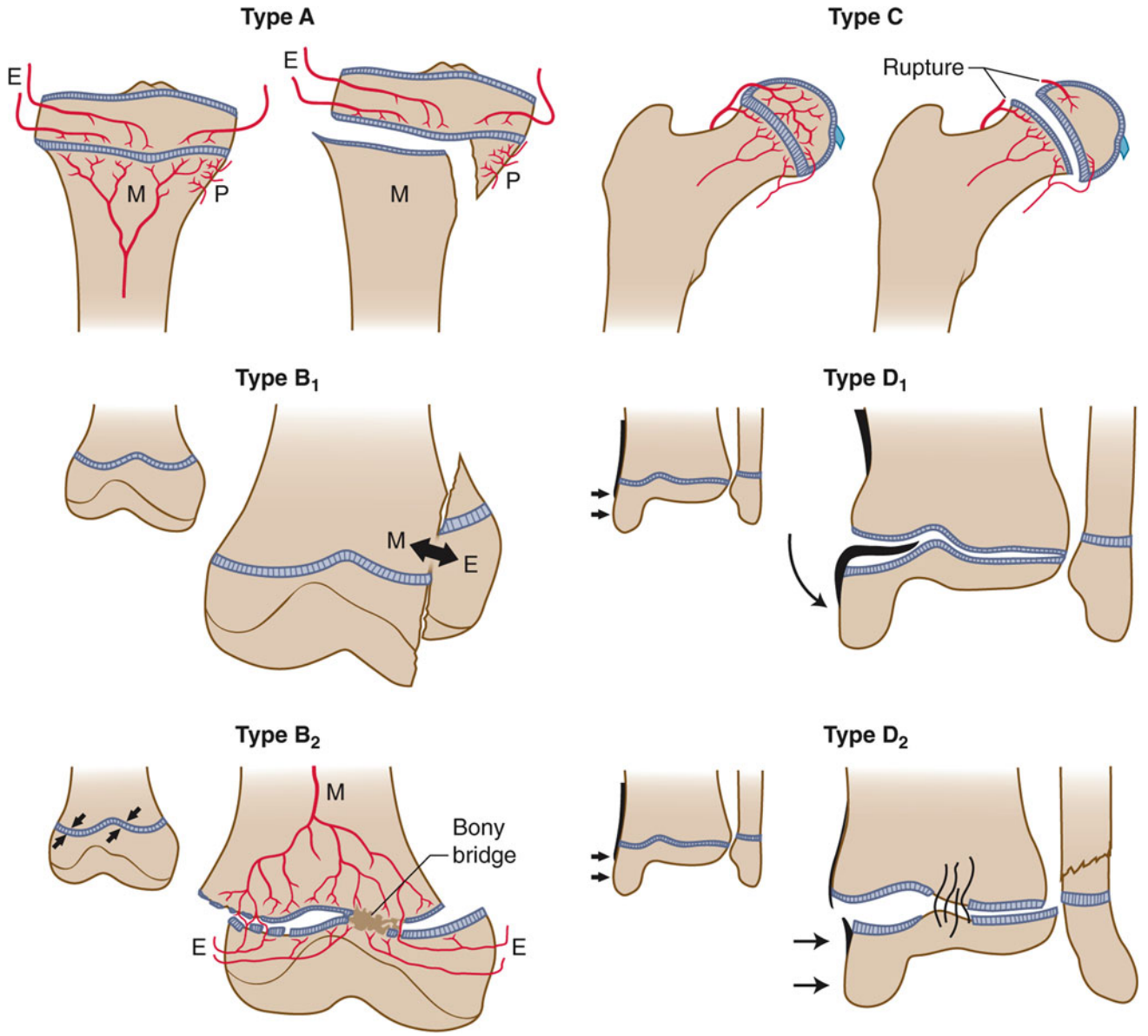


Fig. 5.13 Pathophysiologic fracture types are illustrated. *Type A* fracture of the proximal tibia shows the intact epiphyseal blood supply (E) and a fracture line within the growth plate cartilage that still allows for separation of epiphyseal and metaphyseal vessels. *M* metaphysis; *P* periosteal vessels. *Type* B_1 fracture is shown. Without reduction by closed or preferably open methods, bone bridge formation between epiphyseal (*E*) and metaphyseal (*M*) bone will occur rapidly. A B_2 fracture pattern is shown in which crushing and fissuring of the growth plate allow for transverse separation of the physeal cartilage and longitudinal communication between blood vessels and osteoprogenitor cells of epiphyseal and metaphyseal bone. The *type C* fracture pattern is most clearly illustrated at the proximal femur owing to the tenuous blood supply of this intracapsular epiphysis. The *type* D_1 fracture with interposition of a periosteal flap is seen most often at the distal medial tibia with a type II fracture-separation. A *type* D_2 fracture is characterized by a fibrous transphyseal repair due to cartilage damage, localized avascularity, and motion

epiphysis in particular has a rich circulation penetrating its sidewalls, which are not covered by articular cartilage.

5.4.2.2 Extrinsic Patterns of Epiphyseal Blood Supply

Dale and Harris defined two basic patterns of blood supply to epiphyses [74]. In Type A, the epiphysis is intracapsular and entirely covered by articular cartilage and in type B the epiphysis is extracapsular and only partly covered by articular cartilage. When entirely covered by articular cartilage, the blood supply enters in a vulnerable narrow zone peripherally between the articular cartilage and perichondrium surrounding the growth plate. When the epiphysis is only partly covered by articular cartilage, vessels enter

through the circumferential borders of the epiphysis between the widely separated articular and physeal cartilage allowing for an area of supply that is much larger and thus less vulnerable to extensive damage with trauma.

5.4.2.3 Normal Intrinsic Epiphyseal and Metaphyseal Blood Supply

Trueta and Morgan re-emphasized the dual and separate nature of growth plate blood supply and the fact that the epiphyseal plate itself, with rare exceptions, has no vessels within it [75]. There is a strict separation of the epiphyseal circulation from the metaphyseal circulation. The epiphyseal vessels supply the epiphyseal cartilage, the bone of the secondary ossification center and, by diffusion, the germinal, proliferating, and upper hypertrophic cell layers of the epiphyseal growth plate, which are responsible for growth in the length of the bone. The metaphyseal vessels, most of which are terminal ramifications of the nutrient artery and of the metaphyseal arteries, pass into the lower regions of the hypertrophic cell layer of the growth plate accompanied by osteoprogenitor cells which lay down bone on the calcified cartilage cores. Osteoprogenitor cells are present in intimate association with epiphyseal and metaphyseal capillaries such that bone formation occurs in a richly vascularized environment. The state of these two separate circulations post-trauma plays a major role in determining whether normal physeal-mediated growth will continue or not.

5.4.2.4 Growth Plate Stability

The growth plate has both intrinsic and extrinsic supports. The columns of cartilage of epiphyseal origin and the bone trabeculae of metaphyseal origin that interdigitate with them provide intrinsic support. When the undersurface of the cartilage plate is examined carefully following a Type I or Type II fracture-separation, undulations are seen, which are referred to as mammillary processes. The processes are in essence artifactual, being seen only after fracture-separation has occurred, but they are accurate gross reflections of the histologic cartilage–bone relationships and the slight varying levels at which they occur. Extrinsic support is provided by the cells and tissues of the circumferential perichondrial ossification groove of Ranvier [76–78]. The circumferential sleeve, which is continuous with the periosteum, completely ensheathes the growth plate, attaching into the epiphyseal cartilage beyond the plate. The supportive function of the periosteal–perichondrial sheath has been well documented and provides the large majority of supportive force. Wilson commented in 1820 that the periosteum "strengthened the junction of the epiphysis to the body of the bone" [9]. Relatively greater involution of the sleeve in relation to the epiphyseal growth plate in early adolescence (10–15 years of age) may explain, partially, the higher incidence of growth plate fracture-separation in this time period.

5.4.2.5 Growth Plate Shape

An important factor affecting prognosis following growth plate fracture-separation is the shape of the growth plate (Table 5.4). Not all plates lie in a plane transverse to the long axis of the bone. In those physes which are nonlinear, the irregular shape becomes greater after the first few years of age. The distal femoral and proximal humeral plates in particular have irregular shapes, while those of the proximal and distal tibia have less marked, but consistent irregularities. Thus, at certain epiphyses with Type I, and in particular Type II, fracture-separations the epiphysis and the epiphyseal growth plate do not invariably slide off the metaphyseal fragment along a transverse or gently curvilinear plane. The irregular shapes are often the sites of cartilage crushing and later transphyseal bone bridge formation.

Table 5.4 Epiphyseal growth plate shape

1. *Proximal humerus* From birth to 3 years of age, the plate is slightly curved, concave toward the metaphysis. Once the three ossification centers of the proximal humerus have fused, anteroposterior radiographs demonstrate an inverted V shape to the plate. The epiphysis interdigitates with the metaphysis in a trough-like fashion along the anteroposterior axis
2. *Distal humerus* The plate approaches the transverse plane in the anteroposterior projection. It is somewhat more curved in its lateral projection. In both projections, the concavity is toward the metaphysis. The metaphysis relates to the epiphysis as a cylinder with its long axis in the coronal plane
3. *Proximal radius* The plate approaches the transverse plane in all projections. There is a slight concavity to the plate which relates to the gentle dome-shaped metaphysis
4. *Distal radius* The plate closely approaches the transverse plane in all projections. There is slight concavity relating to a dome-shaped distal radial metaphysis
5. *Proximal femur* From birth to approximately 6 years of age, the plate approaches the transverse plane in all projections. From 6 years onward, there is a gentle dome-shape to the femoral neck metaphysis with the concavity of the epiphyseal plate towards the neck
6. *Distal femur* The growth plate of the distal femur has an irregular shape. From birth to skeletal maturity in the anteroposterior projection, there is a double concave shape toward the metaphysis. From 8 years onward, the depth of the concavity is relatively greater. On the lateral projection from birth to approximately 7 years of age, the epiphyseal growth plate projects in a transverse plane; during the next few years a slight double concave curve can be noted; and over the final few years, a U-shaped growth plate concave to the metaphysis is seen
7. *Proximal tibia* From birth to approximately 2 years of age in the anteroposterior projection, the plate is slightly curved, concave toward the metaphysis. Over the next several years, the plate approaches the true transverse plane but again toward the end of growth a slight double concavity is seen. In the lateral projection from birth to approximately 13 years in the male and approximately 10 years in the female, the plate level appears although it is continuous with the apophyseal tibial tubercle plate anteriorly and

(continued)

Table 5.4 (continued)

curves inferiorly at a sharp angle. This becomes readily apparent when anterior ossification commences
8. *Distal tibia* The plate is transverse in the anteroposterior projection except for slight proximal displacement in the medial third. The lateral projection shows a gentle curvature of the plate convex toward the metaphysis. The distal tibial epiphysis relates to the metaphysis as a cylinder with the long axis in the coronal plane
9. *Proximal fibula* The plate approaches the transverse plane in all projections
10. *Distal fibula* The plate approaches the transverse plane in all projections

5.4.2.6 Damage to Blood Supply and Its Effects on Growth

Experimental interruption of the epiphyseal blood supply causes cessation of growth in the adjacent physis with the amount of growth plate damage proportional to the extent of epiphyseal devascularization [79]. In localized areas, the damaged chondrocyte regions are soon invaded by metaphyseal vessels with their associated osteoprogenitor cells, such that a localized bone bridge forms between the metaphysis and the epiphysis. When massive epiphyseal blood vessel damage occurs there is an accompanying large area of physeal necrosis with metaphyseal vessel and bone cell invasion from the metaphysis leading to premature complete growth plate bone fusion. It is noted that "if the 2 circulations could be kept apart no bridging occurred" [79].

Gomes et al. produced growth plate fracture-separations in 112 rats [80]. Microangiograms showed the normal dual blood supply of the physis with separate epiphyseal and metaphyseal vessels and an avascular physis. Sequelae of several type III and IV fractures were bone bridges shown by microangiographic illustrations of transphyseal vascular communication.

Haas performed extensive studies on the dog growth plate to assess the relation of the blood supply to the longitudinal growth of bone, the localization of the growing point in the epiphyseal growth plate and changes produced in the growing bone after injury to the epiphyseal growth plate [81–84]. These extensive studies both confirmed aspects known previously and added a bulk of new information more precise in detail. His earliest studies demonstrated that "the longitudinal growth of bone is directly dependent upon the integrity of the vascular supply to the epiphysis" [81, 82].

He performed a detailed assessment of the dog metacarpal and metatarsal blood supply in particular concentrating on the epiphyseal region. He noted a particularly rich blood supply in the peri-epiphyseal region. His growth studies were aided by the fact that in the dog, and also human, metacarpals, and metatarsals there was only one epiphyseal growth plate situated distally in the second, third, fourth, and fifth bones. In his initial experiment on the relation of blood supply to the longitudinal growth of bone, he ligated vessels in varying patterns and varying regions of the metacarpals and metatarsals and also cut tissue in specific regions to note the subsequent effect on growth. He concluded that there was no disturbance in growth following an incision through the soft tissue to the level of but not through the periosteum. He also concluded that there was no disturbance of growth when the incision down to the bones also included separation of the overlying tissues. When, however, the entire blood supply to the epiphyseal end of the bone was destroyed by cutting tissues around the entire epiphyseal end of the metacarpal or metatarsal bones, there was an appreciable loss of growth in the bone. When damage was even greater by cutting tissues around the entire distal two-thirds of the metacarpal or metatarsal, there was destruction of both the epiphyseal blood supply and the nutrient artery; there was an even greater disturbance in growth than when only the tissues about the immediate epiphysis were separated. In some of the latter experiments, there was a complete cessation of growth. In another group of experiments, he sought to determine the effect of length growth when the nutrient artery alone was destroyed following cutting of tissue about the region of the metacarpal or metatarsal bone where the nutrient artery entered. The disturbances in growth noted were very small in every case which he interpreted as showing that "diaphyseal or nutrient blood supply is not so important a fact to the length producing property as is the epiphyseal blood supply." He concluded that destruction of the entire blood supply to the epiphyseal end of the metatarsal or metacarpal bone resulted in a marked lessening of its longitudinal growth, even though the nutrient artery remained intact. Conversely, when the nutrient artery was destroyed, there was practically no disturbance in growth length providing the epiphyseal blood supply remained intact. His evident conclusion was that maintenance of the normal longitudinal growth of bone is dependent upon a sufficient blood supply to the region of the epiphyseal cartilage plate.

5.4.2.7 Direct Damage to Physeal Cartilage and Surrounding Regions and Its Effect on Growth

Haas extended his studies to assess the particular part of the epiphyseal growth plate which was most important in the production of growth in length [84]. He summarized well the work of Vogt who reported on experiments from goats and lambs dealing with injury to the epiphyseal cartilage plate. Both Vogt and Haas found that the greatest disturbance in growth took place after injury to the epiphyseal growth plate. Jahn also performed growth plate experiments using rabbits

from 12 days to 4 weeks of age [85]. He noted that simple separation of the growth plate was without effect on growth although excision of the complete cartilage resulted in complete cessation of growth. Injury to the secondary ossification center did not affect longitudinal growth. Jahn felt that the most important part of the epiphyseal cartilage plate in relation to growth was that part of the proliferating cell zone at the beginning of cell columns on the epiphyseal side. Retzius and Leser also concluded from their studies of the cell changes in the epiphyseal cartilage plate that cell proliferation and turnover was greatest in the upper parts of the cartilage columns and that the mitoses continued to decrease as one approached the calcification line [83, 86]. It became evident that focalization of maximal growth and thus maximal damage to growth was in the uppermost parts of the epiphyseal cartilage plate in the proliferating cell regions.

Haas injured the distal metacarpal and metatarsal plates following which histologic sections were performed. The natural line of cleavage between the epiphysis and the metaphysis occurred at the hypertrophic cell region of the growth plate which he referred to as the region of "large vesicular cells" [83]. It was evident that the epiphyseal cartilage plate remained almost exclusively with the epiphyseal fragment in these separations. Once he was able to demonstrate that the separation through the hypertrophic or vesicular cell layers was seen quite commonly then localization of points of damage could be more readily performed. His varying excisions therefore were performed after gentle separation of the cartilage plate. Since the physeal line was quite uniform in these epiphyses, virtually all of these separations were of Type I or Type II category with the transverse line of separation through the hypertrophic zone. After removing a section from the metaphyseal region of growing bones, he concluded that "the metaphyseal region appears to play but little part in the direct lengthening of the bone." In a study of growth effects following simple separation of the cartilage plate, Haas concluded that there was "a definite hindrance to growth" such that the amount of disturbance was dependent upon the amount to injury to the epiphyseal cartilage plate. In clinical practice, however, many growth plate fracture-separations, even with extensive displacement, are not invariably followed by growth damage.

In the next subgroup of experiments, he excised the epiphyseal cartilage plate and noted only a limited amount of further growth concluding, therefore, that the chief growing function was located in the epiphysis. He concluded, in agreement with others, that the greatest growth activity was located in the columns of cartilage as distinct from the hypertrophic regions. He was thus able to localize growth to the epiphyseal cartilage region. In his various subsets, greatest growth damage occurred with excision of epiphyseal cartilage plate and metaphysis with in decreasing order growth affected by excision of the entire epiphyseal cartilage plate, incision through cartilage at the junction of the epiphysis and metaphysis, separation in the natural line of cleavage between epiphysis and metaphysis, and least growth disturbance occurring with excision of a metaphyseal segment alone. He was thus able to conclude that "the most active and important elements necessary for longitudinal growth are located in the columns of cartilage of the epiphyseal plate" [83].

In his next series of studies, Haas produced damage to the growth plate and growth plate region and then sought to assess the effects on longitudinal growth [84]. Haas established from his previous studies that proper functioning of the cartilage plate required an adequate blood supply, that all growth in length was mediated through the epiphyseal growth plate, that the greatest growth activity was localized in the cartilage columns of the epiphyseal cartilage plate, and that the metaphyseal cartilage (by which is meant the persisting cores of calcified cartilage from the endochondral sequence) related to transformation of cartilage to bone rather than growth itself. It was the vessels on the epiphyseal side that contributed to longitudinal growth with the nutrient artery not involved in growth. He then sought to define which injuries to the growth plate lead to negative growth sequelae and which did not.

Bidder had shown in a series of experiments on rabbits that injuries in the periphyseal area caused growth arrest only when the cartilage itself was injured after which time the epiphyseal cartilage plate was either degenerated or entirely missing with tissue substitution by bone trabeculae which directly connected the diaphysis and the epiphysis [24]. Helferich removed the entire cartilage plate from a distal end of the ulna in rabbits and got complete cessation of growth. Many additional studies were performed with the general conclusion being that in some instances, growth arrest occurred following damage to the epiphyseal growth plate while in others it did not. It was becoming apparent that an important point to know was the exact position of the physeal cut as variation in position gave variation in results. Haas' work was performed on the epiphyseal growth plates in young dogs or cats from 6 to 8 weeks of age. The lesions involved cross incisions, longitudinal incisions, cross incisions with elevation of the distal segment, longitudinal incisions with removal of the lateral half of the growth plate, cross incisions with removal of the entire distal segment, and cross incisions with removal of the proximal nonepiphyseal growth plate segment. There was only a very slight, if any, disturbance in growth following a transverse incision across the epiphysis (by which is meant the secondary ossification center). When the transverse incision was made through the epiphyseal cartilage plate, in each instance there was a definite disturbance in growth. In the next group, an incision was made through the periosteum around the growth plate

dorsally and laterally after which pressure was made upon the head of the bone. This caused the epiphysis to separate uniformly in the region of the large vesicular or hypertrophic cells of the columns of cartilage. In many instances, there was no subsequent loss of growth. Incisions through the metaphysis did not cause any disturbance in length. In terms of the transverse incisions, it was really only the incisions through the epiphyseal plate which caused a considerable loss of growth.

Longitudinal incisions through the distal portion of the bone including the epiphyseal cartilage plate, the epiphyseal bone, and the articular cartilage, in his work, did not produce growth problems. This would conflict with current views if there was any displacement of adjacent fragments following injury.

When there was a transverse incision through the secondary ossification center, and then displacement of the distal fragment, there was practically no disturbance in growth, unless the incision line had wandered into the epiphyseal cartilage plate. When the transverse incision was through the epiphyseal cartilage plate followed by raising or displacement of the distal segment, in every instance there was a marked loss in growth but not a complete cessation. Any remaining growth was attributed to the persisting cartilage. When the transverse incision was made through the metaphysis just adjacent to the growth plate and the segment was then elevated and displaced, in practical for every instance there was a complete loss of growth. When longitudinal incisions were made through the epiphysis including the epiphyseal growth plate and part of the metaphysis with removal of the segment, in each instance there was a definite decrease in the length of the bone. The length discrepancy increased with time. There was also a growth disturbance with excision of one lateral half of the epiphysis and metaphysis. When a longitudinal half of the entire bone was removed, a complete cessation of growth occurred. A transverse incision with removal of the distal fragment through the secondary ossification center showed practically no disturbance in growth or structure of the epiphyseal cartilage plate. Removal of the entire epiphysis transversely up to the metaphysis lead to a failure in growth in length. The transverse incision through the metaphysis and diaphysis with removal of the distal fragment was not definitive.

Haas also drilled directly into the epiphyseal secondary ossification center and curetted out a portion of the cancellous bone. There was no hindrance of growth. When, however, the drilling went into the epiphysis and through the epiphyseal cartilage plate, there was a decided hindrance in growth of the bone following the removal of a portion of the epiphyseal cartilage plate from within. This shows that even with an adequate blood supply, there will be a loss in growth if the epiphyseal cartilage plate is injured. If a hole was bored into the metaphysis and the cancellous bone of the epiphysis was removed from within by means of a hole made through the epiphyseal cartilage plate, there was a loss of growth in almost every instance. This was due to injury of the important cells of the epiphyseal cartilage plate.

Haas concluded that "the nearer the injury comes to the cartilage columns, the greater the growth disturbance" and "that there is a relation between the degree of destruction of the cartilage columns and loss of growth." It was these two factors along with disturbances in blood supply which formed the important principles governing epiphyseal bone growth. The overall conclusions from his massive study were that "the result of any injury to the epiphyseal cartilage plate is dependent upon the degree of closeness of the injury to the columns of cartilage and to the amount of destruction of the direct blood supply to the region of the epiphyseal cartilage plate" [84].

5.4.2.8 Pathway of Fracture Line Through Varying Levels of Physeal Cartilage

The issue of the fracture pathway through the cartilage growth plate which so intrigued late nineteenth century investigators has received renewed attention over the past few decades. Histologic sections made in our laboratory in rabbit models show the variable levels within the physis and adjacent metaphysis where transverse separation can occur (Fig. 5.14a–f) [72]. Brashear (1959) studied histologic responses in the rat to Aitken Type I (Salter–Harris Type II) distal femoral growth plate fractures created manually by varus deformation [87]. This resulted in distraction on the lateral side of the plate and compression on the medial side. He noted growth disturbances in several animals as the fracture line involved not only the hypertrophic zone, but, particularly in the central apical area, frequently passed through all layers of the cartilage due to the "grinding of the metaphyseal bone into the epiphyseal plate." Examples of physeal bone bridge formation were illustrated. He thus demonstrated that not all Aitken Type I (or Salter–Harris Type II) injuries had a benign prognosis, noting that "the configuration of a particular portion of the epiphyseal plate… may make this part more susceptible to injury."

Where distracting forces were involved (on the lateral growth plate area in this model), the fracture occurred in the zone of hypertrophic cells. Compression resulted in a fracture medially through the metaphyseal trabeculae. A combination of shearing and compression, however, appeared to result in a grinding of the metaphyseal bone into the epiphyseal plate damaging all layers of cells and predisposing to transphyseal bone bridge formation. The configuration of the distal femoral growth plate with its central apical deviation from the linear plane made this part highly susceptible to injury. He also concluded that the level of injury to the epiphyseal plate determined the healing process and the presence or absence of subsequent growth.

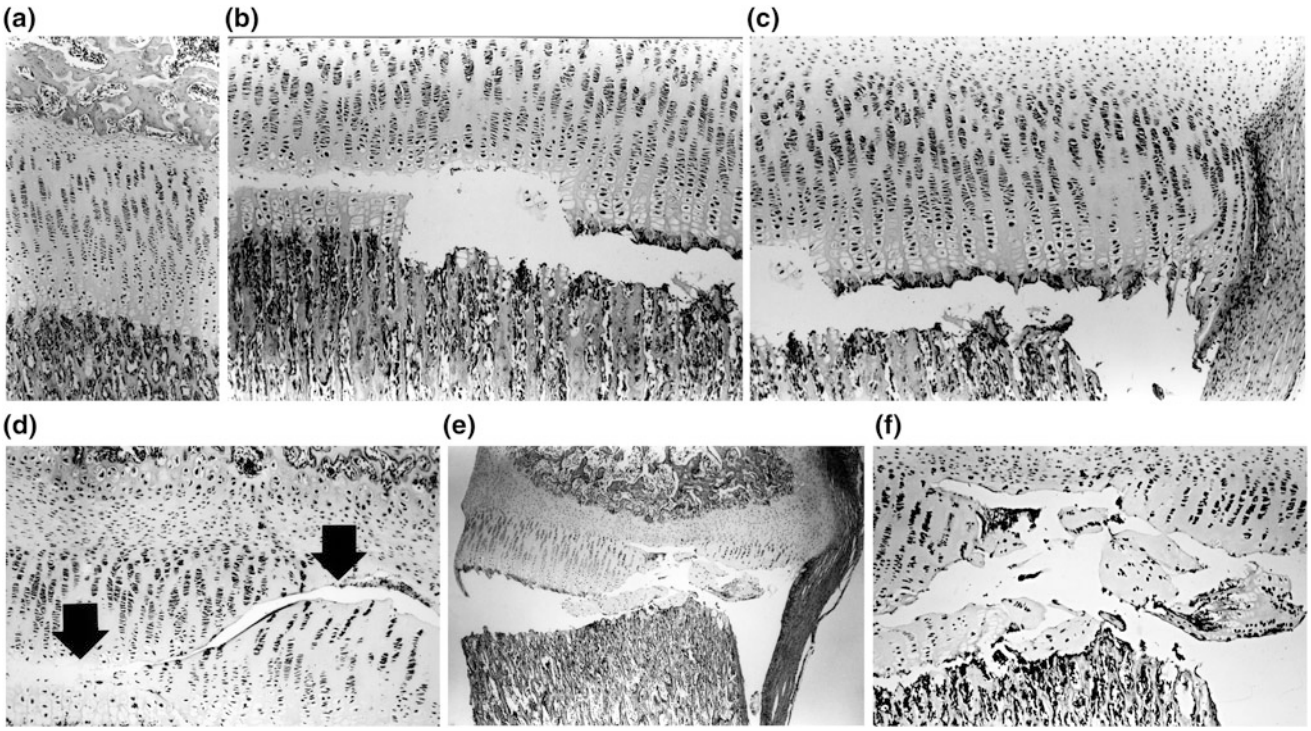


Fig. 5.14 Photomicrographs of histologic sections demonstrate the variable levels of fracture that can occur within the epiphyseal growth plate. The fracture-separations were produced by upward manual pressure against the volar surface of the distal metatarsal epiphysis in 2-month-old New Zealand white rabbits immediately post-sacrifice. The fracture patterns were either Salter–Harris type I or type II. **a** Section of normal growth plate is shown with epiphyseal bone above and metaphyseal bone below. The layers of the growth plate are seen clearly comprising the germinal or resting zone, the proliferating or columnar zone, and the hypertrophic zone. **b** Example of a Salter–Harris I fracture (as it would be described radiographically) shows the differing levels of separation at *left* and *right* that can occur within the same growth plate. **c** A higher power view of B (*left* side) shows the fracture line passing through the zone of hypertrophic chondrocytes. A higher power view of B (*right side*) illustrates the fracture line just within the metaphyseal bone below the hypertrophic zone. **d** Part of the growth plate in another animal shows the fracture line (*arrows*) passing through the hypertrophic zone at *left* but deviating into the zone of proliferating cells and the lower part of the germinal zone at *right*. **e** Photomicrograph of another type I Salter–Harris fracture shows at left a few spicules of bone present indicating the fracture line just below the hypertrophic zone while at right there has been considerable crushing and fissuring of the growth plate within the resting, proliferating, and hypertrophic zones. **f** Higher power view of right side of (**e**) shows how extensive crushing and fissuring of cartilage can occur. Although this fracture and one solely through the hypertrophic zone, would both appear as type I S–H injuries on plain radiographs, it is not surprising that complications due to mechanical damage might be higher in injuries like the one shown here. The multifragmented physeal cartilage injury seen in (**e**) and (**f**) has a high likelihood of evolving into a focal fibrous repair of the D_2 pattern (Reprinted from Ref. [72])

Variable fracture paths through all levels of the growth plate have been demonstrated by Bright et al. in a rat model even though all fractures appeared to be Salter–Harris Type I [88]. There were different patterns of failure with different modes of loading. In only 15 % of cases was the fracture line propagated uniformly through the hypertrophic zone while in 85 % the crack passed at least partially through the proliferating or germinal cell layers.

Peltonen et al. studied the effects of torsional force on segments of bone comprising epiphyseal and metaphyseal bones and the intervening physis. In vitro studies using cadaveric adolescent sheep proximal tibias demonstrated the physeal fracture line to be through the hypertrophic chondrocyte layer in younger animals but fracture in a more undulating pattern with metaphyseal bone involvement in those older [89].

Morscher et al. applied traction force in vitro to the proximal tibial epiphysis of rats at varying ages and after growth with varying levels of circulating hormones. The tensile force was applied through the cruciate ligaments following removal of surrounding soft tissues including the periosteum. In a carefully controlled environment and using a linear growth plate as a model fracture occurred at the weakest point which was always the lower part of the hypertrophic zone within the mineralized component [90].

A biomechanical and histologic study by Moen and Pelker assessed the pattern of growth plate failure when the direction of stress was varied [91]. They assessed 1 cm × 1 cm × 3 cm central cores of physeal cartilage, which contained none of the surrounding perichondrial tissues, from the proximal and distal femur and proximal tibia of immature cows. Their results showed that the histologic failure

pattern varied with each type of applied load. All of the specimens tested in compression failed through the zone of calcification and the distal metaphysis when loaded to the yield point. In this group, there is no evidence for failure of the specimens in the germinal zones. In tension, the majority of the specimens failed in the level of the upper zone of columnization (or proliferation) with the other zones not showing any significant histologic disruption. The shear failure pattern occurred between the upper columnar (proliferating) zone and the lower hypertrophic zone in approximately 80 % of the specimens. Portions showed an extremely varied failure pattern with the fracture line being present both in the lower columnar or proliferating zone and the lower zone of cell hypertrophy. Much of the varying fracture patterns were felt to be due to the complex material nature of the growth plate, in particular the changing orientations of the collagenous matrix. They concluded that the type of mechanical loading applied to the physis determined the histologic zone of failure in a consistent pattern. The pattern would be even more variable when one considered that in a clinical situation, the physis was surrounded by the perichondrial tissues that in most instances added a degree of nonlinearity which would further alter the fracture pattern.

Different histologic fracture patterns with different directions of shear loading were also produced in the proximal femoral capital epiphysis of immature 6–7-week-old rabbits after removal of the perichondrial sheath [92]. Fractures through the physis were not confined to any single zone. Many specimens showed the fracture line weaving through various zones of the plate often including the resting and germinal zones above and metaphyseal bone below. The level of the physeal injury frequently changed when the physis curved altering its conformation from the linear plane. Multiple longitudinal cracks perpendicular to the transverse plate also appeared. When similar shear stresses were applied to progressively older animals, the predominant zone of fracturing changed from the columnar zone in the 2- to 6-week-old group to the hypertrophic zone in the 14-week-old group and from Type I fractures in the young to Type II in the older [93].

Gomes et al. performed experimental studies of types I–IV epiphyseal fracture-separations that they created in 112 rats. The fracture line in type I and II lesions was often within the proliferating zone and occasionally reached the germinal zone [80]. They demonstrated that early vascular anastomoses between the epiphysis and the metaphysis led to the formation of bone bridges in types III and IV lesions. Wattenbarger et al. also used a rat model, creating type I fracture-separations of the proximal tibia in 4–5-week-old animals [94]. They showed the variable pathway of the fracture plane through the physis. While most planes were concentrated in the proliferating and hypertrophic zones several passed upwards into the zone of the resting chondrocytes while others remained on the metaphyseal margin of the hypertrophic zone. Healing was assessed histologically at days 2–10 and 21 post-fracture. Most often repair proceeded uneventfully but when the fracture plane approached the epiphyseal margin there was physeal disorganization characterized by fibrous vertical septa, cellular debris, and generalized physeal disorganization." In some cases, the vertical septum was a precursor of physeal bar formation. They also concluded that the plane of fracture played a role in the quality of healing. In one of the few published studies of the physeal fracture pattern in humans in the modern era, Smith et al. assessed a Type I fracture in the distal tibia of a 9-year-old boy [95]. When they assessed the epiphyseal plate microscopically, the plane of cleavage was found not to be uniform but to involve the zones of resting, proliferating, hypertrophying, and provisionally calcified cartilage cells. Indeed, their quantification showed that of the transverse diameter of the entire growth plate, 64 % had the fracture line through the proliferating zone and 32 % through the hypertrophying zone with approximately 2 % in each of the resting and provisionally calcified zones.

An additional area of continuing study has involved the periosteum and perichondrium in developing bones. It has long been recognized that the periosteum is loosely adherent to the developing diaphysis and metaphysis and yet plays a major role in growth plate support. It is placed circumferentially about the plate and attached by its outer fibrous layer into the epiphyseal cartilage beyond the growth plate. The microanatomic structure of the periphery of the growth plate referred to as the perichondrial ossification groove of Ranvier has been well defined. Chung and colleagues defined the support potential of the periosteal–perichondrial sheath and the histologic plane of fracture in the proximal human femur growth plate from 5 days to 16 years of age [96]. The shear strength of the growth plate varied with age and was dependent on the surrounding periosteal–perichondrial complex, especially in infancy and early childhood. They also found that shear failure was characterized by undulating cracks through the metaphyseal, hypertrophic, and columnar zones of the physis in older specimens. Shear force caused a Type I fracture through the zone of hypertrophy in the younger specimens, but the older specimens fractured in a Type II pattern with an irregular course through the layers of the physis.

5.4.2.9 Crushed Physeal Cartilage. Periosteal Flap Interpositioning

Another area relating periosteum to growth plate fractures is consideration of the effects on the physis of interposed periosteum post-fracture. Phieffer et al. and Gruber et al. studied this in a rat proximal tibia model [97, 98]. Occasionally, there was a slight growth arrest but often physeal growth simply surrounded and bypassed the obstruction.

The periosteum itself did not directly form a bone bridge but on several occasions acted as a vertical septum predisposing to bar formation secondarily.

5.4.2.10 Additional Studies

Ford and Key in one study and Friedenberg in another, both using the distal femur of the immature rabbit, showed that both size and position of transphyseal defects determine whether growth arrest or deformity would occur and if they did how extensive they would be [99, 100]. Friedenberg removed variable amounts of the lateral physeal tissue and noted shortening and valgus deformation which were greater when larger amounts of physeal tissue, approaching the mid-part of the lateral condylar physis, were removed. Transphyseal bone bridges were formed in the gap with no evidence of cartilage growth plate reconstitution seen. When only a small lateral segment of physis was removed, a narrow bone bridge formed linking epiphyseal to metaphyseal bone but no shortening or angular deformity was noted. He pointed out that relatively small bone bridges did not necessarily lead to growth arrest with the normal growth force of the remaining physis appearing to overcome any tethering effect perhaps by elongating the fused area. Ford and Key documented the negligible effects on growth caused by small (1/8″) diameter central drill hole defects passing through the physis. When the central defect was markedly enlarged by additional curettage and when circumferential peripheral physeal cartilage defects were made, also by curettage, the growth limiting effects were marked. These studies indicated that there would be a critical amount of physeal tissue needed for growth to continue.

Duben and Gelbke showed that two crossed K-wires from the epiphysis through the growth plate to the metaphysis led to growth plate arrest in the dog [101]. Gelbke and Ebert also showed that some relatively small transphyseal injuries were still compatible with continued growth, while others of greater magnitude led to growth arrest with bone bridge formation [102].

A large series of experiments by Campbell and associates involving 175 growth plate alterations in the dog documented that variable transphyseal bone bridge formation again dependent on the diameter and physical nature of the defect [103]. Of particular interest was the finding that holes drilled longitudinally across the distal epiphyseal plate of the radius and femur which were subsequently left empty had maximum growth retardation with transphyseal bone bridge formation when the hole was ¼ inch in diameter but minimal growth retardation when it was diminished in size to 5/32 of an inch. When even smaller holes of 0.45 mm in diameter were drilled across the physis, there was no subsequent growth arrest problem. When cortical bone was placed in the defect gap across the physis following drilling of a 5/32 in. diameter hole, a bone arrest occurred in each of eight instances even though that diameter defect when left to heal on its own produced only minimal retardation in 13 cases. When the 5/32 in. diameter drill hole was filled with a smooth Steinmann pin of the same diameter, there was only minimal growth retardation in 14 cases. When the defect was subsequently filled with 5/32 in. diameter threaded metallic pin from the articular surface through the physis into the metaphysis, bone arrest invariably occurred. When growth arrest occurred, therefore, it was due to injury to the epiphyseal plate with the formation of a cancellous bone bridge crossing the defect, or when there was effective fixation of the epiphysis to the metaphysis by means of mechanical devices such as a screw or from bone fusion enhanced by cortical bone graft. When a smooth pin was placed, however, it prevented transphyseal bone bridge formation and allowed the epiphyseal fragment to essentially slide on it growing away from the metaphysis and not leading to growth arrest problems. They noted that defects across the physis were not repaired by cartilage and that if the defect was not filled with any substance but allowed to repair on its own, undifferentiated mesenchymal cells flooded the gap and later formed a cancellous bone bridge. If the diameter of the bone bridge was small, the bone continued to grow in length and the bone bridge did not serve any tethering effect. It was also noted that smooth metallic pins of small gauge inserted from the epiphysis into the metaphysis perpendicular to the epiphyseal plate caused less growth retardation than a cancellous bone bridge of equal size. Growth arrest was particularly marked when threaded pins or screws were placed across the epiphyseal plate as they served to mechanically anchor the epiphysis to the metaphysis.

Ogden et al. have presented the pathology of acute chondro-osseous injury in the child [104–106]. The pattern of growth plate maturation at the distal tibia clearly affects fracture patterns as well [106]. Studies of growth plate fracture models in the rat have demonstrated the sequelae of damage corresponding to the human situation [80, 94].

5.4.3 Pathogenesis of Growth Deformity

There are four possible ways in which growth deformity can occur following a growth plate fracture-separation. The pathophysiologic approach is designed to relate to these occurrences at the cell and tissue level. These determinations are based on the extensive investigational and clinical work reported. If these negative events do not occur, growth continues uneventfully and the type A fracture-separation pattern exists.

5.4.3.1 Intermixture of Epiphyseal and Metaphyseal Circulations with Their Associated Osteoprogenitor Cells

A major mechanism of growth plate abnormality following fracture involves relatively rapid intermixture of the epiphyseal and metaphyseal circulations which, with their associated osteoprogenitor cells, allows focal transphyseal bone bridge formation to occur. The bridge serves as a tether minimizing growth of the adjacent persisting physeal tissue. The pathogenesis of such bone bridges in markedly displaced fractures that are allowed to heal with nonanatomic reduction is quite evident and is referred to as a B_1 situation. The more common and worrisome occurrence, however, referred to as a B_2 type, involves longitudinal fracturing of the growth plate in association with crushing and fissuring. In such instances no radiographic displacement is seen, although transphyseal vessel communication and subsequent bone bridge formation can occur.

5.4.3.2 Damage to Blood Supply on Epiphyseal Side

Another way in which epiphyseal growth plate fracture-separations can lead to growth problems involves damage to the blood supply on the epiphyseal side. This leads to the type C categorization. As the epiphyseal side vessels are responsible for chondrocyte proliferation and hypertrophy and thus trigger the basic growth mechanism of the physis, damage to them brings this process to a halt. With termination of cell turnover and subsequent cell death, vessels with associated osteoprogenitor cells from the metaphyseal side soon invade the nonfunctioning physeal cartilage and establish transphyseal communication with bone on the epiphyseal side. This can occur over the entire width of the growth plate with massive epiphyseal vessel compromise or locally in less than complete instances of epiphyseal vessel compromise. These mechanisms have been demonstrated experimentally with correlative histologic sections by both Haas and Trueta and Amato [79, 81, 82]. The epiphyseal vascular compromise in growth plate fracture-separations is well-documented clinically and tends to occur in intracapsular epiphyses of the proximal femur and proximal radius where the blood supply is quite tenuous. The clinical assumption, backed with extensive clinical examples, is that sufficient blood supply persists after trauma to extracapsular epiphyses because of the more extensive region of blood supply, such that epiphyseal vascular diminution does not occur. It remains extremely difficult to demonstrate partial or focal epiphyseal blood supply loss and thus it may well be that instances of vessel disruption occur after some injuries to extracapsular epiphyses but are simply not recognized. Epiphyseal vessel disruption has been documented in a markedly displaced distal tibial epiphyseal growth plate fracture even though this is an extracapsular epiphysis [107]. Bone scan demonstrated the avascularity well. Avascularity can also be induced in relatively small figments undergoing open reduction. It will be important in the future to consider focal or regional vascular epiphyseal disruption in high-risk situations especially when techniques are developed providing higher resolution of vascular supply than current bone scans.

5.4.3.3 Interposition of Periosteal Flap at Physeal Fracture Site

At the time of injury or in association with closed reduction, a flap of periosteum can become interposed between the physeal fragments and subsequently serve as a barrier to intraphyseal healing and functional reconstitution [108–115]. This leads to the type D_1 categorization. This mechanism is most common with displaced type I and II fractures since there needs to be a relatively lengthy intraphyseal fracture line for the interposed tissue to lie. The periosteum is torn on the convex or tension side of the injury adjacent to the metaphyseal side. The periosteal flap is interposed either just after the fracture or with closed reduction. This has been described at the proximal tibia, distal tibia, distal radius, and proximal humerus and more recently at the distal femur. It is usually found and well described in cases needing open reduction but is demonstrated by MRI [116]. This appears to have greatest clinical significance at the distal tibia. The key radiographic indication is a widened peripheral physeal thickness after reduction.

5.4.3.4 Damage to Growth Plate Chondrocytes in Germinal and Proliferating Zones by Mechanical Crushing Leading to Dysfunction and Premature Cell Death

Growth arrests in association with bone bridge formation, while usually rapid, can occur slowly over a several month to year period. Delayed bridge formation may occur by this slower mechanism after a fracture-separation; epiphyseal vascularity remains intact and separation of the epiphyseal and metaphyseal circulations continues but the considerable crushing of the germinal and proliferating cell regions of the growth plate leads to mechanical disruption and death of chondrocytes in a portion of the plate. Once the physeal cells die, the stage is set for focal vascular invasion which can lead to either bone or fibrous tissue formation. It is this situation that may well lead to the occurrence of a fibrous type bar in the human which is the type D_2 occurrence that then either resolves as it is pulled apart with subsequent growth or turns very slowly over a several month or even few year period to an osseous bridge [104–106].We have not been able to produce such lesions in the rabbit nor have we seen them referred to in the extensive literature involving

damage to growth plates in the experimental animal. They have however been referred to in human cases as persistence of fibrous tissue or radiolucent variations such as fibrocartilagenous collections without longitudinal growth potential. The rapidity of response in the rabbit may preclude occurrence of this lesion that, nevertheless, is an important sequel to some human growth plate injuries.

5.4.3.5 General Considerations in Relation to the Pathophysiologic Approach

Knowledge of the exact level of the transverse fracture line, which has characterized writings on growth plate injuries from the work of Foucher on, has an important bearing on the possibility of subsequent growth deformity. As we noted in a previous section, although a frequent path of transverse injury is through the hypertrophic zone [52, 81], there is abundant evidence that the transverse injury can involve all levels of the physis [16, 88, 91–93]. One of the eventual advantages of high resolution MR images or other technologies will be the more exact localization of transverse separation within growth plate cartilage. This is felt to be of prognostic significance since fractures along the germinal and proliferating cell layers can cause mechanical damage to those cells providing longitudinal growth. An additional example of the significance of the transverse level of fracture involves the Salter–Harris Type III fracture of the distal tibia (Fig. 5.15). Certain Type III fracture-separations have a good prognosis, while others are at risk for transphyseal bone continuity. If the fracture line through the epiphyseal growth plate is contained completely within the hypertrophic cell zone, bone block formation should not occur. The fractured bone fragments are intraepiphyseal and the metaphyseal bone remains in its separate compartment such that there is no epiphyseal–metaphyseal vessel communication. If the fracture line is intra-metaphyseal and the growth plate is slightly displaced, the epiphyseal and metaphyseal circulations with their respective osteoprogenitor cells can come into close association and form a bone block. Plain radiographs do not have sufficient resolution to allow for the subtle but vitally important distinctions concerning the exact transverse level of fracture. They may not demonstrate the presence or absence of longitudinal fractures that allow epiphyseal–metaphyseal vessel communication.

All bone bridges do not lead to growth arrests. When the bridge is sufficiently small, forces generated in the adjacent persisting physis may pull apart the bone bridge and minimize or negate any sequelae. This has been shown both in clinical studies and also by experimental investigations [99, 117]. When a bone bridge has formed, the extensiveness and precise location of the bridge must be documented.

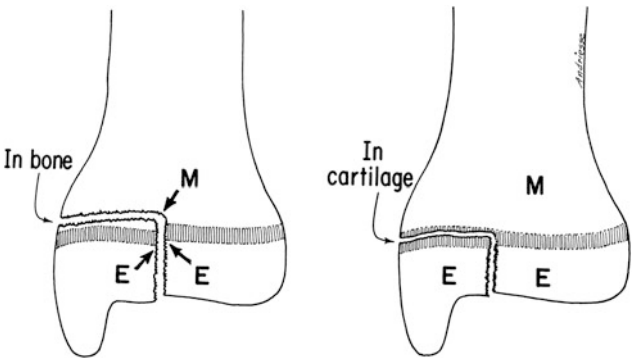


Fig. 5.15 Possible fracture pathways in what appear radiographically as type III distal tibial epiphyseal growth plate fracture-separations are shown. The specific level of transverse fracture through or immediately adjacent to the growth plate cartilage can change the prognosis. At *right*, the fracture remains totally within the cartilage plate in the hypertrophic zone. Even with displacement of the fracture through the secondary ossification center of the epiphysis and the articular cartilage there is still no epiphyseal-metaphyseal vessel communication. This line of fracture would be analogous to that seen in Fig. 5.14b, c on *left*. At *left*, the line of fracture is just beyond the hypertrophic zone within the outer reaches of the metaphysis. With separation of the epiphyseal fragment there is a communication between epiphyseal and metaphyseal vessels allowing bone bridge formation. Further worsening of prognosis would occur if the growth plate was damaged as seen in Fig. 5.14e, f. In the example at *left*, a more worrisome situation concerning negative growth sequelae exists. The plain radiograph does not have sufficient resolution to delineate the line of transverse fracture while MRI studies can make such a delineation. (Reprinted with permission from Shapiro F, Epiphyseal growth plate fracture-separations: A pathophysiologic approach. Orthopedics. 1982;5:720–736. Copyright 1982 SLACK Incorporated)

5.4.4 MR Imaging in Assessment of Growth Plate Fracture-Separations

5.4.4.1 Assessment of Experimental Transphyseal Bone Bridge Formation by MR Imaging and Correlative Histology

A considerable amount of experimental work has been done using MR imaging in relation to growth plate injury. Studies in rabbits have involved the effectiveness of MR imaging (i) in assessing cell and matrix responses to transphyseal focal defects and (ii) in assessing the level of transverse fracture in experimental growth plate fracture-separations of the distal femoral and proximal tibial growth plates. When MRI became a practical clinical tool, the possibility of imaging the level of transverse and longitudinal fractures of the cartilage growth plate and transphyseal vascular communication seemed feasible. The MRI technique is a dynamic physiologic indicator as it images soft tissues such

as cartilage, blood vessels, and fat as well as a structural indicator differentiating both bone and cartilage. CT scans provide more precise resolution of the bony anatomy in particular. Animal experiments have been done to investigate the usefulness of MRI studies in relation to growth plate injury [118].

A focal cylindrical drill defect was made in the medial proximal tibial growth plate of immature rabbits, which led invariably to transphyseal bone bridge formation (Fig. 5.16a–e). Vessels from the epiphyseal and metaphyseal regions flooded the defect and mesenchymal cell differentiation led to woven bone and then lamellar bone formation with epiphyseal–metaphyseal bone marrow cavity continuity. Following injury, a series of MRI studies was correlated with plain radiographs, tomograms, and histologic sections. On the day of injury plain radiographs of the growth plate were normal, but MR images clearly showed cartilage damage with the absent of signal at the defect (Fig. 5.16a). The degradation of blood products within the lesion at 1 week registered as increased signal intensity on T_1-weighted, T_2-weighted, or gadolinium enhancement images. Once a bone bridge was formed, the image also varied depending on whether a dense lamellar bar or a marrow filled trabecular accumulation predominated (Fig. 5.16b). This work successfully demonstrated the changing transphyseal magnetic resonance signals across the defect site associated with the intercommunication of the epiphyseal and metaphyseal circulations and the eventual and invariable bone bridge formation. In the experimental model used, the physeal changes noted on the day of surgery were due to exclusively to the drilling. Proton density and T_2-weighted images clearly depicted the damage to the cartilage showing interruption of the cartilage signal at the point of injury at the medial proximal tibial physis. A halo of increased signal intensity on the T_2-weighted images appeared to represent edema. There was no contrast material enhancement at the time of surgery. In one animal, the signal intensity in the defect decreased markedly after contrast material enhancement. This was probably due to the T_2-shortening effect that predominates at high concentrations of Gd-DTPA, which indicates spillage of contrast material into the lesion because of hemorrhage. The degradation of blood products in the transphyseal component of the lesion and in adjacent hematomas accounts for the increased signal intensity seen on T_1-weighted images obtained 1 week after surgery.

The development of early, inhomogeneous contrast material enhancement correlates well with the histologic detection of blood vessel ingrowth in the animals sacrificed 4 days after surgery. The enhancement increases and becomes more homogeneous at 1 week and is maximal at 2 weeks. At this time, there is histologic evidence of vascular communication between epiphyseal and metaphyseal vessels. The enhancement decreases and becomes inhomogeneous as bone deposition increases. It is faint and finally disappears as the bone bridge matures and is no longer hypervascular.

Deposition of bone by the osteoprogenitor cells accompanying the vessels begins at 1 week and continues thereafter. The ossification in the lesion occurs initially in the periphery, where the newly formed vessels cover the persisting cartilage. This corresponds to the dark rim seen on MR images. At week 5, marrow signal continuity across the physis is dramatic. By week 7, well-formed bone fills the bridge. The signal characteristics of the mature bridge will depend on whether it is composed mainly of dense lamellar bone or of trabeculae interspersed with fatty marrow.

Changes in the signal intensity from the cartilage not directly related to the drill hole are also seen with MR imaging. The growth plate enhances with GD-DTPA due to diffusion of Gd-DTPA into the cartilage, since the physis is avascular. In one rabbit, significant portions of the plate increased in thickness 1 week after creation of the lesion. This may have represented metaphyseal ischemia, since the interruption of metaphyseal vessels stops ossification.

In all the rabbits studied, Gd-DTPA enhancement at the defect site preceded the deposition of bone. The enhancement was distinguishable from the high signal intensity originating from the plate in every case. Thus, enhanced T_1-weighted images can be useful as an indicator of early bony bridge formation. Since we were successful in demonstrating various phases of bone formation histologically in every case, we cannot know whether smaller lesions display enhancement early, but never form a clinically damaging bone bridge. MR imaging can be useful in the detection of small disruptions in the growth cartilage and can depict the vascular and osseous changes that lead to formation of a bony bridge. The earlier and most significant developments in this process occur in tissues that are undetectable radiographically. The bone bridge is imaged during the weeks it is actually forming whereas with plain radiographs, it is appreciated only when fully formed and often only after negative growth sequelae such as shortening and angular deformity have already occurred.

5.4.4.2 Assessment of Experimental Transverse Level of Physeal Fractures by MR Imaging and Correlative Histology

MR imaging assessments of the transverse level of fracture within growth plates have also been correlated with histologic studies [119] (Figs. 5.17 and 5.18ai–biii). Experimental physeal injuries were made in distal femoral and proximal tibial growth plates in 14 3-month-old New Zealand white rabbits immediately after sacrifice. MR fracture levels were classified along six physeal segments medial to lateral as grade 1 (hypertrophic zone), grade 2 (middle third of the physis), or grade 3 (germinal third of the physis). The bones were prepared for light microscopy using the JB4

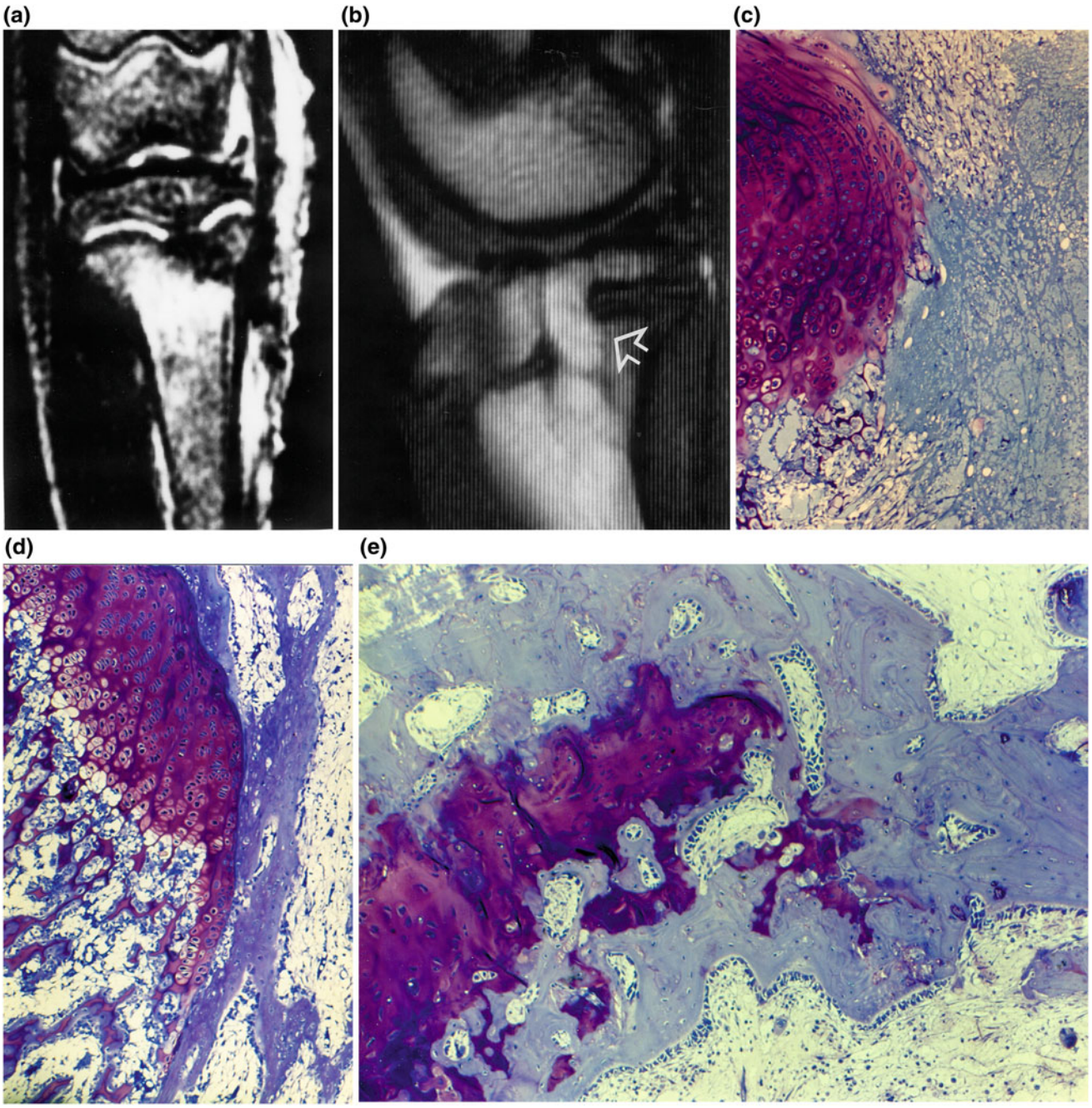
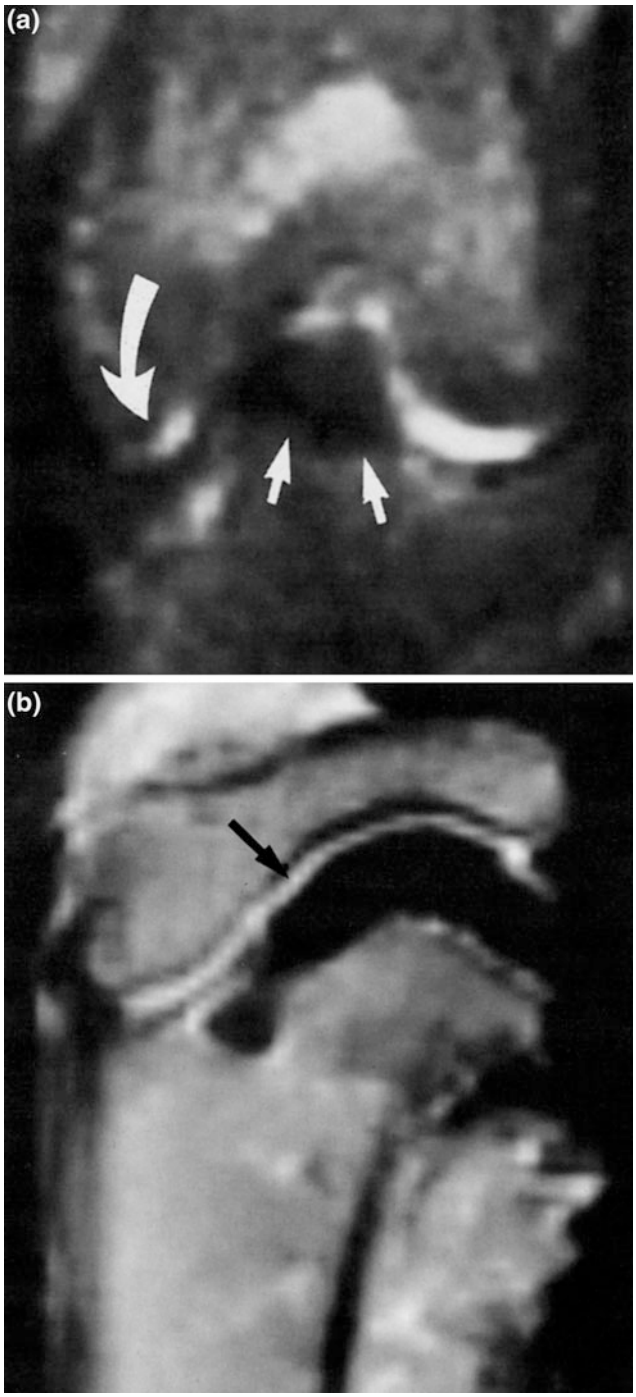


Fig. 5.16 A series of MR images and correlative histologic sections from a rabbit model of a focal medial proximal tibial growth plate defect demonstrates the ability of the imaging technique to document bone bridge formation in the early weeks post-injury. (Reprinted from Ref. [118]). (Reprinted with permission from Jaramillo et al. Post-traumatic growth plate abnormalities: MR imaging of bony bridge formation in rabbits. Radiology. 1990;175:767–773. Copyright 1990 The Radiological Society of North America (RSNA)). **a** MR image immediately after creation of the focal proximal medial tibial growth plate defect in the rabbit model. Signal interruption at the defect site across the physeal cartilage is clearly evident. A plain radiograph failed to define the defect since both the physeal cartilage and the defect site are radiolucent. **b** MR image (*sagittal plane*) at 5 weeks post-injury shows clear transphyseal signal continuity (*arrow*) between marrow of the epiphysis and metaphysis. **c** Histologic section at 1 week shows early cell response to the transphyseal defect. Persisting physeal cartilage is at *left*. The blood clot is still present but mesenchymal cell ingrowth from epiphyseal and metaphyseal sides is shown. There is no tendency for physeal cartilage itself to repair the site with chondrocytes. **d** Early mesenchymal cell differentiation to woven bone in the transphyseal region is shown at 2 weeks. There is no tendency to cartilage formation in the gap either from the ingrowing mesenchymal and vascular communication or from the persisting physeal cartilage. **e** Photomicrograph at 8 weeks shows transphyseal bone bridge which has now been converted to lamellar bone. The persisting physeal cartilage is shown at the *left*. The transphyseal MR imaging signal is dependent on the relative amounts of marrow and lamellar bone in the section of the defect being assessed



plastic technique. The histologic sections were also graded 1, 2, or 3 in terms of level of transverse fracturing.

In the more horizontal proximal tibial physis, the mean level of fracture by MR imaging was 1.1 indicating a concentration in the hypertrophic zone (mean grade 1.1 ± 0.2; $p = 0.02$) (Figs. 5.17b and 5.18bi–iii). In the less regular distal femur, the physeal fracture level more often approached the epiphysis in particular in the central angulating portion of the physis (mean grade 2.1 ± 0.3) (Figs. 5.17a and 5.18ai, ii). When there was MR imaging demonstration of extension into the juxta-epiphyseal segment, histologic study correlated well. The course of transverse physeal fracture was shown to be demonstrable by MR imaging and its accuracy was confirmed by histologic study (Fig. 5.18ai–bii). This work shows the feasibility of determining the transverse level of the fracture within the physis at time of initial assessment, a matter which can be of clinical importance in certain physes if it involves large segments of the proliferating and germinal cell layers.

5.4.4.3 Clinical MRI Studies

Information and techniques established from the laboratory studies were applied to a series of 28 human growth plate fracture-separations and an additional 20 human cases [120, 121]. MRI was performed in those growth plates where problematic situations were expected and primarily involved the distal femur, the proximal tibia, and the distal tibia. Prognostic evidence is beginning to appear that MRI can

◀ **Fig. 5.17** MR images in **a** and **b** show how the transverse level of physeal separation can be detected in many instances. In **a** a type II fracture-separation of the femur in an experimental rabbit model assessed by MR imaging shows regions where the physis is primarily attached to the epiphysis (at *left*, *curved white arrow*) while in other regions (at *right*) the fracture line clearly has gone through the upper part of the germinal zone since virtually all of the cartilage is persisting with the metaphysis. The two smaller white arrows point to the fracture line isolating an epiphyseal segment of bone with the metaphysis. In **b**, which is a type I fracture-separation of the proximal tibia in the rabbit, all of the physeal cartilage (*arrow*) is part of the epiphyseal segment. Histologic sections confirmed that the line of fracture was within the hypertrophic zone with essentially all physeal cartilage persisting on the epiphyseal fragment. (Reprinted from Ref. [119]). (Reprinted with permission from Jaramillo et al. Cartilagenous path of physeal fracture-separations. Radiology. 2000;215:504–511. Copyright 2000 The Radiological Society of North America (RSNA))

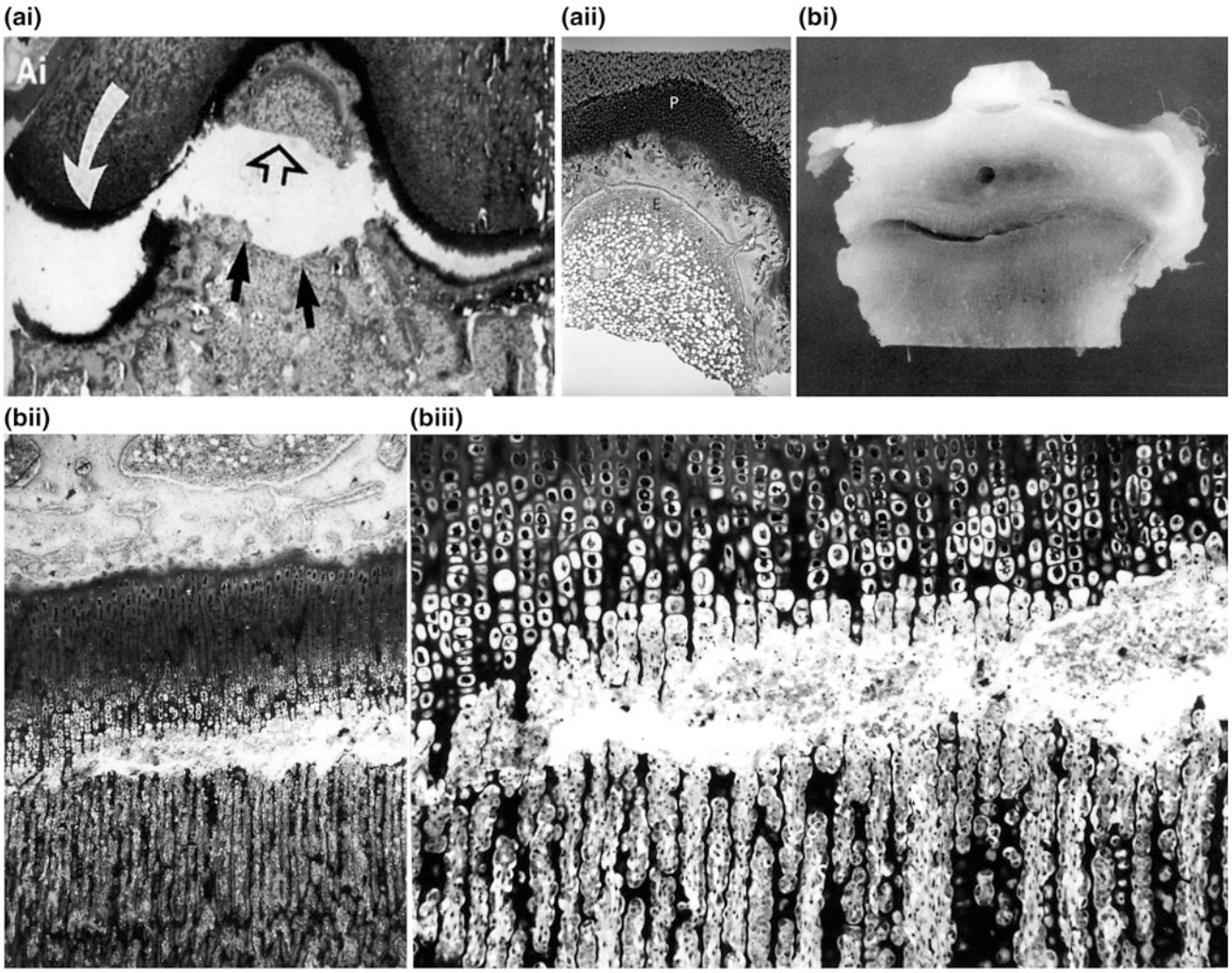


Fig. 5.18 **a** A histologic section of the distal femur pictured in Fig. 5.17a shows the epiphyseal bone which has remained on the metaphyseal segment and has become separated from its nutrition source (**ai**) while the adjacent area (*centrally*, *open arrow*) shows the fracture passing through various levels of physeal cartilage (*curved white arrow*). **aii** Highlights the central region of the physis showing how the fracture line can deviate into epiphyseal bone in high force injuries affecting nonlinear physes. (Reprinted with permission from Jaramillo et al. Cartilagenous path of physeal fracture-separations. Radiology. 2000;215:504–511. Copyright 2000 The Radiological Society of North America (RSNA)). **b** Decalcified specimen photograph (sectioned in mid-coronal plane) (**bi**) and histologic sections of the proximal tibia (**bii**, **iii**) show a type I fracture line separating the hypertrophic zone above from the metaphysis below.

detect abnormalities that subsequently have gone on to growth plate defects or evolving growth plate bone bridges earlier than seen with plain radiographs (Fig. 5.19a–i). MRI has been shown clinically to aid in the assessment of growth plate fracture-separations in four areas. (1) Interruption of the continuity of growth plate cartilage can be demonstrated. These interruptions can be longitudinal fissures allowing communication between epiphyseal and metaphyseal circulations or horizontal fractures within the physeal cartilage, the level of which may have a bearing on subsequent growth. Neither of these injuries within the cartilage mass can be detected by plain radiography; (2) the accompanying bone fracture pattern can be demonstrated with much greater resolution than on plain films. Not infrequently, subtle and wandering pathways through adjacent epiphyseal and metaphyseal bone are well depicted; (3) bony bridge formation can be seen as it evolves rather than waiting until it is fully formed when plain radiographs demonstrate them; and (4) growth arrest lines, which occur secondarily but clearly point to areas to focal growth arrest, and metaphyseal abnormalities such as avascular segments are revealed earlier and with greater resolution than on plain films. Examples of MR images from some clinical cases are presented. Some of these findings are seen within a few days of injury but others

(a)
(b)
(ci)
(cii)
(d)
(e)
(f)
(g)
(h)
(i)

are evident over a several week to several month period. We are still in the early phases of interpreting the role of MR in growth plate fracture-separations but expect that advances with clinical MR techniques should enhance resolution capabilities beyond those presently obtainable.

In general, proton density sequences with fat suppression and T_2-weighted gradient echo images are best for distinguishing between physeal cartilage and adjacent bone, thereby detecting focal abnormalities in the cartilage such as bony bridges. T_2-weighted images are best for distinguishing between the physeal cartilage, which is relatively hyperintense, and the epiphyseal cartilage, which is hypointense. Gadolinium-enhanced T_1-weighted images show increase in the signal from the physis, and, in experimental animals, have shown vascular abnormalities associated with growth disturbances.

Growth plate fractures can be evaluated with MRI by obtaining high resolution, continuous interleaved thin slices in the coronal and sagittal planes. Coronal T_1-weighted images identify abnormalities in the hypointense zone of provisional calcification and growth recovery lines. Coronal gradient echo images detect bony bridges as areas of low signal intensity within the substance of the hyperintense physeal cartilage. Sagittal fat-suppressed T_2-weighted images separate the physeal cartilage from the adjacent nonossified epiphyseal cartilage and detect abnormalities in the adjacent marrow.

Preliminary review of the use of MRI to evaluate physeal fractures "at risk" for growth complications in children in the first 4 months following injury shows that fractures through epiphyseal and metaphyseal bone are more accurately revealed by MRI than by plain radiography in the acute phase. MRI scans occasionally allow determination of the transverse fracture level within the cartilaginous physis (if there is some displacement), something which cannot be observed on plain radiographs. This enhanced depiction of subtle fracture anatomy by MRI permits a more accurate analysis and classification of physeal injuries, which should ultimately direct treatment more appropriately as well as provide a more accurate prognosis.

MRI scanning in the acute setting (3–10 days after injury) helped to define fracture anatomy in four patients. In three of those patients, the Salter–Harris fracture class based on plain radiographs was found to be incorrect compared to information provided by MRI scans. Although this more accurate designation of the Salter–Harris fracture type did not alter the treatment in these individuals, it provided a better understanding of the potential prognosis of these fractures. MR identification of Type III or Type IV injuries unappreciated by plain radiographs would have definite treatment and prognostic implications.

MRI scans were obtained in 12 patients between 3 and 17 weeks following physeal fractures to assess for transphyseal vessel communication and bony bridge formation and thus for possible early growth arrest. One mechanism for the development of physeal bridges following fracture is the vertical or longitudinal disruption of the physis, which permits mixing of the otherwise separate metaphyseal and epiphyseal circulations. Deposition of the bone across a physis has been shown experimentally to start as soon as 7 days following injury. The radiographic diagnosis of physeal bars or bridges may not be possible for months, may require the presence of bony deformity to suggest their existence, and may necessitate further studies such as CT scanning with additional ionizing radiation exposure to define their location. MRI scans demonstrated findings not readily apparent by plain radiography, such as physeal narrowing, physeal tethering, and vertical interruption of the growth plate, which in light of subsequent follow-up, were highly suggestive of future growth abnormalities.

MRI scans are particularly valuable in demonstrating growth arrest lines, which can provide important information about physeal function. Harris growth arrest lines are generated by physeal injury, through a temporary slowdown of physeal growth. Upon resumption of physeal growth,

◀**Fig. 5.19** Plain radiograph and MR images of growth plate fracture-separations and developing sequelae are shown. **a** An anteroposterior knee radiograph in a 13½-year-old male demonstrated, in retrospect, a slight widening of the medial proximal tibial growth plate but no other evidence of fracture. **b** MR image of the same area shown in figure a identifies a large metaphyseal fragment documenting a type II fracture-separation. This example clearly illustrates the ability of the MR image to detect fracture patterns through adjacent bone that may not be demonstrated on plain radiographs especially when the standard clinical study in only anteroposterior and lateral projections is done. **c** Distal radius fracture-separation is seen (anteroposterior (**i**) and lateral (**ii**) views; volar displacement). **d** Sagittal MR image 6 months following the severe type II fracture of the distal radius in figure c in a 13-year-4-month-old male demonstrates a lack of cartilage signal centrally replaced by a continuous epiphyseal–metaphyseal signal and an almost obliterated physis in the dorsal 1/3rd indicating early transphyseal bone bridge formation with bone and vessel communication between epiphyseal and metaphyseal tissues across the physis. **e**–**i** Common sequence of events in a type II distal tibial fracture-separation caused by considerable force in a 10-year, 10-month-old male is illustrated. **e** Anteroposterior radiograph demonstrates the fracture with displacement. **f** Anteroposterior radiograph illustrates accurate closed reduction. **g** MR image at 7 weeks show irregularity in cartilage signal in central plate area suggestive of a developing problem. **h** MR image at 7 months shows the dark growth plate cartilage signal interrupted centrally by a transphyseal signal almost continuous with signal from epiphyseal and metaphyseal bone. This indicates transphyseal vascular communication with early bone bridge formation. **i** At 18 months post-injury, a much larger bone bridge involving the central third of the transverse width of the growth plate has formed

thickening or coarsening of the trabeculae serves as a marker, appearing radiographically at the metaphyseal–physeal junction. Growth lines parallel to the physis indicate normal growth, but tilting, angulation, or disruption of an otherwise parallel arrest line suggest adjacent physeal abnormality. The association of abnormal physeal arrest lines and traumatic growth plate injuries has been documented previously. Although the physeal arrest lines may appear radiographically as early as 6 weeks after injury, reliable determination of physeal function using these lines is often not possible for 12 weeks after injury. More subtle or partial growth disturbances, especially those causing angular deformity, may not become clinically or radiographically apparent for as long as 18 months to 4 years after injury. The resolution and visualization of arrest lines on MRI scans is significantly better than that on plain radiographs. By 2–3 months after fracture, growth arrest lines were easily identified on coronal and sagittal MRI studies, particularly on spin-echo T_1-weighted images. Tilting of arrest lines on MRI scans in several patients was not appreciated on plain radiographs at that stage of recovery.

Early physeal bridging was also seen in several MRI studies. Several patients with small focal bridges subsequently had no growth disturbances which indicates that the growth plate can recover from or "pull apart" small developing or established bony bridges. There is a physeal bar size threshold that the intrinsic physeal recovery capacity cannot overcome, although this appears to vary in different physes at different ages and still must be the subject of study. Owing to the marked sensitivity and resolution of MRI, a distinction must be made between transphyseal vessel and new bone formation and clinically significant growth arrest. In some patients, however, the transphyseal bar increased in size on subsequent studies. We caution that the early identification of transphyseal vessel communication mandates repeat MRI studies, rather than immediate surgical excision or application of chondrodiatasis. If the bar increases in size, a growth problem will likely occur. MRI has previously been shown to demonstrate early fibrous physeal bars, which may represent transphyseal vascular communication.

In summary, in the acute setting (the first 3–10 days in our study), MRI provides valuable information about fracture anatomy that may more accurately reveal the extent of the injury than plain radiography, even to the point of changing the Salter–Harris class initially designated from the trauma radiographs. During this period, MRI defines cartilaginous injury more clearly than radiography so that both physeal and articular injuries not appreciated on plain films can be identified. In addition, MRI scans can detect associated soft tissue injuries, such as muscular, tendinous, ligamentous, and meniscal cartilage abnormalities that can be overlooked clinically and radiographically. In the next phase of assessment post-injury, defined as 3–17 weeks, developing bony bars or bridges may be identified or predicted from the MRI assessment of the pattern of physeal disruption. Evaluation of Harris growth arrest lines with MRI before they are apparent on radiographs may disclose developing growth disturbances and allow therapeutic intervention before bony deformity occurs. An additional use of MRI following physeal fractures is to delineate established transphyseal bony bars, usually more than 6 months after injury.

An MRI study of 111 children with physeal bone bridges, 70 % (78/111) of which were post-traumatic, further clarified the value of the technique in assessing fracture-separations [122]. Larger bridges had higher T_1 signal intensity; smaller bridges had variable signal intensity. T_1 weighted images reveal growth recovery lines well and indicate differential physeal growth. Intermediate and T_2-weighted images reveal metaphyseal cartilage extensions. Metaphyseal avascular necrosis adjacent to the transphyseal bridges represented a finding not appreciated on plain radiographs. The use of fat-suppressed 3D spoiled gradient-recalled echo imaging was particularly useful in outlining the bone bridges. On this fat-suppressed image, the low signal intensity bridge was easily contrasted with the high signal intensity physeal cartilage. Other studies also support the value of MRI in assessing negative sequelae of growth plate injuries and guiding surgical interventions [123].

Guffer et al. used MR to study 23 children ages 3–15 years (mean 10.7 years) who had injury to a joint, open physes, swelling, pain, and limitation of function and no evidence of fracture on plain radiographs [124]. Fractures with MRI were excluded in 15/23 (65 %) but were seen in 35 % (8/23). Fractures involved 5/10 in the elbow, 2/10 in the distal tibia, and 1/3 in the distal femur. All patients with fractures and 11/15 without fractures showed bone marrow edema, indicating the nonspecificity of that finding. Knowledge of the presence of a fracture however could influence management (longer immobilization) or the development of growth abnormality in a seemingly benign injury.

5.4.5 Clinical Use of the Pathophysiologic Approach

The pathophysiologic approach can be applied in a practical way owing in part to advanced imaging modalities [72]. Pathoanatomic classification remains essential since much valuable information has been documented. The pathophysiologic approach is meant to be superimposed on a pathoanatomic classification (Fig. 5.20). It attempts to provide better prognostic considerations for specific injuries by defining more accurately the fracture planes within the cartilaginous growth plate and adjacent bone of the epiphysis

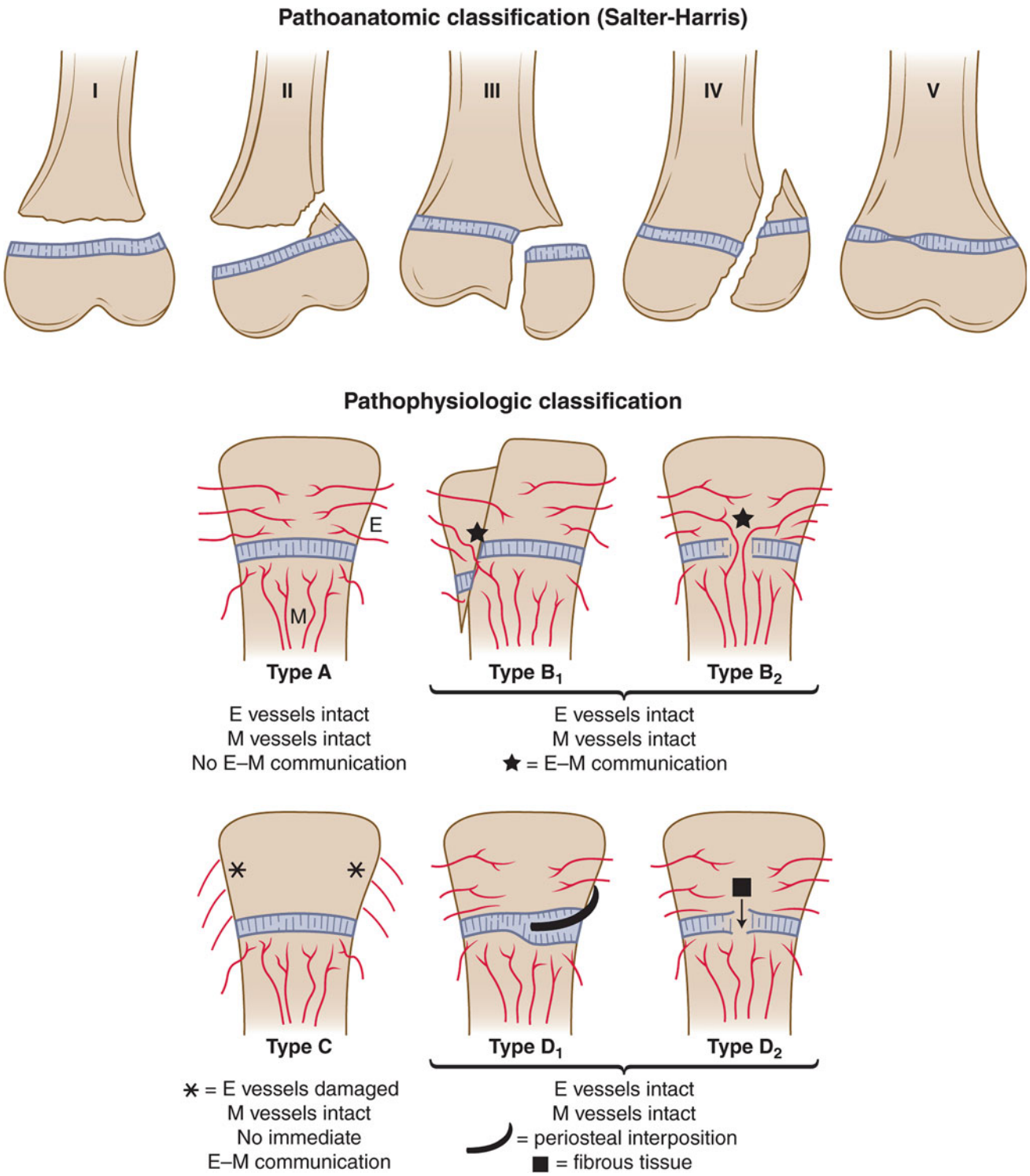


Fig. 5.20 The pathophysiologic approach is meant to be superimposed on a pathoanatomic pattern. One could identify, for example, a S–H type II fracture-separation of the distal femur. Attention would then focus on whether one was dealing with a type *A*, B_2, D_1, or D_2 situation in regard to events at the cell and tissue level. The pathophysiologic categorization is given on the basis of epidemiologic features concerning the fracture, an understanding of the literature pertaining to each injury of this epiphysis as to whether or not significant growth arrests have been documented, the mechanism of injury that might lead to concern about a possible growth arrest and more specific CT, MRI, or bone scan studies to define vascularity and possible longitudinal transphyseal communication

and metaphysis. Awareness of vascular, chondrogenic, and osteoprogenitor cell activities helps to determine the outcome of any growth plate fracture-separation but these parameters are beyond the resolution powers of plain radiographs. The pathophysiologic approach considers the adequacy of epiphyseal vascularity, the presence or absence of transphyseal vessel communication, and the presence or absence of intraphyseal nonfunctional soft tissue interposition which are the three primary determinants of growth post-injury. Use of the pathophysiologic approach is based on a cumulative picture provided by: (1) specific epidemiologic features of each fracture such as the anatomy of the particular epiphysis fractured, the age of the patient, the force of the trauma, and the displacement that occurred; (2) previous reports concerning the outcome of fractures of the various pathoanatomic types at each specific epiphysis; and (3) imaging techniques that can provide information with greater pathoanatomic and pathophysiologic resolution than that provided by plain radiographs. The modalities currently involve plain tomography, CT scanning ultrasound, bone scans, and MRI [107, 118, 120, 121, 125–133]. CT scans provide clearer resolution of fracture lines through adjacent metaphyseal and epiphyseal bone and enhance the three-dimensional appreciation of the injury but they are not able to assess cartilage and other soft tissue components. Tomograms are infrequently used today. More dynamic physiologic information is provided by the bone scan, which serves as an index of the vascularity of the fractured segments, and by MRI, which is specific for soft tissue components and thus gives excellent information about the state of the growth plate cartilage and the vascularity of the adjacent marrow in the weeks and months following injury. Ultrasound is very useful in neonatal fractures to assess position of nonossified epiphyses.

Extensive imaging studies for each growth plate fracture-separation are not suggested. It is well known that the incidence of growth problems after fracture-separations of the proximal humeral epiphysis, for example, is minimal. One would thus refer to a common pattern of this injury as a Salter–Harris Type II A fracture giving the pathophysiologic A on the basis of epidemiologic considerations, literature reviews, and an avulsion mechanism of injury, none of which point to potential long-term problems with this fracture. A different situation exists, however, in terms of Salter–Harris Type II, III, or IV fracture-separations of the distal femur. Retrospective studies indicate a fairly high incidence of growth plate damage with each of these injuries. It thus is helpful clinically to grade these injuries as A, B_1, B_2, C, or D_1, D_2 dependent on additional studies. The pathophysiologic approach is used in a dynamic fashion. Initial consideration of a fracture can yield a diagnostic indication of a Type IV B_1 lesion, which after open reduction and screw fixation is converted to a IV A situation since the epiphyseal blood supply remains intact and surgery has minimized concerns about epiphyseal–metaphyseal vessel communication. Concern about a II B_2 lesion currently mandates close observation and efforts to document transphyseal vessel communication and growth slowdown with intervention occurring as clinically warranted. A widened medial distal tibial growth plate after closed reduction of a displaced type I or II fracture-separation could represent a pathophysiologic D_1 injury best managed by open reduction to remove an interposed flap of torn periosteum. A completely displaced femoral head in relation to the femoral neck post-trauma is usually a type I fracture-separation but clearly raises concern about a pathophysiologic C injury. Distal femoral or distal tibial type I or II fracture-separations, especially if widely displaced due to severe trauma, often soon show a pathophysiologic B_2 sequel but a slower developing D_2 status may also evolve. The eventual therapeutic goal would be to convert all clinically worrisome pathophysiologic B_1, B_2, C, and D_1, D_2 fractures to clinically safe A fractures. This approach thus moves the conceptual and practical management of growth plate fracture-separation beyond the static pathoanatomic designation to active consideration of events at the cell and tissue level. In the following section, we comment in greater detail on the pathophysiologic approach at the major long bone epiphyses. The pathoanatomic types I to IV represent the Salter–Harris (S–H) terminology.

5.5 General Clinical Profile of Growth Plate Fracture-Separations

5.5.1 Overview

Epiphyseal growth plate fracture-separations account for approximately 15–20 % of major long bone fractures in children. They are approximately twice as common in males as in females and approximately three times as common in the upper extremity compared to the lower extremity. In those studies which accurately document all physeal fractures, it is those of the hand and in particular of the phalanges of the fingers which are the most common. In the major long bones, the fracture of the distal radial epiphysis is most common in all series with injuries of the distal tibial epiphysis and distal humeral epiphyses next in frequency. The age at occurrence documents peak incidences of female fractures approximately 1.5 years earlier than those in males. The large majority of epiphyseal growth plate fracture-separations occur between 10 and 15 years of age although fracture patterns at specific epiphyses tend to have characteristic age ranges.

5.5.2 Distribution of Physeal and Non-physeal Fractures in Childhood

Physeal fractures constitute approximately 15–20 % of all childhood fractures but studies as high as 30 % have been reported [56, 63, 134–138]. In assessments of childhood hand fractures, 34 % involve the epiphyses which represents a higher percentage than in major long bones [139]. Data establishing the percentages of physeal and non-physeal injuries are somewhat variable owing to several factors including: the number of patients in a particular study, the upper age limit of patients included in the study, the referral pattern of the institution reporting the profile, and the inclusion or noninclusion of hand fractures.

Sakakida reported on the frequency of affected sites of epiphyseal fracture-separations and non-physeal fractures of the long bones under 16 years of age (excluding hand and foot fractures) [137]. He documented a 12.7 % incidence of epiphyseal fracture-separations with 117 epiphyseal fractures and 800 metaphyseal and diaphyseal long bone fractures. Hanlon and Estes noted a 17 % incidence of epiphyseal fracture in 698 patients suffering fractures from birth to 18 years of age [135]. Ogden indicated that approximately 15 % of all fractures in children involve the physis, a number derived from reference to a large number of articles in the literature over a period of several decades [63]. Lichtenberg documented only a 6.5 % incidence of epiphyseal fractures in 2,058 childhood fractures but his study included children only to the end of the 12th year of age [140]. Compere reported a 14.4 % incidence of epiphyseal fractures in 211 children under 15 years of age [134]. Three additional detailed studies specifically documented the incidence and pattern of fractures including those of physeal and non-physeal regions. Worlock and Stower assessed all children 12 years of age and younger who sustained a fracture over a 6 month period in Nottingham, England [138]. They documented an 18.5 % incidence of physeal injuries involving 171 epiphyseal injuries in a total of 923 fractures. This study did include hand and foot injuries, but included children only 12 years of age or less. The peak concentration of growth plate fracture-separations is between 10 and 15 years of age. Mizuta et al. noted an incidence of 17.9 % physeal injuries based on a study of all acute fractures over a 24-month period at the Adelaide Children's Hospital, the center for pediatric care in the Adelaide metropolitan area of Australia [56]. They noted 353 physeal injuries in a total of 1,974 fractures. Their study also included hand and foot injuries. Mann and Rajmaira documented a 30 % incidence of growth plate injuries in childhood fractures which is the highest percentage in the literature [136]. Their study involved records of patients treated in the pediatric emergency room at Cook County Hospital in Chicago over an 11-year period. The study did not include hand or foot fractures but did follow children from birth to 16 years of age and included 943 growth plate fracture-separations out of a total of 2,650 fractures. Kawamoto et al. showed that 17.9 % of all pediatric fractures in their institute in Japan involved the epiphyses in a study between 1992 and 1997. The most frequently injured epiphyses were the finger phalanges (21.9 %). Type involvement in the series was I-28.6 %, II-60.9 %, III-6.7 %, and IV-3.7 %. Type V was not recognized [141].

5.5.3 Incidence of Epiphyseal Growth Plate Fracture-Separations in Males and Females

There is an approximate 2:1 male/female incidence in epiphyseal growth plate fracture-separations. Mizuta et al. documented 231 fractures in males and 122 fractures in females (1.9/1.0); Peterson et al. a 637 to 314 male/female incidence (2.01/1.0); Mann and Rajmaira, a 505 to 227 male/female incidence (2.22/1.0); and Ehlers and Eberlein a 75/28 male/female incidence (2.68/1.0) [56, 136, 142, 143].

5.5.4 Incidence of Epiphyseal Growth Plate Fracture-Separations at Specific Epiphyses

The percentage distribution of growth plate fracture-separations throughout the body is greatly dependent on whether or not the assessment included hand and to a lesser extent foot fractures and also the extensiveness of the study in relation to those two regions. Most of the studies of epiphyseal fracture-separation published prior to 1970 concentrated almost exclusively on the major long bones. Four major studies after 1972 included hand and foot injuries and clearly demonstrated how common they are. Peterson and Peterson in their 1972 assessment indicated that finger phalangeal and metacarpal fractures comprised 14.8 % of all injuries; Ogden in 1981 showed that these hand fractures involved 11.1 % of all injuries; Mizuta et al. in 1987 that they involved 30 % of all growth plate fracture-separations; and Peterson et al. in a Mayo Clinic study of 1994, showed their involvement in 43.8 % of all fractures with 37.4 % involving the finger phalanges and 6.4 % the metacarpals [56, 57, 63, 142]. Table 5.5 indicates a compilation of major long bone epiphyseal growth plate fracture-separations from several recent papers, excluding hand and foot involvement. Almost 70 % of long bone growth plate fractures occur at only three areas; distal radius 38 %, distal tibia 20 %, and distal humerus 11 %. The two

Table 5.5 Frequency of growth plate fracture-separations at major long bone epiphyses

	Series A		Series B		Series C		Series D		Summary values A, B, C, D	
	#	%	#	%	#	%	#	%	#	%
D. Radius	98	37	114	35	100	47	170	37	482	38
D. Tibia	59	22	60	18	33	15	104	23	256	20
D. Humerus	20	8	56	17	24	11	37	8	137	11
D. Fibula	21	8	15	5	12	6	68	15	116	9
P. Humerus	22	8	27	8	7	3	18	4	74	6
D. Ulna	12	5	11	3	16	7	27	6	66	5
D. Femur	18	7	17	5	1	0.46	13	3	49	4
P. Tibia	6	2	8	2	4	2	8	2	26	2
P. Radius	1	0.4	5	2	16	7	6	1	28	2
P. Ulna			3	1	1	0.46	4	1	8	1
P. Femur	7	3	9	3			1	0.2	17	1
P. Fibula			2	1			1	0.2	3	0.2
n =	2.64		327		214		457		1262	

Code n, # = number, *Series A* Peterson and Peterson (Ref. [57]) 1972; *Series B* Ogden 1981 (Ref. [63]); *Series C* Mizuta et al. 1987 (Ref. [56]); *Series D* Peterson et al. 1994 (Ref. [66])
% based on value nearest to full number from 0.5 % and upwards

most common fracture areas in the study by Ehlers and Eberlein were also the distal radius (38 %) and the distal tibia (36.2 %) [143]. Examples of more unusual epiphyseal fracture-separations were indicated in some papers but not in others such as those involving the trochanters of the proximal femur or the tibial tubercle apophysis.

5.5.5 Age at Occurrence of Physeal Fractures

The large majority of epiphyseal growth plate fracture-separations occur between 10 and 15 years of age, although the entire age spectrum is involved from the newborn to those in the process of undergoing final growth plate fusion. Peterson et al. documented the age incidence of physeal fractures in males and females from 1 year of age to skeletal maturity [142]. The incidence rates were greatest for boys at age 14 with the largest number occurring between the ages of 10 and 15 years, while in girls the peak years of incidence were at 11 and 12 years with the ages from 9 to 3 showing the largest number of fractures. When the fractures at each specific epiphysis are assessed, some clinically meaningful differences are shown. Mann and Rajmaira also noted that female patients tended to have physeal fractures on average about 1.5 years younger than male patients with the same type fracture in the same location [136]. In their studies, the mean patient age for most physeal fractures was 10–12 years. Ehlers and Eberlein noted peak age for males at 14 years and for females at 12 years [143]. Mizuta et al. noted the most common occurrence of epiphyseal fracture-separation in boys at age 12 years, with the most common occurrence of injuries from ages 8 to 15 years, and in girls age 11 years was the most common year of occurrence with most of the fractures occurring between 7 and 13 years [56]. They also calculated the ages of occurrence between 0 and 5 years of age (infancy), 6 and 11 years of age (preadolescence), and 12–17 years (adolescence). The percentage of physeal fractures in relation to non-physeal fractures increased at each time period. The results were the same in males and females. Of the fractures that occurred in infancy, 9.3 % were physeal; in preadolescence, 15.7 % of fractures were physeal; and in adolescence, 29.9 % of fractures were physeal. Peterson and Peterson and Mann and Rajmaira broke down the age of the fractures at each specific physis in both males and females [57, 136]. Fractures of the distal humerus occurred at a much younger age than those of the other physes with girls showing a mean of 4–5 years and boys 5–8 years (Peterson and Peterson). In the most common distal humeral fracture, the Type IV lateral condyle fracture-separation, Mann and Rajmaira also documented a relatively younger age with 41 boys averaging 8 years of age and 14 girls averaging 5.3 years of age.

5.5.6 Distribution of Specific Salter–Harris Types Per Long Bone Region

Peterson et al. have summarized the distribution of physeal fractures by type in each of several studies (Table 5.6) [142]. The findings in several series over a 60-year period show similar pathoanatomic patterns. Virtually, 60 % of fractures are of the Type II pattern with an additional 15 % Type I. Type III fractures account for 11 % of injuries and Type IV 8.6 %. Many authors have failed to recognize the occurrence of the Type V lesion while others have diagnosed it on occasion, but the collected series document only a 0.3 % incidence. Peterson, in the most recent pathoanatomic classification, pointed out that a considerable number of fractures do not fit into the Salter–Harris classification and for that reason he deleted Type V and added twoadditional types [66].

5.5.7 Epiphyseal Fracture-Separations with Difficult Births

Epiphyseal fracture-separations accompanying traumatic births were well recognized in the late 1800s in the preradiographic era as described by Simpson and others [29]. Owing to some difficulty in diagnosis, however, they continued both to occur and to result in delayed recognition even after the onset of radiographs. Truesdell was instrumental in pointing out, not only the continued occurrence of these injuries, but also ways to recognize them both clinically and radiographically [144]. By 1918, he had described 11 cases from his own experience involving 5 epiphyseal separations at the proximal humerus, 3 at the distal humeral epiphysis, two at the distal femoral epiphysis, and 1 at the proximal femoral epiphysis. Traumatic neonatal joint dislocations did not occur but owing to the major point of weakness at the physeal level extreme trauma would be associated with epiphyseal fracture-separations. These were almost invariably associated with difficult births most of which were from the breech position, or in those instances where forcible version had been performed. Footling presentations owing to the difficult delivery which followed also presented a high likelihood of epiphyseal separation. The characteristic clinical profile, therefore, involved a difficult and often prolonged delivery characterized by breech or footling presentations, swelling in a joint region, and disinclination of the infant to use the limb, and radiographic studies showing no metaphyseal or diaphyseal fractures. As only the distal femoral and proximal tibial secondary ossification centers are present at birth with those of the proximal and distal humerus and proximal femur being absent, plain radiographs were often indistinct in terms of diagnosis. The diagnosis was frequently suspected when radiographs at 7–14 days showed evidence of new bone formation in relation to periosteal elevation. Clinically, the infants gradually began to use the affected extremities and often to clinical exam there was extreme swelling and hardness in the epiphyseal areas. Truesdell stressed, in agreement with opinions today, that operative replacement of a displaced epiphysis was rarely, if ever, indicated and that even when a displacement had been wide and not recognized for some time, the outcome had been good. He stressed that "no better evidence of the restorative and corrective ability of Nature during the early years of life can be obtained than in these cases."

Ekengren et al. reported on 20 patients with birth injuries to the epiphyseal cartilage and also showed predominant involvement of the upper extremity bones [145]. Their series

Table 5.6 Distribution of physeal fractures by type (Salter–Harris classifications)

Year	Author (Ref.)	I	II	III	IV	V	Other	Total
1933	Bergenfeldt [41]	23	251	19	13	0	4	310
1970	Rogers[a]	7	89	9	12	1		118
1974	Oh et al.[b]	34	73	14	12	0		133
1979	Mbindyo[c]	18	42	4	5	2		71
1986	Worlock, Stower [138]	30	121	5	15	0		171
1987	Mizuta et al. [56]	30	257	23	42	1		353
1990	Mann, Rajmaira [136]	210	483	143	102	5		943
1994	Peterson et al. [142]	126	510	104	62	0	149	951
2006	Kawamoto et al. [141]	26	61	7	4	0	0	101
Total		207	1887	328	267	9	153	3151
Percentage		16.1	59.9	10.4	8.5	0.3	4.9	

[a]Rogers LF. The radiology of epiphyseal injuries. Radiology. 1970;96:289–299
[b]Oh WH, Craig C, Banks HH. Epiphyseal injuries. Pediatr Clin North Am. 1974;21:407–422
[c]Mbindyo BS. Considerations on cases of epiphyseal injury observed at a Kenyatta national hospital. East Afr Med J. 1979;56:431–435
Modified from Peterson et al. (Ref. [142])

comprised epiphyseal fracture-separations of the proximal humerus in 9, distal humerus 5, proximal femur 1, distal femur 5 (4 patients), and distal tibia 1. They also noted difficulty primarily with breech deliveries which were reported in 14 cases with two other cases having complicated deliveries in other ways. They also concluded that every newborn infant with pain, swelling, or impaired movement of a limb or joint should be suspected of having an epiphyseal fracture-separation and examined radiographically. At present, ultrasound has been extremely useful in assessment of these disorders. Broker and Burbach described the use of ultrasonography in a newborn proximal humeral epiphyseal separation [131]. Two cases of separation of the proximal humerus with a review of the diagnostic criteria as listed above were presented by Lemperg and Liliequist [146].

5.6 Clinical Features of Acute Epiphyseal Fracture-Separations

5.6.1 General Principles of Management

The pathoanatomic classifications describe the patterns of breakage in epiphyseal growth plate fracture-separations and are useful in the management and reporting of such injuries. Those of Aitken, Salter and Harris, Ogden, and Peterson are sufficiently detailed that they have been and will be used as reference points for clinical studies. If one superimposes the pathophysiologic classification upon any of the pathoanatomic classifications, an approach centering on consideration of such injuries at the critical cellular level ensues [71]. In assessing these lesions, a threefold approach is assumed: (1) A knowledge of the gross and histologic anatomy of the growth plate involved provides an expectation of which fractures are likely to produce significant problems. Fracture-separations involving displacement of the proximal femoral capital epiphysis and the proximal radial epiphysis, for example, both of which have a relatively tenuous blood supply, have a poor prognosis with concern about a type C pattern on this basis as is borne out by the reported results. Considerations of growth plate shape, capsular relation, and severity of trauma are also important. (2) The effects of fracture-separations classified by pathoanatomic type at each specific epiphysis are now reasonably well known. Knowledge of the accumulated results allows for a good level of awareness concerning which fracture at each specific epiphysis is likely to lead to problems. (3) The most accurate predictions of the outcome follow from consideration and demonstration (at time of injury and following treatment) of (a) the presence or absence of damage to the epiphyseal blood supply, (b) vertical fissuring and transverse separation of the growth plate, (c) the exact level of the transverse fracture line (in relation to the proliferating zone of cartilage, the hypertrophic zone, or metaphyseal bone), (d) the extent of communication between the epiphyseal and metaphyseal circulations, and (e) the presence of soft tissue interposition at the fracture site. These are the factors that are most important, rather than the pattern of breakage as demonstrated radiologically. On the basis of anatomic and empiric knowledge a high percentage of excellent results may be expected, for example, with distal radial Type II fracture-separations, and specific investigation of the 4 criteria listed above might be unnecessary. For those epiphyses where the pathoanatomic type of injury can lead to varying results, as in Type II injuries of the distal femur, an awareness of the pathophysiologic approach can lead to more intensive investigation and perhaps in time to more specific therapy. It is expected that in the next few decades further refinements of diagnostic techniques will permit early and easier assessment of these parameters, thus allowing the precise delineation previously attainable only by histologic studies and retrospective review. The current use of bone scanning to assess vascularity of the femoral head after transepiphyseal lesions is an example of this approach.

We have attempted to show the value of investigating the sequelae of injury at the biologically important cell and tissue levels by use of newer imaging modalities to provide three-dimensional anatomic and dynamic physiologic information. The possibility of early diagnosis of a developing problem has been greatly improved by the use of bone scan in relation to epiphyseal vascular injuries, CT scanning to allow a more accurate pathoanatomic designation of the pathway of fracture within epiphyseal and metaphyseal bone, and MRI to provide indication of the level of fracture within bone and the cartilage growth plate, of vascular communication across the plate, and of soft tissue interposition at the fracture site.

The pathophysiologic approach refers not only to classifications of the injuries but also to a more biologic treatment of them. At time of fracture, early recognition of a potential growth arrest problem allows for treatment, usually operative, directed at changing, if possible, a B_1, B_2, C, or D_1, D_2 situation to a more favorable A type. In displaced Type IV lesions, which in the pathophysiologic approach appear as type B_1, open operative reduction converts the B_1 lesion in many instances to a type A lesion. The open reduction brings into anatomic alignment the articular cartilage surface, the epiphyseal bone, the growth plate, and the metaphyseal bone thus minimizing the long-term negative growth sequelae. The two areas where the pathophysiologic approach could have the greatest potential for change relate, however, to the B_2, C and D_1 type lesions. The situation of the B_2 lesion in which there is radiologically undetectable longitudinal crushing and fissuring of the growth plate thus allowing the epiphyseal and metaphyseal circulations to communicate

with each other has been accepted previously as a part of the injury about which nothing could be done. Physeal widening may be a D_1 situation where MRI and open reduction can allow for removal of interposed periosteum. Reviews of epiphyseal growth plate fracture-separations in which such lesions occurred are filled with examples of premature growth arrests, significant shortening, and major angular deformities. We are beginning to see that this situation can be changed and the negative sequelae at least minimized if not eliminated. The pathophysiologic approach utilizing MRI studies and other modalities may provide very early indication of a developing bone bridge. With close observation of the affected limb, one can resort to complete fusion of the growth plate to minimize angular deformity and eliminate the need for corrective osteotomy or apply additional responses to bone bridge formation that allow growth to continue. The pathophysiologic approach to epiphyseal growth plate fracture-separations is outlined in Table 5.7 and considerations regarding prognosis for growth plate fracture-separations are outlined in Table 5.8.

Table 5.7 Pathophysiologic approach to epiphyseal growth plate fracture-separations

I. Pathoanatomic diagnosis
Made by plain radiographs
II. Pathophysiologic approach
Superimposed on pathoanatomic classification to yield A, B_1, B_2, C, D_1 or D_2 categorization based on following considerations:
• *Fracture profile*
Age of patient, specific epiphysis injured, anatomy of epiphysis (intracapsular/extracapsular; linear, or convoluted shape), amount of displacement
• *Literature review*
Reported correlation of outcome with pathoanatomic type for specific epiphysis injured
• *Mechanism of injury*
Extent of trauma; avulsion (epiphyseal separation), compression (epiphyseal fracture)
Additional investigations (if warranted in problematic fracture-separations)
• Adjacent epiphyseal/metaphyseal bone fracture pathway: MRI, CT scan
• Longitudinal growth plate cartilage fracture with epiphyseal/metaphyseal vessel and bone cell communication or localized replacement of viable chondrocytes by dense hypovascular fibrous tissue: MRI (early); CT scan (once bone bridge formed or fibrous bar suspected)
• Epiphyseal vascularity: bone scan, MRI
• Level of fracture within growth plate: MRI
• Nonossified epiphyseal displacement: ultrasound
• Growth arrest lines: MRI most sensitive
III. General aims of pathophysiologic approach
• Perform specific treatment to convert B_1, B_2, C, D_1, or D_2 type fractures to type A, if possible
• Reveal negative growth plate sequelae early to allow intervention to minimize degree of shortening and angulation
• Consider events at the cell and tissue levels as well as at plain radiographic level

5.7 Management of Growth Plate Fracture-Separations at Specific Epiphyses

5.7.1 Proximal Humerus

Proximal humeral growth plate fracture-separations are almost exclusively Type I and Type II injuries [44, 131, 147–151]. Type III and IV fracture-separations at this epiphysis are extremely rare; not described in most series or if present due to severe high-energy trauma [152–154]. In the Type I and II fractures, the metaphysis is virtually always displaced anteriorly. As the apex of the inverted, V-shaped growth plate is superior with a trough along the anteroposterior axis, permanent damage to this irregularly shaped plate is not great. The large metaphyseal fragment left behind at the posteromedial part of the epiphysis also spares damage to the plate. Angular deformity has not been of clinical significance owing to the excellent remodeling potential of the proximal humeral epiphysis, which accounts for 80 % of the growth in length of the bone, and the fact that the shoulder joint has such a wide arc of movement that an anatomic glenohumeral articulation is not required. Shortening is documented in a fairly high percentage of cases, although this is rarely of clinical significance since it is minimal (<2 cm) and since mild length inequality of the upper extremities is not important. Dameron and Reibel noted shortening in 30 %, with 15 % having 1.5 cm or more involvement [149]. Neer and Horwitz documented 16 % with 1 cm or more shortening in their entire series [151]. In mildly to moderately displaced fracture-separations they noted 11 %, and in severely displaced lesions 30 % with such shortening. Aitken described a 64 % incidence (7/11) of shortening, all in nonoperated fractures, with a range from 1/4″ to 1½″ [44]. Some of the shortening in these cases was felt to be due to malposition with imperfect remodeling, but Aitken commented on premature fusion due to growth plate damage associated with severe trauma and an irregularly shaped plate, even though he noted all injuries to be types I and II (by S–H criteria). The late age at injury also limits the extent of discrepancy. Shortening in those <11 years of age at time of injury was not seen, probably due to the relatively greater thickness of the plate. Baxter and Wiley reported on 57 fractures and noted an age range at occurrence between 8 years 11 months and 15 years 1 month [147]. There was

Table 5.8 Considerations regarding prognosis for growth plate fracture-separations

• S–H commentary re prognostic value of their classification cautioned that, beside the pattern, age, blood supply, method of reduction, and open injury influenced the outcome
• Growth plate damage can occur: (i) at time of fracture by crushing the growth plate, allowing epiphyseal–metaphyseal vascular communication, or leading to periosteal interposition or (ii) at time of treatment which can add further damage with more crushing of the plate by forceful reduction or further devascularization with open reduction
• Age considerations. (i) Where no growth sequelae have occurred, a *younger age* of occurrence with several years of growth remaining can allow for essentially anatomic remodeling of markedly displaced type I or II fractures (e.g., distal radius, proximal humerus) while an *older age* of occurrence near skeletal maturity for these same fractures suggests need for active reduction by closed or even open methods. (ii) Where growth sequelae have occurred, a *younger age* of occurrence leads to severe length discrepancy and/or angular deformation while an *older age* of occurrence significantly limits problems as growth plate closure is about to happen
• Prognosis is not related to the S–H (or any pathoanatomic) categorization: type II fractures of the proximal humerus have virtually no negative growth sequelae; type II of distal radius have infrequent but increasingly documented growth sequelae; and type II of distal femur have a high level of negative growth sequelae (as many as 50 % in some studies)
• S–H and other pathoanatomic categorizations remain valuable for what they describe, the plain radiographic appearance of the fracture pathway in relation to the growth plate, but the plain radiograph cannot define events at the cell and tissue level that are the main determinants of the outcome
• Prognosis is related to many pathophysiologic and pathomechanical factors including: the shape of the growth plate; the force direction and mechanism of injury; the extent and position (physeal level) of growth plate crushing; and any epiphyseal–metaphyseal transphyseal vascular communication
• The *pathophysiologic* considerations are superimposed on (used along with) the S–H or other *pathoanatomic* classifications including those of Ogden and Peterson and the *pathomechanical* categorizations of Weber and Morscher

more than 1 cm shortening in 30 % (9 of 30) with a maximum of 2 cm and insignificant angulation regardless of method of treatment or age at fracture. Excellent results were seen regardless of the degree of displacement or the age at injury. Open reduction seemed not to be warranted since results were so good even where healing was allowed to occur with virtual full displacement.

Kohler and Trillaud described 49 cases of epiphyseal growth plate fracture-separation of the proximal humerus in the course of reviewing 136 proximal humeral fractures [150]. They too saw only Type I and Type II fractures with Type I seen in 16.3 % and Type II in 83.7 %. The epiphyseal separations were seen throughout the childhood years; 45 % of the fractures occurred between 10 and 14 years of age and 76 % occurred between 8 and 16 years of age. Although 45 % of the patients (22 of 49) had surgical intervention, the authors reached the conclusion that surgery was only of marginal benefit and thus infrequently indicated. Length discrepancy was not a problem being mild to moderate in the 1 cm range with the greatest amount of shortening being 3 cm. In those 5 cases of epiphyseal separation where some subsequent growth injury could be identified, 4 occurred after surgical treatment and only one after nonoperative treatment. The Type I epiphyseal separations were seen in all ages while the Type II were concentrated in older children. They commented that "the function of these patients is always good or very good regardless of the anatomy of the lesion or the treatment". The appearance of the scar was felt to be a particularly negative aspect of surgical intervention and they commented that "the appearance of the scar is very often unattractive" owing to its hypertrophic or keloid characteristics. They also raised the possibility that reduction, whether open or closed, and open surgical intervention with internal fixation were as capable of inducing growth damage as they were of minimizing it. They concluded that "surgical treatment presents no advantage over nonoperative treatment on the basis of functional results or long-term anatomical results" and that "nonoperative treatment should be recommended with surgery being discussed only in special cases". Anatomical reduction was not felt to be essential. Surgery would be considered primarily for major displacement when there was virtually no growth remaining and even then the simplest form of fixation should be used.

Burgos-Flores et al. were more supportive of a surgical approach with open reduction [148]. They analyzed 22 patients who had marked displacement of the proximal humeral fracture-separation from a total group of 65 patients. The group which was more displaced underwent closed or open reduction and Kirschner-wire fixation. All the epiphyseal injuries were of the Salter–Harris Type II variety. Following closed reduction, two or three percutaneous Kirschner wires, were passed from the lateral cortex of the metaphyseal fragment across the physis into the humeral head. Open reduction was required in three. Two patients suffered final length discrepancies of 4.0 cm (1 having had an open reduction and the other closed) with virtually all other patients showing either no discrepancy or discrepancies below 1.5 cm. It was concluded that patients under the age of 13 years should be treated conservatively regardless of degree of displacement or post-reduction angulation. They felt, however, that in certain patients over the age of 13 years, if marked displacement or angulation were seen on initial radiographs, accurate reduction should be obtained usually involving closed reduction and maintenance with K-wire fixation, but on occasion warranting open reduction.

Beringer et al. also supported obtaining and maintaining anatomic reduction for markedly displaced proximal humeral epiphyseal fractures especially in those 15 years of age or older [155]. Dobbs et al. assessed 28 severely displaced

proximal humeral fracture-separations, all of which were type I (4) or Type II (24) injuries [156]. They used the Neer grading system for displacement severity (grade I, <5 mm of shaft diameter; grade II, <1/3 shaft diameter, grade III, 2/3 shaft width; and grade IV, >2/3 shaft width) and considered severe lesions to be grades III–IV. All underwent successful reduction under general anesthesia in the operating room to grade I or II displacement (closed reduction and shoulder spica-3, closed reduction and K-wire fixation-20, open reduction and AO screw fixation-3, or open reduction and pin fixation-2). Nineteen of the 28 were aged 15 or 16 years (range 5y–16y). At follow-up (average 4 years) all had near-normal glenohumeral motion and full strength and function [156].

Binder et al. studied 72 proximal humeral physeal fractures seen at their institution between 1992 and 2009 [157]. There were 303 proximal humeral fractures with 231 (76 %) metaphyseal and 72 (24 %) physeal. The type distribution was: SH I 23 (32 %), SH II (58 %), SH III (6 %), and SH IV (4 %). Fifteen fractures were reconstructed/repositioned anatomically by open or closed reduction with 93 % excellent results. Fifty-seven fractures were treated conservatively with 95 % excellent results. The treatment was dependent on the age of the patient with open/closed reduction in the older patient where relatively little remodeling could be expected. The average age at SH fracture type increased by grade; type I 9 years, II 10 years, III–IV 13 years. They tended to intervene with angular tilt >30° regardless of age, but in particular for the older patients (11.5 years or greater). Fixation when needed was by K-wires, which also helped in reduction by leverage. Two other studies have concentrated on management of severely displaced proximal humeral physeal fracture. Schwendenwein et al. performed closed/open reduction in 6 with a SH II lesion with no shortening or angular rotation resulting [158]. K-wire fixation was used.

Sankar et al. used intramedullary stabilization following closed reduction with a centromedullary rod inserted from the distal lateral humerus [159]. Two adolescents were treated this way with absence of a shoulder scar an additional advantage.

Since 80 % of humeral growth occurs at the proximal end and fracture at this epiphysis is relatively common, the absence of reports of extensive angular deformities or growth discrepancies is convincing evidence of the benign nature of this injury. The Type I and Type II injuries are graded, therefore, as A lesions in the pathophysiologic classification. There is no reported evidence of vascular problems involving epiphyseal blood supply. The epiphysis is mainly extracapsular assuring persistence of an excellent blood supply after injury, although parts of the epiphysis are intracapsular. There may be some occasional B_2 type injuries, but these occur toward the end of growth and as noted above do not cause clinical problems.

Other than the use of ultrasound or arthrography to diagnose neonatal fractures, specific radiologic measures other than plain films should virtually never be required with this injury [131]. The vast majority of proximal humeral epiphyseal fracture-separations are treated by conservative means using either a sling in nondisplaced or minimally displaced fractures or closed manipulation followed by a sling or long arm cast in those cases that are more markedly displaced. Closed reduction can be stabilized by K-wire fixation, ideally from the large metaphyseal fragment to the adjacent metaphysis, although fixation into the epiphysis does not appear to cause problems. Immobilization in the abducted position in an upper extremity spica, open reduction or internal fixation seem not to be warranted except with neurovascular compromise or with marked deformity in those at or near skeletal maturity in the 14–15 years or older range. The remodeling potential of the proximal humerus is great since 80 % of the growth of this bone occurs at this region. Figure 5.21a–c illustrates a type II proximal humeral fracture-separation managed by nonoperative means.

5.7.2 Distal Humerus

5.7.2.1 Lateral Humeral Condyle

The lateral humeral condyle fracture is a Type IV fracture-separation. This injury was clearly recognized and illustrated by Poland in 1898 [4]. The mechanism of injury is a varus force with the elbow extended and the forearm supinated. This mechanism was demonstrated anatomically by Jakob et al. [160] and previously by Mouchet in 1898 [161] and Stimson in 1907 [162]. The fracture is effectively pulled away from the bone by the lateral elbow ligament and the long extensor muscles. The fracture begins laterally and proximally and passes distally and medially towards the joint surface. In nondisplaced or minimally displaced fractures, an intact cartilage bridge maintains the cartilage surface. Displacement occurs if this cartilage hinge is divided. The undisplaced fracture of the lateral condyle is of the incomplete type and the displaced fracture is complete. It represents a clear-cut example of the value of operative intervention in particular epiphyseal growth plate fractures with significant beneficial results documented by Badelon et al. [163], Conner and Smith [164], Crabbe [165], Foster et al. [166], Hardacre et al. [167], Jakob et al. [160], and Thompson et al. [168]. Epiphyseal injuries in the elbow region were recognized in the 1930s to be especially problematic and often poorly responsive to closed reduction and cast techniques [169, 170]. With the exception of undisplaced fractures, or of fractures minimally displaced by 2 mm or less, it is widely accepted that open reduction and internal fixation be done for all these injuries. Closed reduction followed only by cast immobilization is not

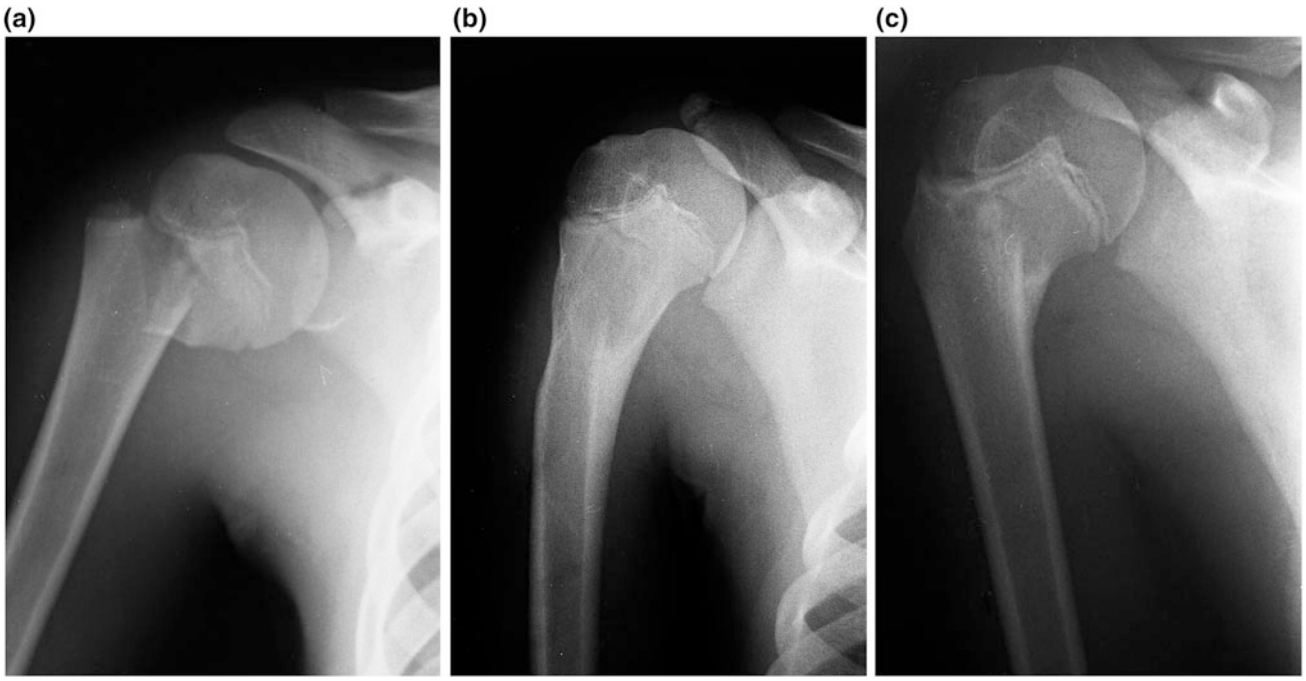


Fig. 5.21 Proximal humeral epiphyseal fracture-separation is shown. **a** Radiograph demonstrates a type II proximal humeral fracture-separation with moderate displacement in a 12-year, 3-month-old male shortly after injury. Literature reviews of these fractures so overwhelmingly demonstrate a benign post-injury course that the pathophysiologic A grading can be assigned without the use of additional imaging procedures. **b** Anteroposterior radiograph at approximately 4 months post-injury shows healing and metaphyseal remodeling medially mediated by periosteal new bone formation. **c** Anteroposterior radiograph at 1 year, 2 months post-injury showing complete healing and advanced remodeling

recommended as imperfect reduction or subsequent loss of reduction by slippage in cast can lead to severe growth disturbances. Review of many cases from the literature indicates that open, anatomic reduction with K-wire or screw fixation or periosteal suturing is highly desirable for the displaced fracture, and if done the likelihood of an excellent result is very high in the 90–95 % range. Malunion, nonunion, avascular necrosis, and deformity due to premature epiphyseal fusion appear to be related almost exclusively to closed reduction with imperfect positioning or delayed or imperfect operative intervention. The open reduction with anatomic repositioning converts a Type IV B_1 to a Type IV A fracture. It reconstitutes the smooth intra-articular cartilage surface eliminating the risk of degenerative arthritis and relates epiphyseal bone to epiphyseal bone, growth plate cartilage to growth plate cartilage, and metaphyseal bone to metaphyseal bone greatly minimizing post-fracture growth sequelae. More accurate diagnoses of the line of fracture, its relation to the joint surface, and the degree of displacement have been achieved by high resolution ultrasonography especially in children <9 years of age where the fracture line involves the cartilagenous trochlea [171].

Flynn, based on his extensive experience with these injuries, described instances of nonunion of minimally displaced fractures in the lateral condyle and advocated open reduction and internal fixation of any fracture displaced >2 mm [172]. He reported on several cases of nonunion of the lateral condyle over a period of 12 years. He noted that "the anatomic cause of nonunion is instability of the distal fragment but the most common cause is inadequate treatment of the fresh fracture." The reasons for inadequate treatment were failure to present to a physician, failure to diagnose the fracture at initial assessment, failure to recognize displacement, failing union during the course of management, and failure to pin the fracture when there was >2 mm of displacement [173, 174]. Late criteria for successful treatment of a nonunion of a lateral condyle fracture are that the fragment is in an acceptable position and the physis of the fragment is still open. The danger of not treating is that the physis of the condylar fragment will grow imperfectly or close prematurely and lead to progressive valgus deformation. The negative end result is the valgus unstable elbow with ulnar neuropathy. A post-healing fishtail appearance of the distal humerus represents a central physeal disturbance of growth at the junction between the fractured lateral condyle and the more medial distal humeral physis. It is of no clinical consequence as it causes no symptoms. Lateral condylar overgrowth is increasingly recognized with more careful follow-up analyses but appears to be without evidence of functional abnormality. It was

documented radiographically in 135 of 175 patients (77 %) with closed or open reduction and K-wire fixation [175].

Milch defined two types of fracture, type I with the fracture line crossing the capitular (capitellar) epiphysis and entering the joint lateral to the trochlea and type 2 with the fracture fragment including the capitellum intact and entering the lateral part of the trochlea [176]. Jakob et al. referred to undisplaced and displaced fractures. A current classification based on their paper (although not explicitly defined in it) refers to type I fractures with the articular surface intact, type II fractures complete (entering the joint) but minimally displaced (2–3 mm), and type III fractures complete, displaced (>4 mm) and usually rotated [160].

There is increasing delineation of the grades of fracture, by which is meant the degree of displacement at time of treatment, and clearer indications of the sequelae. Badelon et al. have defined 4 grades of this fracture although all represent a Type IV S–H categorization [163]. In A lesions (their terminology), the fracture is nondisplaced and can be seen as a crack on only one radiographic view; (B) there is a visible fracture line with minimal displacement <2 mm and generally distinguished by a slide in the lateral cortex; (C) displacement of >2 mm on all radiographic views; and (D) major displacement with complete separation of the fracture edges. They reviewed 47 patients. In 10 cases of the first group, all results were excellent being achieved either with long arm casts or long arm casts with percutaneous K-wire pinning. Results were progressively further from perfect in Groups 2, 3, and 4. Their basic recommendation was to perform open reduction and Kirschner-wire fixation and they came to the belief that "open reduction and internal fixation are essential" in anything other than a simple nondisplaced fracture with <2 mm of separation. It is important to preserve the condylar blood supply if open reduction is done. There were examples of axial deviation of >10° in either valgus or varus which they felt corresponded to incorrect positioning of the condyle at the time of either fracture or immobilization. Although the injuries were Type IV, in most cases, the fracture line crossed the cartilaginous epiphysis of the distal humeral segment but did not touch the secondary ossification center of the capitellum minimizing the risk of epiphysiodesis. They went on to note, however, that "nevertheless, we have observed 8 cases of lateral condyle epiphysiodesis without clinical manifestations. The epiphysiodesis mainly concerned the medial part of the lateral condyle." The epiphysiodesis was "relatively central" which "explains the absence of axial deviation and the fishtail aspect of the lower extremity of the humerus after growth is completed."

Foster et al. also concurred that closed treatment resulted in satisfactory results if the initial displacement did not exceed 2 mm [166]. Percutaneous pinning of nondisplaced or minimally displaced fractures was an acceptable approach to management. They also concluded that those fractures with >2 mm of displacement should be reduced, pinned, and immobilized for 6–8 weeks. Evidence of delayed union after 8 weeks was an indication for internal fixation and possibly bone grafting. Even established nonunions in good position were best treated by open reduction and bone grafting. Valgus deformity was the most common deformity resulting. They stressed that "the functional results were invariably good regardless of the radiographic or clinical findings." Imperfect results radiographically involved an enlarged lateral condyle, delayed union, nonunion, and avascular necrosis. The fracture rarely crosses exactly between the trochlea and capitellum, but it usually includes a variable amount of the lateral trochlea. In the younger patients, therefore, there is very little bone-to-bone opening to allow for transphyseal bone bridge formation although other complications can ensue. All 8 of their poor results were in fractures widely displaced and rotated and treated by open reduction. Much of the problem may relate not so much to cartilage destruction at the time of injury, but to avascular necrosis induced by the fracture and the surgical intervention. The "fishtail" deformity which refers to a notch between the trochlea and capitellum on the AP radiographic view is thought to result from damage to the growth plate centrally with premature fusion of the capitellum to the lower humeral metaphysis. This has been described in the older literature from 5 to 32 % of cases. This group found the deformity in only 4 patients without early clinical significance. "We did not encounter any angular deformities as a result of an epiphyseal bridge or bony bar as one might expect from this injury. Our functional results were generally good regardless of the radiologic findings." The fact that the bar was central would indicate why no angular deformities were seen. The fishtail deformity corresponds to the central bone bridge formation in distal femoral fracture-separations.

Song et al. felt that closed reduction to decrease displacement of fracture fragments to 2 mm or less allowed for excellent results with internal fixation [177]. They classified into 5 groups: stage 1 limited fracture line within metaphysis ($\leq$2 mm displacement); stage two lateral gap ($\leq$2 mm displacement); stage 3 gap of same width throughout fracture line ($\leq$2 mm displacement); stage 4 without rotation of fragment (>2 mm displacement); and stage 5 rotation of fragment (>2 mm displacement). It was only where reduction exceeded 2 mm that open reduction was resorted to. These were mostly in group 5 patients where there was associated rotation of the fragment.

Rutherford reviewed 39 fractures of the lateral condyle of the humerus and concluded that less than perfect results radiologically rarely led to any clinical problem [178]. He took exception with the fact that some had commented on epiphyseal arrest with transphyseal bone bridge between metaphyseal and epiphyseal bone segments. This bone bridge

is frequently present as noted by the works of others but tends to appear centrally and is thus rarely a cause of valgus malformation directly. With premature closure of the lateral condylar physis, however, such deformation can occur. The fishtail deformity of the distal part of the humerus occurs commonly, caused by bone bridge formation centrally. The abnormalities of growth of this fracture involve overgrowth of the lateral condyle, formation of a cleft in the trochlea with widening of the distal part of the humerus (fishtail deformity), and premature epiphyseal closure. He indicated that premature epiphyseal closure was seen in one elbow with no associated angular deformity. Thirty-nine fractures were assessed with average time of injury of 6.3 years and the average length of follow-up 5.5 years. Some patients still had growth at the termination of the study. It is well recognized that many of the negative sequelae of lateral humeral condylar fractures such as tardy ulnar palsy occur in mid-adulthood. Rutherford feels that bone bridge formation does not occur in the sense that in his series and others valgus angulation is not detectable. The valgus deformation is described as occurring owing to nonunion, late reduction, and avascular necrosis, and malunion. He indicates that "no cases of metaphyseal-epiphyseal cross-bridging and subsequent epiphyseal arrest were reported." He concludes that cross-bridging of the epiphyseal cartilage is a rare cause of cubitus valgus after a fracture of the lateral condyle in a child. The fishtail deformity is felt by most to be a central growth arrest or due to a formal separation between the trochlear epiphyseal plate and the trochlear portion of the capitella (capitellar) epiphyseal plate. He concluded that "uncomplicated separation of the 2 portions of the distal epiphyseal plate of the humerus is the real cause of the deformity."

Wadsworth reviewed the types of displacement in the lateral humeral condylar entity and commented on the complications such as malunion, premature fusion, nonunion, avascular necrosis, or cubitus valgus with ulnar palsy [179]. Malunion refers to the imperfect union between the trochlea and capitellum. It occurs with a Type II injury. The fully displaced Type III injury results in a nonunion. Premature epiphyseal fusion is mentioned by Wadsworth as well as Blount and Salter and Harris [52, 179, 180]. According to Wadsworth, in the first type, the capitellar epiphysis alone fuses prematurely to the metaphysis and as this epiphysis accounts for ossification of the outer part of the trochlea disturbance of growth commonly referred to as a fishtail deformity results. In the second type, the normal pattern of fusion is followed with the capitellar and trochlear epiphyses first fusing to each other and then to the metaphysis but the capitellar epiphysis fuses in advance of that of the trochlea leading to valgus angulation. Avascular necrosis can be seen and is most common with operative intervention which has led some to be wary of such an approach. Valgus deformity results from a disturbance of the important osseous link between the trochlea and capitellar centers. This may occur in the first type of premature fusion, in malunion or established nonunion, all of which result in loss of the outer lip of the trochlea and fishtail deformity. Additional factors are union in malposition, nonunion, avascular necrosis, or premature fusion with diminished growth in the outer half of the lower end of the humerus. Ulnar palsy is an additional delayed complication.

Skak et al. concluded that a reduced growth potential at the trochlear groove is a regular complication of a SH type IV, referred to in the older literature as a Milch I and II fracture [53, 176].

Cates and Mehlman demonstrated three cases of growth arrest of the capitellar physis after displaced lateral condyle fractures in children (all of which had been treated operatively) [181]. Two of the three were functionally asymptomatic.

More recent studies advocate slight changes in management regarding surgical intervention. Hasler and von Laer showed the value of operative intervention for lateral condyle distal humerus fractures. Sixty-six fractures over a 20 year period were prospectively treated by open reduction and internal fixation with a metaphyseal lag screw. Results were considered to be superior to the "relatively unstable fixation with Kirschner wires" showing anatomic union, symmetric carrying angles and full range of motion in all 27 operated cases with no lateral condylar overgrowth. The overgrowth was felt to be frequently seen with instability during healing with casts alone or with K-wires [182].

Launay et al. assessed two treatment modalities used in different centers due to continuing controversy regarding management in both nondisplaced and displaced fractures. They reviewed 97 fractures. Longarm immobilization alone resulted in additional fracture displacement and a higher number of nonunions than did surgical management. Operative stabilization with excellent results could use two smooth or threaded K-wires and could pass through the ossific nucleus of the capitellum if necessary but must engage the far cortex and should be subcutaneous. In one of the institutions, all lateral condyle fractures were treated operatively regardless of the presence or absence of displacement, held with K-wires subcutaneously and immobilized for 6 weeks. A convincing argument was made for the value of adopting this method. If nondisplaced fractures (<2 mm gap) were treated by cast alone frequent assessment was needed since fractures could further displace on occasion in casts [183].

Koh et al. have reported on a large series of 175 fractures of the lateral condyle of the distal humerus [175]. There were 113 males and 62 females (1.8/1.0). According to the Milch classification, there were type I 18 and type II 157, while the Jakob classification showed type I 41, type II 85, and type III 49. Treatment was by cast alone in 39 (38 type I, 1 type II), closed reduction and internal fixation with

K-wires in 33 (3 type I and 30 type II), and open reduction and internal fixation with K-wires in 103 (54 type II and 49 type III). End results were described as excellent in 116 and good in 59. Analysis looked for each of the known complications of lateral condyle fractures: varus, valgus, lateral condyle overgrowth, fishtail deformity, nonunion, malunion, and avascular necrosis. Lateral overgrowth and cubitus varus were the two commonest sequelae although they were not functional problems. Varus deformities occurred in 9.7 % but none require surgical correction. No cases of avascular necrosis, fishtail deformity, nonunion, or significant decreased range of motion were encountered. Lateral condylar overgrowth or lateral osteophytes were seen in 77 % but were of no clinical significance. Only three valgus deformities (1.7 %) due to partial growth arrest were seen. Intervention as determined by the three type classification seemed fully appropriate.

Weiss et al. also showed that fractures with greater displacement (≥2 mm) and articular surface not intact (type 3) (as demonstrated by arthrogram) had higher major complication rates that fractures with similar displacement (≥2 mm) but an intact articular surface (type 2) [184]. The major complication rate for type 2 was 1.5 % (1/65) and 10 % (9/93) for type 3. They found that all type 2 patients had displacement <4 mm and all type 3 had displacement ≥4 mm.

Two uncomplicated cases treated by open reduction and internal fixation with Kirschner wires are illustrated in Fig. 5.22a–f. In Fig. 5.23 operative approach to a delayed union described by Flynn is shown and in Fig. 5.24a–e a case of growth deformity resulting from incomplete closed reduction is shown.

5.7.2.2 Distal Humeral Physis

These fracture-separations, which occur almost exclusively in the first 5 years of life, are invariably Type I or Type II injuries (DeJager and Hoffman; DeLee et al.; Dias et al.; Downs and Wirth; Holda et al.; Mizuno et al.; Siffert) [132, 185–190]. The disorder had been considered rare but is probably more common than previously believed. These injuries are being diagnosed more often owing to increased clinical awareness and the use of ultrasound [132] and MRI techniques. Hutchinson (1893) noted that "before 5 or 6 years (in cadaver experiments) it is easy to detach the lower epiphysis of the humerus en bloc … but that after that age the separation is usually in part a fracture" [30, 132]. Smith in 1850 and Farabeuf in 1886 clearly demonstrated distal humeral epiphyseal separations [11, 191]. Neither angular deformity nor shortening due to growth arrest have been reported, although slight persisting, nonprogressive varus due to malposition at time of healing is relatively common. This fracture-separation conforms to the type A pathophysiologic type even without more detailed imaging studies. The persisting epiphyseal blood supply after injury in this extracapsular fracture and the relative thickness and gentle curvilinear plane of the cartilage plate in young patients can be inferred to protect against growth arrest problems based on the literature reviews showing minimal problems post-injury. Treatments by closed reduction or open reduction with K-wire fixation have been used. Fracture-separation of the distal humeral epiphysis is now an increasingly recognized injury and reports in the literature indicate a fairly consistent pattern. The fracture-separation is often misdiagnosed initially either as a dislocation of the elbow or a fracture of the lateral condyle [43]. De Jager and Hoffman reported on 12 cases [185]. The primary problem with the fracture is cubitus varus after healing. This is reported in many papers and is an example of a malunion rather than of an asymmetric growth plate damage. The fracture is most common in those under 2 years of age and not infrequently occurs either as a birth injury in association with a difficult delivery or as a result of childhood abuse. The common recommendation is for closed reduction followed by percutaneous K-wire pinning and long arm casting to insure appropriate position. Displacement is characteristically posteromedial with only occasional posterolateral or anterior displacement. The injury is almost invariably a Type I fracture-separation in the very young and a Type II fracture-separation in those >2 years of age. De Jager and Hoffman reviewed 6 reports as well as their own totaling 48 fractures. The normal carrying angle was maintained in only 22 patients. The cubitus valgus was decreased in 12 patients and was sufficiently decreased to lead to a cubitus varus in an additional 12. The age at occurrence was 55 % of the fracture-separations under 2.5 years and 45 % over that age.

In a large series of 21 children with fracture-separations of the distal end of the humeral epiphysis, 15 developed cubitus varus after treatment with 9 undergoing corrective osteotomy (Abe et al.) [192]. The study, which used the Ogden classification system, defined one Type IA fracture (S–H I), 16 Type IIA (S–H II), and 4 Type IIC (S–H II). The average age of occurrence was slightly older than in other groups averaging 5.1 years and ranging from 1 to 11 years. Accuracy of diagnosis was enhanced by the frequent use of arthrograms. The abnormal cubitus varus was due to initial malposition and not to a true growth arrest since in virtually all cases the cubitus varus as measured 1-year post-injury did not change over the subsequent 4–15 years. The common pattern of displacement was posteromedial with only occasional posterolateral displacement. Closed reduction and percutaneous pinning followed by long arm cast immobilization for 3 weeks is recommended. Cubitus varus was again identified as the most common complication with 7 of 13 patients treated at the authors' own institution and all 8 treated elsewhere developing the deformity.

Mizuno et al. reported on 6 patients with this injury [189]. All were between 2 and 18 years old at the time of injury and

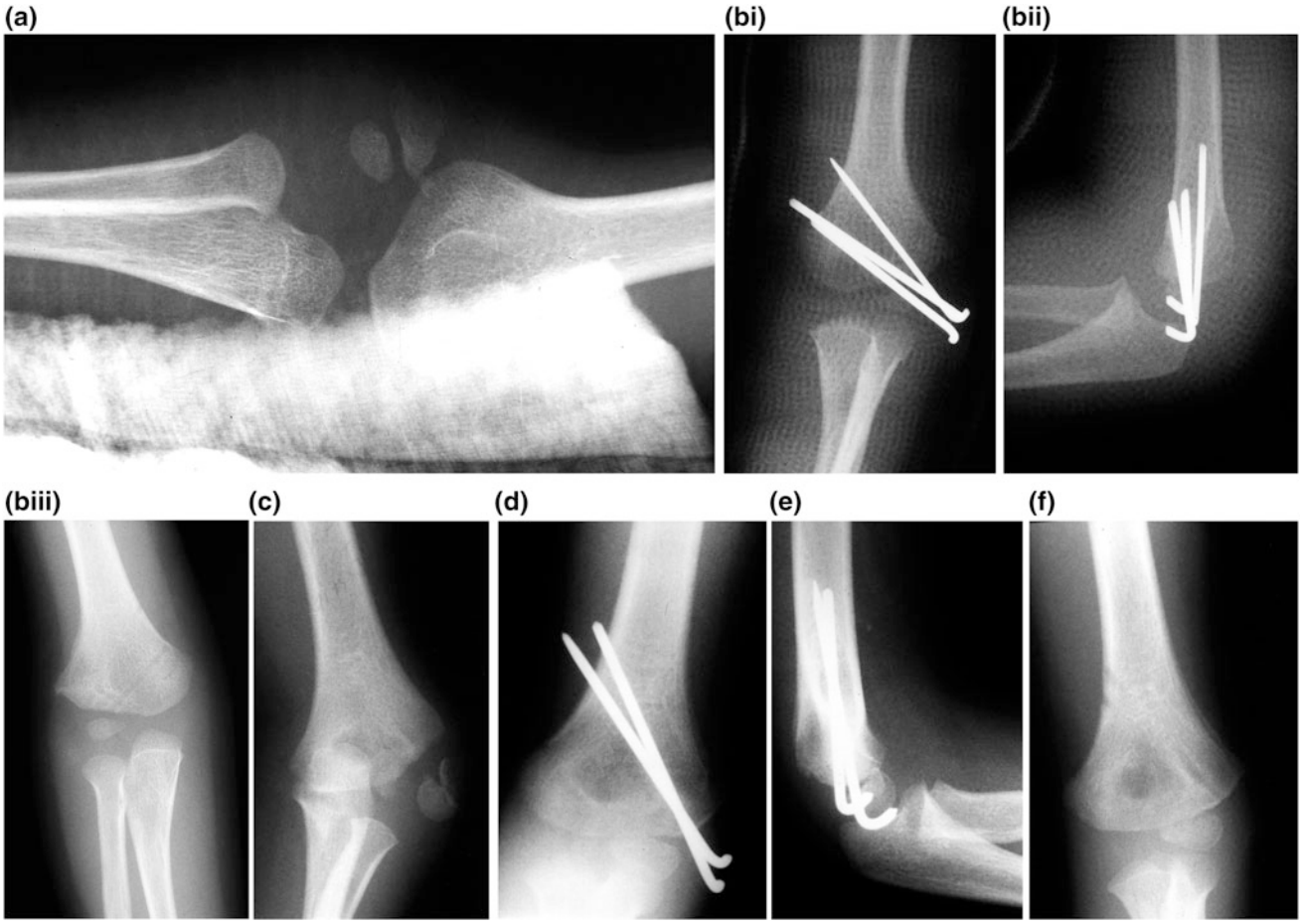


Fig. 5.22 Two cases of displaced fractures of the lateral humeral condyle are shown. (Figure a–bii and c–f). **a** An anteroposterior radiograph of a displaced type IV distal lateral humeral condyle fracture in a 6-year-old male is seen. The pathophysiologic B_1 situation exists. **b** Anteroposterior (**i**) and lateral (**ii**) radiographs show conversion of the fracture to a type A following open reduction and internal fixation with K-wires. The intervention anatomically related metaphysis to metaphysis, growth plate to growth plate, epiphysis to epiphysis, and articular cartilage surface to articular cartilage surface. Results with this intervention have been excellent in terms of minimizing long-term growth sequelae. **iii** Anteroposterior view at time of healing is seen after K-wire removal. **c** Anteroposterior elbow radiograph shows characteristic position of fragment with complete separation and 180° rotation of the lateral condyle. This is a type IV pattern. Open reduction and internal fixation is clearly mandatory to allow for appropriate healing. **d** Anteroposterior radiograph shows postoperative correction with 2 K-wires stabilizing the reduced fragment. **e** Lateral radiograph shows wires in place. **f** Anteroposterior radiograph shows healed fragment following removal of K-wires

diagnosis of fracture of the lateral condyle and traumatic dislocation of the elbow were frequently made initially. In these fracture-separations, the capitellum maintains its relationship to the head of the radius but not to the humerus. In a fracture of the lateral humeral condyle, the axes of the humerus and forearm remain the same but the relationship of the capitellum to the radial head frequently changes. With a dislocation of the elbow, the relationship between the epiphysis of the capitellum and the radial head is changed. The lesions were Type I (often confused with elbow dislocations) or Type II (often confused with lateral condyle fractures).

Jacobsen et al. reported 6 neonatal fractures. All were treated with closed reduction or simply placing the child in a longarm cast with the elbow flexed at 90° and the forearm in pronation. All healed uneventfully with no varus deformity. The literature supports the occurrence of varus when the injury is sustained after 6 months of age [193].

Dias et al. reported on the value of ultrasound in diagnosing neonatal separation of the distal humerus [132]. This modality is increasingly used for epiphyseal growth plate fractures in the neonatal age group, not only with this lesion but also with those of the proximal humeral and proximal femoral epiphyses. The authors reported 15 cases of neonatal separation of the distal humeral epiphysis including their own. The disorder was generally associated with a difficult labor, birth trauma, or a footling breech delivery. The tendency in neonatal cases was to manipulate the arm to the correct position and hold it in a collar and cuff or posterior

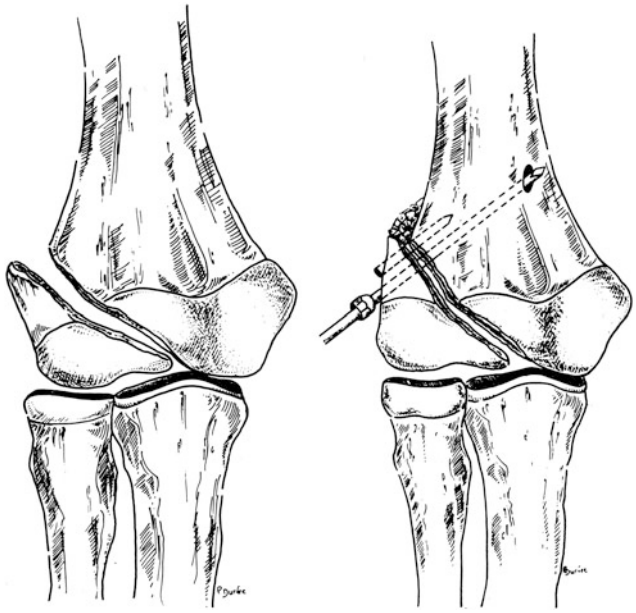


Fig. 5.23 Illustration shows the surgical approach to treating a nonunion of the lateral humeral condyle [172]. Open reduction and internal fixation removes intervening fibrous tissue, and realigns the fragment linking metaphysis to metaphyseal bone, physeal tissue to physeal tissue, epiphyseal bone to epiphyseal bone, and articular cartilage to articular cartilage. Metallic pin fixation is then used, care being taken if at all possible not to traverse the physis. (Reprinted with permission from Flynn JC. Nonunion of slightly displaced fractures of the lateral humeral condyle in children. J Pediatr Orthop. 1989;9:691–696. Copyright 1989 Wolters Kluwer Health)

long arm splint. Long-term results were reported as normal in each of the cases with only one example of 10° varus reported. Barrett et al. reporting on two cases also noted posteromedial displacement [49]. Treatment was by closed reduction with position maintained by flexing the elbow 90°, pronating the forearm, and immobilization in a posterior splint for 3 weeks.

5.7.2.3 Medial Humeral Condyle

These injuries are infrequent but have the potential to cause major growth problems. They are all Salter–Harris Type IV injuries with an intra-articular component. Diagnosis is difficult in the younger child since the trochlea ossifies later than the more lateral capitellum and is not completely ossified until 9 years of age. The fracture line passes mostly through cartilage in the younger child but a metaphyseal segment of bone is usually seen proximally. Diagnosis is aided by oblique radiographs (as well as anteroposterior and lateral views), arthrograms, and now more commonly magnetic resonance imaging. The mechanism of injury is usually a valgus force on an extended elbow [194]. Bensahel et al. described 27 cases, providing a good overview of the problem [73]. The average age of the patients was 6 years, 7 months with a range from 6 months to 11 years. Although all the injuries were Type IV in nature, there were three categories seen: (a) undisplaced fractures with the fracture line just visible proximal to the physeal plate (12 cases—48 %); (b) marked displacement medially and proximally without rotation of the fragment (9 cases—30 %); and (c) severe displacement with rotation of the fragment such that the articular surface faces medially and may be incarcerated in the elbow joint (6 cases—22 %).

Leet et al. studied 21 medial humeral condyle fractures and used the Bensahel classification with 11 type 1, 3 type 2, and 6 type 3 injuries [194]. The average age at injury was 4.6 years (range 1–11 years) with type 1 patients younger (4.0 years) than types 2–3 (5.2 years). The treatment approach in both these series was similar to that used for lateral condylar fractures. Undisplaced type 1 fractures were treated in a long arm cast for 4–6 weeks. Minimally displaced type 2 fractures had either closed reduction or open reduction with K-wire pinning and all type 3 fractures had open reduction with K-wire fixation. Leet et al. adopted the >2 mm displacement rule for reduction and pinning.

Undisplaced fractures gave consistently good results as did the majority of mildly displaced group b fractures. Poor results in groups b and c were seen only in cases with delay of diagnosis and treatment. Loss of position during casting or imperfect reduction can lead to stiffness, nonunion, and progressive elbow varus. Rare instances of trochlear avascular necrosis can occur because of the relatively restricted blood supply entering from the posterior trochlear metaphyseal region. Older series showed an age predilection between 8 and 12 years of age but this was probably due to unrecognized younger cases. The youngest case report of fracture of the medial humeral condyle was in a 6-month-old infant reported by De Boeck et al. and suspected of having suffered from child abuse [195]. Open reduction was performed along with K-wire fixation with normal clinical and radiological development at 3 years of age. Peterson has reviewed each of the three main types of distal humeral epiphyseal fracture-separations [196, 197].

5.7.2.4 Medial Humeral Epicondyle

The medial humeral epicondyle is an extra-articular traction apophysis attached to the distal medial humerus. It does not contribute to humeral longitudinal growth. It frequently suffers an avulsion injury in childhood mediated by the flexor muscles and medial collateral ligament attachments and usually with a valgus stress that can dislocate the elbow. The fracture fragment is usually displaced distally. This injury accounts for 10–12 % of elbow fractures in children. Fifty percent or more of medial epicondyle fractures are associated with posterior elbow dislocations [198]. It is most common between 9 and 14 years of age. In a literature review of 498 patients, the average age was 11.93 years [199]. The fragment may be trapped in the elbow with

reduction, an occurrence that requires surgery to reposition it. If minimally displaced (<2 mm) nonoperative cast treatment is fine. Some will operate to reposition if displacement is >2 mm for some or >5 mm for others. Stabilization is by suture, tension band wiring, K-wire or 4.0 cannulated cancellous screw [199, 200]. Long-term negative sequelae are minimal with or without surgery. Many will operate only for the late-term symptoms of instability or ulnar nerve irritation. Long-term studies show that even for 5–15 mm displacement, nonsurgical treatment leads to excellent results comparable with K-wire fixation. There was no significant difference noted between operative and nonoperative treatments in terms of pain or ulnar nerve symptoms. Operative treatment however did provide a significantly higher union rate. Future athletic and occupational demands might be better served with union of the fragment achieved by surgical fixation. If the fragment remains intra-articular after elbow reduction, surgical removal is warranted.

5.7.3 Proximal Radius

It can often be difficult to differentiate pure radial neck metaphyseal fractures and proximal radial epiphyseal fracture-separations, especially as the latter are almost invariably Type II with a prominent metaphyseal fragment. There is an equal rate of occurrence between epiphyseal fracture-separations and pure radical neck fractures in most studies, but some indicate a predominance of the purely metaphyseal fracture. Unless several oblique films are taken, it can be difficult to determine at which level fracture has occurred. In papers that make a clear distinction concerning the level of fracture, there are reports of 17 epiphyseal fracture-separations and 17 radial neck fractures, 25 fracture-separations and 20 neck fractures, 7 fracture-separations and 24 neck fractures, and 16 fracture-separations and 20 neck fractures [201–203]. The largest published series of 100 fractures, however, documented 79 physeal fractures and only 17 purely metaphyseal [204]. Some papers do not even attempt to make a distinction between the level of fracture and simply assess pediatric proximal radial fractures. The treatment approaches are essentially the same regardless of the level of injury, as are the complications. Prognosis is dependent more on the initial amount of proximal fragment displacement than the exact level of fracture.

The vast majority of fractures of the proximal radial epiphysis are either Type I or Type II with very few Type III or IV patterns reported (Tables 5.9 and 5.10) [201–203, 205–210]. D'souza et al. reported 71 type I and II injuries and 8 type IV injuries [204]. In spite of these patterns, there is a considerable incidence of avascular necrosis leading to shortening and angular valgus deformity. Premature epiphyseal fusion and avascular necrosis are particularly common in injuries with marked epiphyseal displacement with articular surface tilt from 60° to 90°. Other negative sequelae are limitation of movement—primarily supination and pronation, pain and radial head overgrowth. The Type I injury can present with complete posterior displacement of the radial epiphysis that, on lateral radiographs, is tilted 90°, lying on the posterior surface of the neck.

The proximal radial epiphysis is completely intracapsular and analogous to the proximal femur as its blood supply enters the epiphysis from distal to proximal and with any displacement is subject to rupture. There can also be considerable crushing of the growth plate, as the severe valgus stress on the elbow pins the physis between the capitellum and the radial metaphysis. These injuries can have both type C and type B_2 pathophysiologic phenomena associated with them.

As the damage from one or both of these occurrences is currently irreparable, accurate repositioning of the radial epiphysis may not prevent premature growth plate arrest, although restoration of the radiohumeral joint is important. Complications include avascular necrosis of the radial head, premature physeal closure, malreduction predisposing to osteoarthritis, joint stiffness, and heterotopic ossification. These are seen more often after open reduction. Futami et al. reported a 40 % incidence of premature physeal closure [211]. (This may not produce much of a length problem since only 10 % of growth is at the proximal radius.) Near anatomic reduction and stability are essential for a good long-term result. With each injury care must be taken to discern either a pathophysiologic type A, B, or C situation. Focal bone scans and MRI studies are helpful in this regard.

Accurate and gentle reduction frequently performed by closed or, if necessary, open means should be helpful in markedly displaced fractures. The highest degree of interrater and intrarater reliability in assessing angulation of the proximal radial fragment on plain radiographs is with measurement of the angle between a line parallel to the proximal radial articular surface and the radial shaft [212]. If the clinical situation post-reduction still appears relatively unstable, K-wire fixation is recommended by many. Many authors however have documented the frequently poor results with this injury regardless of the method of treatment. One treatment protocol which seems acceptable to many is immobilization only with displacement of <30°, closed reduction with displacement >30° and open reduction only for complete 90° angular displacement. Open reduction has a high degree of complication especially contributing to further devascularization of the proximal fragment.

Steele and Graham have reported on reduction of fractures with >30° angulation by leverage using a percutaneous Kirschner-wire generally placed in the metaphyseal type II fragment [213]. D'souza et al. opted for immobilization only for fractures <45° angulation, closed reduction for deformity

Fig. 5.24 A series of radiographs demonstrates the long-term negative sequelae of a slightly displaced lateral humeral condyle type IV fracture-separation in which the B_1 pathophysiologic state was not converted to type A, allowing imperfect growth to occur. **a** The initial injury shows minimal displacement of the type IV fracture-separation in a 16-month-old male. The position was accepted and the patient was treated with a long arm cast. **b** Anteroposterior radiograph 10 months following the injury shows a well established nonunion without valgus deformation. **c** Anteroposterior radiograph 4 years post-injury shows nonunion and some valgus deformation. **d** Anteroposterior radiograph 11 years post-injury shows nonunion and valgus deformity that measured 45° clinically. **e** A distal humeral varus osteotomy realigned the elbow. The nonunited lateral condyle was nonpainful and operative union was not attempted

>45°, and open reduction only when closed attempts were unsuccessful. Oblique K-wire fixation has been used.

Increasingly, elastic stable intramedullary nailing, as described initially by Metaizeau et al. has become widely adopted [214]. The initial Metaizeau report used closed intramedullary pinning with a K-wire but this has been replaced by flexible or elastic stable intramedullary nailing (ESIN). A series of 28 patients with severe displacement of a radial neck fractures by Klitscher et al. from Germany shows its value [215]. The Judet classification grades severity of displacement (I-undisplaced, II-angulated <30° and translation <50 %, III-angulation 30°–60° and translation <100 %, and IV-angulation >60° and translation >100 %). III–IV represent severe displacement. In these severe cases ideal reduction is by closed manipulation, followed by K-wire manipulation if not successful and only then by open reduction if still unsuccessful. For unstable fractures crossed K-wires can be used but ESIN is now the treatment of choice. The nail crosses into the epiphysis pointing laterally with stabilization and reduction following rotation to point the tip medially. Type II did slightly better than IV fractures. Current treatment recommends Judet I–II type by immobilization alone and Judet III–IV types with reduction. The Judet classification is used increasingly to define the degree of displacement of the proximal radial childhood fracture, including true epiphyseal and neck fractures without differentiation [216]. Malmvik et al. found relatively few long-term clinical problems with these injuries (in terms of osteoarthritis) although radiologic growth abnormalities were common [217]. The Metaizeau technique, or variations of it, has become the standard treatment in many countries over the past 15 years in efforts to enhance healing and eliminate growth problems [218–222].

5.7.4 Distal Radius

Greater than one-third of epiphyseal growth plate fracture-separations involve the distal radius. The vast majority of these are either type I or Type II injuries [223–226].

The characteristic small dorsal diaphyseal (metaphyseal) fragment in the Type II fracture was clearly defined by C. Thurstan Holland in 1929 who used it to confirm occurrence of epiphyseal separation and to note that the diaphyseal (metaphyseal) fragment was present accompanying (attached to) the epiphysis "in the direction in which the displacement takes place" [227] (Fig. 5.25a). This plain radiographic finding is now referred to as the Thurstan Holland sign. Werenskiold of Oslo also commented on the presence of a dorsal diaphyseal (metaphyseal) fracture associated with distal radial epiphyseal injuries [228]. His radiologic report on epiphyseal injuries published in 1927 concentrated on the most frequent fractures, those at the distal radius. He demonstrated the ability of plain radiographs of high resolution to define even undisplaced pure or "genuine" epiphyseal fractures by the presence of "a thin lamella detached from the diaphysis (metaphysis) at the boundary between bone and cartilage and when displacement is not present this may be the only but sufficient proof of the existence of an epiphyseal separation". Distal radial epiphyseal injuries however generally occurred in mixed form with epiphyseal separation being part of the pathway and passage through the diaphyseal spongiosa the other. This describes the common Salter–Harris Type II pattern. When the fracture line passed from epiphyseal cartilage into bone "on the dorsal side in the diaphyseal (metaphyseal) spongiosa… the fracture proceeds as in a typical fracture of the radius so that we have a more or less large three-cornered diaphysis (metaphysis)-dorsal side". When the bone fragment was large the epiphysis and fragment were almost always displaced.

Lodes reviewed various patterns seen on plain radiographs [229]. In a review of 423 distal fracture-separations from one institution there was a distribution as follows: 110 Type I injuries (26 %), 288 Type II (68 %), 13 Type III (3.1 %), 10 Type IV (2.4 %), and 2 Type V (0.5 %) (Lee et al.) (Fig. 5.25a–c) [225]. Operative management is indicated for the rare type III and IV injuries [230].

Garcia-Mata and Hidalgo-Ovejero reported a distal radial triplane fracture in 2006 in a 13-year-old male treated with closed reduction and cast immobilization but with complete premature physeal closure [231].

In a study of 85 patients with type II distal radial fracture-separations the average age at fracture was 11 years (range 4–15 years) [232]. [It was previously recognized that average age was younger in girls (9–10 years) than boys (13–14 years)]. The distal radial growth plate, which is extracapsular, retains its blood supply even with extreme displacement, and the level transverse orientation of the physis generally protects against crushing or fissuring such that the large majority of the injuries can be considered as pathophysiologic A in nature. In Type I and II fractures that heal in considerable malposition but in which growth plate continuity persists, extensive remodeling occurs. Although reduction is desirable, repeat reduction carries an increased risk of growth plate injury. The excellent remodeling mechanism, in particular in those with 2 or more years of growth remaining, should be allowed to work.

A series of three papers by Friberg documented this remodeling potential of the growth plate itself [233–235]. Where dorsal tilt predominates, periosteal remodeling involves filling in of bone on the concave side of deformity, but it is growth plate differential growth which leads to actual correction of the angular deformity of the physis, epiphysis and joint surface. This occurs by a relative overactivity of the cells at the dorsal half of the plate in relation to those in the volar position. Friberg studied the effect of residual fracture angulation on the distal radial and ulnar epiphyseal plates in children 1–15 years of age. Thirty-eight fractures located in the distal fifth of the forearm bones were observed from 1 to 25 months after healing. He clearly demonstrated that an abnormal inclination of the epiphyseal plate induced growth alterations in the plate. The redistribution of growth served to correct the abnormal inclination with the rate of correction following an exponential course. Neither the age of the child at the time of fracture nor the distance from the fracture to the epiphyseal plate (at least within the lower fifth of the bone) influenced the capacity for correction. The studies involved angulation of the radius in the dorso-volar plane and in the radioulnar plane as well as angulations of the ulna in the dorso-volar plane. The distal epiphyseal plates of both radius and ulna altered their inclinations in relation to the long axis of the bones. The only bones which did not tend to correct were those where the post-fracture angular deformities were very small with a mean of 4°. Otherwise, without exception, changes in inclination tended toward normalization of the spatial orientation of the epiphyseal plates. These structures were seen in the radius in the dorso-volar and radial-ulnar planes as well as in the dorso-volar plane of the distal ulna. It is important to note that the correction did not relate to filling in by the periosteum of the concavity but rather to a change in angular tilt of the epiphyseal growth plate itself toward the normal plane. The mean correction at the distal radial epiphyseal growth plate was 0.9°/month in the dorsal-volar plane and 0.8°/month in the radial-ulnar plane. The ulnar epiphyseal plate showed a correction of 0.8°/month. The rate of correction was high in the groups with larger primary angulations and the rate of correction tended to diminish as angular position closer to normal was achieved.

In conclusion, he noted that the epiphyseal plates had a definite and spontaneous ability to change their inclinations in relating to the forearm bones with change invariably in a direction of correction toward the normal angle (Fig. 5.26). The greater the angular deviation, the greater the tendency toward correction. The correction was in some way related to the changes in direction and amplitude of the

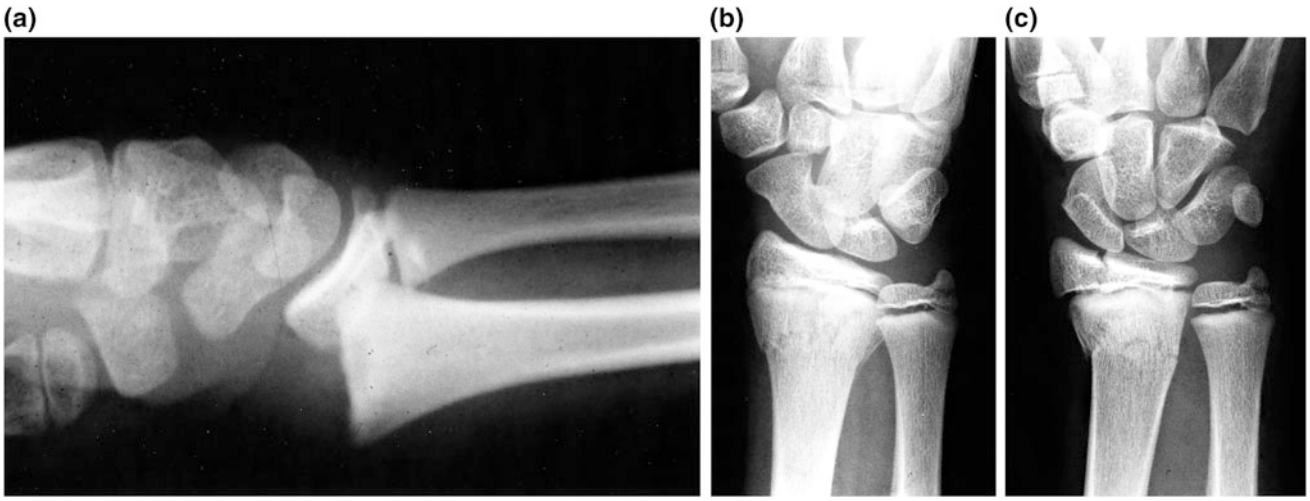


Fig. 5.25 **a** A displaced type II fracture of the distal radius with a small dorsal metaphyseal fragment is shown. Lateral radiograph shows the characteristic type II fracture-separation of the distal radial epiphysis. The small metaphyseal fragment is referred to as the Thurstan Holland sign. **b** Anteroposterior radiograph of the distal radius shows an irregular metaphyseal fragment with minimal displacement and the hint of a longitudinal component passing toward the physis. The ulnar styloid is also cracked. The lateral radiograph was unremarkable. **c** Oblique radiograph of the fracture shows a clear type III pattern with epiphyseal and intra-articular involvement. The complexity of many epiphyseal growth plate fracture-separations often increases in terms of adjacent bone involvement whenever more detailed imaging is performed beginning with simple oblique films and progressing to CAT scans or MR imaging

biomechanical forces acting on the plate, although no direct studies in this regard were done. In assessing fractures in the distal fifth of the bones, no differences in the rate of correction of the epiphyseal plate were found in fractures located at different distances from the plate.

In a second study of these patients Friberg assessed the orientation of both the distal and proximal epiphyseal plates of the radius to assess overall forearm bone remodeling in those fractures distally which had healed with residual angulation. The residual fracture angulation induced a change in orientation in both the distal and proximal epiphyseal plates. The tendency was to a normal inclination with the proximal epiphyseal plate obtaining virtual normal orientation and the distal epiphyseal plate tending toward some overcorrection. The upper limit for angulations permitting normalization of the orientation of the distal epiphyseal plate of the radius was 20° as the 4 cases with angular deformity >20° improved but did not reach the normal state. The final angulation of the distal epiphyseal plate was 2°or less (with a normal at 0) in 33 of the 39 fractures. Complete normalization could not be seen after a distal forearm fracture with a primary angulation of more than 20°. The angle of 20° or less, acceptable to allow for spontaneous remodeling, was the same as that described by Blount who also concluded that angulations of more than 20° should not be accepted [180]. Nonnemann was a little more liberal accepting angulation up to 30° with the expectation that spontaneous remodeling would be sufficient [236]. Friberg also noted that when the fracture was of the distal radial epiphyseal growth plate, the residual angulation after healing also influenced distribution of growth within the proximal epiphyseal growth plate of the radius. The younger the patient at the time of the fracture, the more complete was the correction. It is not the age of the child, however, that governs the extensiveness of correction but rather the time remaining to epiphyseal closure. As long as there was growth remaining, the age at fracture was not a principal concern. In the distal radius and ulna, the direction of the angulation of the fracture was of no importance for the corrective result. The wrist joint, however, does have a range of motion that incorporates all directions that the fracture was measured in. In a pure hinge joint, the correction is maximal in the plane of motion of the joint. Friberg stresses that the correction is within the physis itself as only such a mechanism can correct the angular inclination of the physis.

In an assessment of distal radial epiphyseal injuries (not distal radial metaphyseal fractures as studied by Friberg above), remodeling was assessed in the 85 patients using anteroposterior and lateral forearm radiographs. At follow-up 73 patients (86 %) were anatomically normal with full remodeling of volar and radial inclination of the distal radius. Complete remodeling was seen in all patients up to 10 years of age except 1. The slightly incomplete remodeling in those older had no apparent clinical significance. Remodeling occurred in both planes. Correction of volar inclination (by which is meant correction of dorsal tilt) in ages 1–5 was complete in each of 3, ages 6–10 complete in 30 of 31, and in ages 11–15 complete in 41 of 51. Radial inclination was complete in these groups in each of 3, in 30 of 31, and in 47 of 51, respectively. Clinically, in the entire

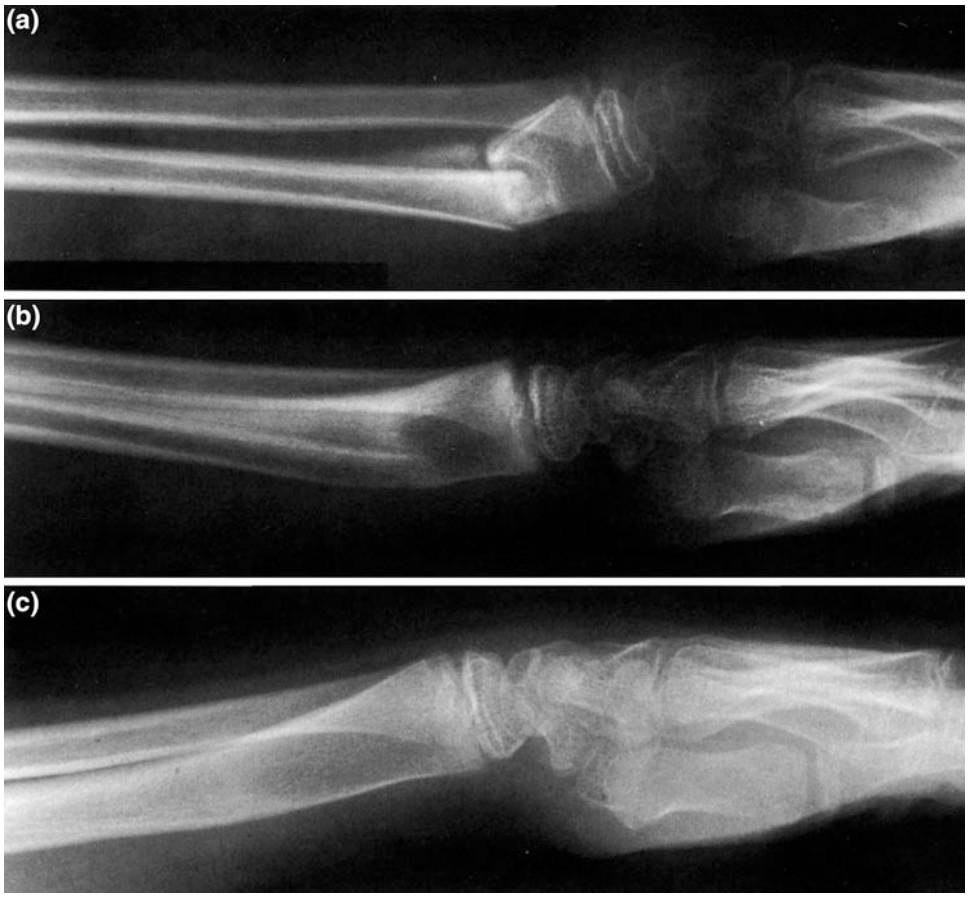


Fig. 5.26 A series of radiographs shows remodeling after an angulated distal radial metaphyseal fracture in a 10-year-old male was allowed to heal without anatomic reduction. Note the change in orientation of the physis in relation to the shaft of the bone indicating that altered physeal growth itself was partly responsible for the remodeling phenomenon. The top radiograph (**a**) shows position at 2 weeks post-fracture; the middle radiograph (**b**) shows position approximately 4 months post-fracture with complete healing; and the bottom radiograph (**c**) shows remodeling approximately 1 year post-fracture

series there was no restriction of motion or weakness of grip strength with 2 complaining of some discomfort.

Although historically this has been considered a relatively benign injury in terms of growth sequelae, increasing numbers of post-traumatic growth arrests of the distal radial physis are being reported. These are seen in association with three mechanisms of trauma: recognized distal radial epiphyseal fracture-separations; after fracture of the distal radial metaphysis; and with chronic repetitive stress injury to the physis in gymnasts and other athletes.

(i) Premature distal radial growth late closure following recognized distal radial epiphyseal fracture-separations. Although there were early reports of isolated cases [237–239], there were ten post-traumatic arrests in one of the above mentioned series [225]. Eight of these followed Type II fracture-separations with one Type IV and one Type V also diagnosed. The authors felt that "the mechanism of injury is of more value than the Salter classification for predicting the severity of growth plate injury" with a compression mechanism leading to greater trouble. Although the vast majority of fracture-separations of the distal radius are type A injuries, the possibility of a B_2 situation exists. Concern for a B_2 injury is greatest in those fractures that are associated with extensive trauma, open injury, or repeated manipulations. Figure 5.19a–i illustrates MR findings in an evolving post-traumatic transphyseal bone bridge.

(ii) Premature distal radial growth plate closure following fracture of the distal radial metaphysis. Reports are beginning to appear of premature closure of the distal radial physis after fracture of the distal radial metaphysis. Aminian and Schoenecker presented 2 cases of premature closure of the growth plate secondary to an associated fracture near but seemingly not involving the distal radial growth plate itself [240]. One was a complete distal radius fracture and the other a torus fracture. The injury to the growth plate did not become recognized until 2–3 years later when patients reported symptoms referable to a shortened distal radius with ulnar growth having continued. It was felt that compression injury occurred in association with the original trauma and that ischemia after plaster immobilization was not at fault. Abram and Thompson also reported premature growth arrest after a seemingly simple torus fracture of the metaphysis in a 10-year-old girl with an associated fracture of the ulnar styloid [173]. Tang et al.

reported growth arrest of the distal radius epiphysis in a 12 year old girl 9 months after sustaining a complete fracture of the distal radius and ulna metaphysis [241]. The rarity of this injury is shown by the report of Davis and Green who noted only 1 case of a patient who had premature closure of the distal radial physis in a review of 547 consecutive fractures of the forearm, including 92 torus fractures of the distal radius or of the radius and ulna [242].

(iii) Premature distal radial growth plate closure following chronic repetitive stress injury with excessive gymnastic activities. In chronic overuse syndromes, there can be discomfort in the region of the growth plate and radiographs showing the distal radial growth plate to be widened and hazy due to irregularity of the border between the cartilage and the metaphyseal zone of ossification. This represents inability of the growth plate to fully withstand rotational and compressive forces. With decreased sporting activity and 3–4 weeks of immobilization of the involved joint, the symptoms generally disappear and the radiographs return to normal. The injury is particularly common in gymnasts where compressive and torsional forces with extreme weight bearing are prominent, for example with vaulting. Stress-related widening of the radial growth plate in adolescence has also been noted by Fliegel and Albanese et al. [174, 243]. Both Carter and Aldridge and Roy et al. reported 21 cases each in young gymnasts [244, 245]. In the former series, the average age was 13.5 years for the boys and 14 years for the girls. Albanese et al. documented three female patients in their group who developed premature fusion of the distal radial growth plate with continued growth of the distal ulnar plate [174]. Fusion was noted at 12 years, 13 years 10 months, and 14 years 1 month of age. The ulnar positive variance in all three was felt to be due to growth inhibition of the distal radius.

Several treatment options are available for premature distal radial growth plate closure. This can result in or be associated with ulnar overgrowth and altered radial inclination as well as triangular fibrocartilage complex tears and distal radioulnar joint instability [246]. Waters et al. have reviewed the surgical treatment options in 32 cases [246]. If complete radial closure has already occurred, then the distal ulnar growth plate can be fused surgically (epiphyseodesis) if their relationship is still appropriate. It may be necessary to complete the distal radial closure if incomplete. If there is excess ulnar overgrowth, then ulnar shortening can be performed. A Z-shortening or complete segment resection with plate stabilization is done. If the radius has not closed symmetrically and there is angular deformity, then radial osteotomy and on occasion lengthening can be performed with completion of physeal closure. If there is a focal bone bridge and there appears to be sufficient physeal tissue remaining to allow growth to continue, then bone bridge resection can be performed. Procedures may have to be accompanied by distal ulnar growth plate fusion depending on the degree of ulnar variance. In their series most patients had a combination of procedures with 25 having ulnar shortening/epiphyseodesis and 7 radial osteotomies as the primary corrective interventions.

Median nerve compression syndromes can occur following physeal fractures of the distal radius [247]. In a review of 8 patients with post-fracture median neuropathy, some resolved spontaneously but some required carpal tunnel releases and percutaneous pin fixation.

De Pablos et al. attempted to assess post-fracture growth of the radius to see if clinically significant patterns occurred [248]. The post-fracture growth differential was minimal but appeared greatest when there was associated ulnar fracture. In 11 cases with ulnar fracture radial overgrowth was 0.54 cm but in 29 without ulnar fracture (most of which were greenstick or buckle radial fractures) overgrowth was only a mean of 0.13 cm. The rapidity of healing probably limits excess physeal response. The overgrowth phenomenon appears not to be of clinical significance in childhood forearm fractures.

5.7.5 Distal Ulna

Distal ulnar physeal injuries in 18 patients and from 2 traumatic amputation specimens have been assessed by Golz et al. [249]. Simple ulnar styloid fractures were excluded. All patients had associated distal radial fracture. Types I and II predominated but growth arrest was found in each of the I to IV categories (Type I 10, Type II 1, II 6, Type IV 1). Excellent histopathologic sections demonstrated both unappreciated Type I injuries and examples of transphyseal bone bridge formation. Premature physeal closure occurred in 10 patients (55 %) and in 7 there were secondary structural changes (ulnar curvature) in the distal radius due to the tethering effect on medial radial growth.

The occurrence of growth plate problems is shown again to relate quite often to the degree of trauma and displacement. Although the distal ulnar epiphyseal fracture-separation is infrequent it has a relatively high degree of growth sequelae when it occurs. Lipschultz reported 5 distal ulnar physeal fractures, all with associated distal radial fractures, with three Type III and two Type IV patterns and three of the five causing growth arrest with ulnar shortening of 9, 14, and 29 mm [250]. Nelson et al. reported 4 distal ulnar premature growth arrests with 22–39

mm shortening and secondary radial and carpal growth changes [251]. The distal ulna physis can separate as part of the Galeazzi fracture complex in children where the distal radius metaphyseal fracture is associated with a type II distal ulnar physis fracture-separation (rather than a soft tissue disruption of the distal radial-ulnar joint, as occurs in the adult.) The Galeazzi fracture in children, sometimes called the Galeazzi-equivalent lesion, has been reported by Landfried et al. (three cases) [252] and Imatani et al. (1 case) [253]. Letts and Rowhani described 6 lesions with separation of the distal ulnar growth plate, one of which fused completely prematurely [254]. Treatment is by closed reduction with the forearm in full supination in a long arm cast. Walsh et al. pointed out the need to recognize the injury [255].

Ray et al. reviewed 28 cases of traumatic ulnar physeal premature arrest involving 5 of their own cases and 23 from the literature [256]. They defined three patterns of arrest and noted the compensatory radial changes. In their type 1 distal ulna growth arrest, the physis closed uniformly across its entire diameter leading to symmetric shortening. In the type 2 configuration, the physeal arrest was asymmetric occurring at the lateral part of the physis and leading to predominantly lateral ulnar shortening and in the type 3 configuration, the distal physeal injury was at the medial side of the physis leading to predominantly medial ulnar shortening. The asymmetric growth arrests were most common in the Salter–Harris Types III, IV, and V fracture-separation patterns. In their categorization in those cases where there was sufficient radiologic evidence for determination, 11 (39 %) cases exhibited the type 1 symmetric shortening pattern, 3 (11 %) the type 2 lateral ulna shortening pattern, and 6 (21 %) the type 3 medial ulna shortening pattern. The ulnar shortening tended to tether the distal radial growth plate primarily on its ulnar or medial side. There was thus increased ulnar slope of the distal radial articular surface and ulnar bowing of the distal radial diaphysis and metaphysis. The carpal bones also shifted in relation to the altered radial-ulnar articulation.

Surgical indications for treatment are progressive carpal subluxation, decreased ranges of motion, and cosmetic deformity [246]. If caught early, treatment of the ulna alone would be appropriate involving ulnar lengthening with or without epiphyseal arrest of the distal radius and distal ulna if good alignment had been achieved. Radial osteotomy was often needed. The Suave-Kapandji procedure was done for some of these injuries involving a lateral closing wedge radial osteotomy and distal radioulnar arthrodesis with segmental ulnar resection.

5.7.5.1 Ulnar Styloid

Ulnar styloid fractures have a relatively high rate of nonunion, up to 80 % in one study [257]. In a study of 46 ulnar styloid fractures, all were associated with a distal radial fracture. Most were styloid tip fractures (38) with 6 cases of styloid base avulsion. No specific treatment had been directed to the ulnar styloid. The ulnar styloid fracture had not healed in 80 % of cases. In the large majority of these cases, the nonunion was asymptomatic. In 7 patients with discomfort, investigation, and operation showed symptoms to be due to the associated tears of the triangular fibrocartilage complex (TFCC) [257]. Tables 5.9 and 5.10 summarize upper extremity growth plate fracture-separation issues.

Table 5.9 Major upper extremity growth plate fracture-separations

• Proximal humerus
– Virtually all fractures are S–H I or S–H II
– Negative growth sequelae rare even with no interventional treatment due to high remodeling potential (80 % of humeral growth occurs proximally)
– Tendency to closed/open reduction with significant displacement after 12–13 years of age with K-wire, screw fixation metaphyseal fragment to metaphysis (due to limited time for remodeling).
– Wide range of motion at glenohumeral joint and relative clinical insignificance of mild/moderate upper extremity length discrepancies also limit clinically significant negative sequelae
• Lateral humeral condyle
– Virtually all are S–H IV injuries
– Accurate repositioning of displaced (>1–2 mm) fragment by closed/open reduction and K-wire or screw fixation has almost completely eliminated negative growth sequelae (fishtail deformity, valgus deformity, nonunion, avascular necrosis).
– Increasing use of Jakob I, II, III or Milch Classifications for better guidance.
– Main problems even with surgery are varus-direction (carrying angle) angular deformities (which are actually due to lateral overgrowth), lateral condylar hypertrophy (also overgrowth) and lateral osteophyte formation. The overgrowth may be due to relatively poor fixation with a K-wire, favoring consideration of a metaphyseal to metaphyseal screw
• Proximal radius
– Virtually, all fractures are S–H I or II injuries if at growth plate. At this site about equal distribution of growth plate fracture-separations and pure metaphyseal neck fractures. Prognosis often poor (even though S–H I and II) in growth plate or metaphyseal sites due to damage to blood supply of this intrarticular epiphysis (similar to proximal femoral capital epiphysis). Negative sequelae are premature growth plate fusion with avascular necrosis, malunion, and radial head enlargement. Worse prognosis with initial head displacement >50°. Open reduction improves position but can increase damage to blood supply
• Distal radius
– Virtually all type S–H I or S–H II fractures
– Generally considered to have a benign growth profile but forceful closed reduction and repeat reduction should be avoided. Growth sequelae are increasingly reported so long-term follow-up needed. Remodeling potential is excellent so repeat anatomic reduction after one attempt not warranted

5.7.6 Metacarpals and Phalanges

The large majority of metacarpal and finger phalanx growth plate fractures are Type I and II injuries, although occasional Type III and IV patterns occur, particularly with ligament avulsion mechanisms [139]. In the finger metacarpophalangeal joint, the collateral ligament originates from the metacarpal epiphysis and attaches completely to the epiphysis of the proximal phalanx and on the epiphysis and metaphysis in the middle and distal phalanges [258, 259]. Fischer and McElfresh reasoned that, based on these observations, if ligament attachment played a major role in determining fracture pattern, the SH III would be common at the MP (metatarsophalanged joint) and SH II and IV would be more common at the distal 2 joints [260]. They found the opposite, however; SH II made up the overwhelming percentage of injuries at the MP joint and SH III predominated at the PIP joint and was relatively common at the DIP joint. In children 34 % of hand fractures were epiphyseal fracture-separations. The prognosis overall, except with severe mutilating trauma, is good, although open reduction and pin fixation is usually warranted for the rare intra-articular Type III and IV fractures [260]. Al-Qattan et al. reviewed 103 consecutive fractures of the base of the proximal phalanx of the fingers in children prior to epiphyseal closure [261]. The mean age was 10 years (range 4–14 years). The most common fracture observed was the juxta-epiphysial type II fracture (53 %) followed by the S–H type II (26 %), S–H I (4 %), S–H IV (5 %), juxta-epiphyseal I (8 %), and metaphyseal (4 %). The juxta-epiphysial fracture demonstrated a triangular metaphyseal fragment from the base of the phalanx on the side of angulation with the fracture line then continuing through the metaphysis 1–2 mm distal to the growth plate [262]. The more displaced fractures often required open reduction and k-wire fixation.

Stahl and Jupiter used a tension band wiring technique for the type III and IV avulsion fractures [263]. They placed a small gauge wire through the insertion of the ligament into the fracture fragment allowing for accurate reduction and stability and early mobilization. These fractures are more common in the proximal phalanx owing to anatomic structure. With injury, the ligament remains intact directing force to the epiphysis and physis and avulsing bone in the type III (6 cases) or type IV (1 case) pattern. With displacement anatomic reduction is needed. Skewering the small bone fragment with a K-wire can rupture or damage the bone but the tension wire method leaves the bony fragment intact. A 26-gauge stainless steel wire is passed through a 0.035 in. drill hole in the proximal phalanx and then, in figure-of-8 fashion through the ligament and, with reduction held by a forceps, tightening the wire reduces the fracture and stabilizes it. The vast majority of fractures being S–H I and II or transverse juxta-epiphyseal are treated by splinting/casting, even after closed reduction if needed.

5.7.7 Clavicle

The clavicle is a long bone and has epiphyses at both ends but develops in an atypical fashion [264, 265]. It is the first bone in the body to ossify (in the embryo) and does so via two adjacent centers in the mid-diaphyseal region by an intramembranous mechanism on an atypical fibrous scaffold. The two regions soon coalesce into one center. Fawcett indicated that “no cartilage cells are to be recognized at this stage in either mass” (the central bone forming region) [266]. Cartilage is present at both ends of the developing bone but is atypical [264, 266]. Laterally (distally), there is never a secondary ossification center and the cartilage is similar to those ends of metacarpals, metatarsals, and phalanges where secondary centers are absent but articular cartilage still forms. The medial (sternal) end is a true epiphysis although the secondary center of ossification is very thin, forms (ossifies) late, and does not fuse with the metaphyses until early adulthood [264, 265, 267]. The specific pattern of medial ossification has been categorized into 5 stages and is of great interest in the field of forensic medicine/pathology to determine age after the rest of the skeleton has reached skeletal maturity in the mid-teenaged years [268]. There is considerable variability with the medial center appearing between 11 and 22 years (commonly 15–18 years), partially fusing at 16–24 years and not fully fusing until 20–27 years of age (commonly 23–25 years) [264, 265, 267–269]. The center is very difficult to visualize by plain radiographs and is best assessed by CT scanning.

Freyschmidt has well summarized clavicular development [265]. “the clavicle is a long bone that is… ossified from two primary centers, one medial and the other lateral (in the central diaphyseal region), which appear in the 5th and 6th weeks of the intrauterine life and fuse during fetal development.” Endochondral (epiphyseal) (development) takes place at both the acromial and sternal ends of the bone. In the clavicle, then, we have the unusual situation of membranous diaphyseal and metaphyseal ossification coexisting with endochondrol longitudinal growth in the same bone. Membranous ossification of the diaphysis contributes most to longitudinal growth during both the intrauterine and postnatal periods. Longitudinal growth at the acromial end of the clavicle is insignificant by comparison. Ogden has estimated the distal growth at only 20–30 % [270].

5.7.7.1 Medial Clavicular Epiphyseal Fracture-Separations

The sternoclavicular joint (SCJ) is a diarthrodial joint with a fibrous disk, a thick fibrous capsule (anterior and posterior) and strong sternoclavicular, interclavicular and costoclavicular ligaments [267]. The posterior support is considerably stronger than the anterior and the SCJ is better protected (stronger) than the medial clavicular physis. Many injuries that are true SCJ dislocations in the adult are in fact medial clavicular epiphyseal fracture-separations in childhood, adolescents, and (because of its late persistence) early adulthood to the mid-twenties [267, 271, 272]. Posterior SCJ dislocations and fracture-separations are particularly dangerous due to retrosternal damage (by the displaced clavicle) causing such injuries as airway compromise, trachea-oesophageal fistula, pneumothorax, great vessel damage, brachial plexus lesions, and thoracic outlet syndrome [267]. CT imaging and greater awareness of these regional injuries have greatly improved recognition [267, 272]. In patients <20 years of age trauma with pain in the sternoclavicular region must lead to careful assessment and CT imaging if possible [267]. Denham and Dingly described 4 cases in 1967 with an example of a medial clavicular epiphyseal segment [271]. The fracture-separations appear almost always to be S–H I/II displacements [264, 272]. This was also noted by Waters et al. in 11 of 13 patients with traumatic posterior medial clavicular displacements treated by open operation with reduction and nonabsorbable suture fixation via metaphyseal-epiphyseal drill holes. The mean age of occurrence was 14.6 years (range 13–17 years) with 6 S–H I and 5 S–H II epiphyseal fractures seen (and two true dislocations) [272].

5.7.7.2 Distal (Lateral) Clavicular Physeal Fractures

The distal (lateral) epiphysis has no secondary ossification center and is similar to the non-physeal ends of the metacarpals, metatarsals, and phalanges. Ogden has estimated that only 20–30 % of clavicular growth in length occurs at the distal end [270]. The distal acromioclavicular joint is strongly supported by the acromioclavicular ligament and the strong coracoclavicular ligament (trapezoid and conoid ligaments). The childhood and adolescent analog of the common adult injury of acromioclavicular separation is distal physeal fracture-separation. The epiphysis is rigidly held in place by the ligaments and the metaphyseal component is variably displaced upwards. These physeal injuries are also essentially all of the S–H I/II pattern [270, 273]. The degree of displacement, pre- or post-reduction, determines whether K-wire fixation or periosteal suturing is done [272]. The age incidence is variable but the study of 10 patients by Havranek had a mean age of 12 years (range 9–15) [273] while Ogden described 12 patients ranging from infancy to 15 years of age [270].

5.7.8 Triradiate Acetabular Cartilage

A rare but potentially serious physeal fracture is that involving the triradiate cartilage of the acetabulum [274–280]. The triradiate cartilage is responsible for growth of the acetabulum, deepening it and contributing to lateral growth throughout development. The physis relates to each of the ilium, ischium, and pubis (hence the triradiate conformation) and is bipolar with physeal tissue relating to each of the three bones. Fractures can occur at any time from shortly after birth to skeletal maturity. Three patterns are seen—types I, II (with the metaphyseal fragment generally medial in the ilium), and V (not appreciated until growth arrest seen). Prognosis is more favorable with the type I and II injuries. CT scanning allows this injury to be diagnosed more accurately and more often in relation to childhood and adolescent massive pelvic-thigh trauma. Those injured under 10–11 years of age often manifest growth arrest which presents as progressive acetabular dysplasia, thickening of the subchondral bone medially and hip subluxation. Tables 5.10 and 5.11 summarize lower extremity growth plate fracture-separations.

5.7.9 Proximal Femur

Fracture-separation of the proximal femoral capital epiphysis is a rare, but potentially serious injury. The first documented case was described by Bousseau secondary to massive trauma in which a 15-year-old patient died and postmortem exam was performed [69]. Childhood fractures of the femoral head and neck are infrequent, and the transepiphyseal fracture-separation, a Type I injury, accounts for only 4–8 % of these. In a review of 471 fractures of the head and neck of the femur in children (as summarized from many reported series) only 39 (8 %) were transepiphyseal fracture-separations [281]. This is similar to the report by Bagatur and Zorer where only 1 transepiphyseal fracture was seen with 17 childhood hip fractures at a mean age of 11 years [282]. The predominant age at fracture clusters in two groups, 2–6 years (9 cases) and 12–15 years (10 cases). The prognosis in terms of avascular necrosis, premature fusion and coxa vara was previously felt to be almost uniformly bad but improved results in certain situations have been reported more recently. The blood supply of the intracapsular epiphysis is tenuous. The fractures are

Table 5.10 Distribution of S–H types and growth sequelae of epiphyseal growth plate fracture-separations at major epiphyses in the 1950–1980 time period

Author(s) (cases) (Refs.)	Salter–Harris classifications	Effects on growth
(i) *Lateral humeral condyle fracture-separations*		
Jakob et al. (26) [160]	IV 26	In 11/11 patients treated within 8 days of fracture by open reduction and K-wire fixation, the results were excellent with no growth arrest. All poorer results were treated 3 weeks or more after injury. Complications involved premature epiphyseal fusion, malunion, nonunion, and avascular necrosis
Crabbe (17) [165]	IV 17	Results were excellent in 16/17 cases treated with open reduction and catgut suture or K-wire fixation. One poor reduction (10° varus) due to faulty technique. No avascular necrosis, nonunion, epiphyseal arrest, or clinically significant deformity in all other patients
Conner and Smith (30) [164]	IV 39	Displaced fractures all treated with open reduction, screw fixation. Results almost uniformly excellent except for one nonunion, and only two with mild valgus deformity in all other patients
Haracre et al. (52) [167]	IV all	Open reduction internal fixation in 23 yielded many fair-good results. "Nonunion, significant angular deformity, avascular necrosis, and tardy ulnar palsy are complications that are avoidable."
(ii) *Proximal radial fracture-separation*		
Jeffery (24) [206]	No differentiation between epiphyseal and metaphyseal fractures	Premature epiphyseal fusion in 2/2 causes with head rotated posteriorly 60°–90°, and in 6/18 (33 %) with head tilted 30°–60°. The greater the displacement the worse the prognosis due to "risk of the blood supply to the displaced head particularly in those cases treated by operative reduction."
Tibone and Stoltz (7) [203]	II 5 III1 IV 1	Seven epiphyseal fracture-separations and 24 neck fractures in these proximal radial fractures; 5/5 type II injuries with excellent results but none of the five were displaced. Fair-poor results in the type III and IV lesions
Jones and Esah (17) [201]	II 7	Seventeen epiphyseal fracture-separations and 17 radial neck fractures in proximal radial fractures in children. Results assessed for entire series; not broken down by level of fracture. Many instances of avascular necrosis, malunion, radial head enlargement, and deformity. Results: good 13, satisfactory 10, poor 11. End result correlated very well with the degree of initial displacement; if 50° or more, 15/22 (68 %) with satisfactory or poor rating
Reidy and Van Gorder (30) [209]	No numerical distinction between epiphyseal and epiphyseal fractures. All epiphyseal fractures were I or II	10/24 (42 %) with marked displacement (60°–90°) had premature epiphyseal fusion
Newman (48) [202]	I 1 II 24	Twenty-five epiphyseal fracture-separations and 20 metaphyseal neck fractures. Avascular necrosis (9); premature fusion of epiphysis (24)l abnormal radial head (2). Level of fracture (growth plate versus neck) had only a "minor bearing on the outcome" although plate injuries had slightly better results. Results of growth plate injures: good 14, fair 5, bad 6. Open reduction risks increasing the avascular necrosis
(iii) *Distal femoral fracture-separations*		
Stephens and Louis (20) [299]	I 1 II 15 III 1 IV 1 V 2	Angulation occurred in 4/20 (20 %)(3 were Type II. In all fractures, shortening 1.5 cm or greater in 8/20 (40 %); in type II, 5/15 (33 %)(average 2.3 cm)
Lombardo and Harvey (34) [297]	I 1 II 24 III 5 IV 3 V 1	Shortening 2.0 cm plus in 36 % overall. In type II injuries 1.2 cm plus in 10/24 (42 %). Angulation 5° plus occurred in 33 % overall and in 8/24 (33 %) of type II lesions
Aitken and Magill (16) [45]	II 15 III 1	Shortening occurred in 3/15 (20 %) with a range from 1/8 to 5/8 in.
Czitrom et al. (42) [296]	I 2 II 27 III 2	Angulation (varus/valgus 3°–30°) I–II 38 %, IV–V 55 %; shortening 0.1–3.8 cm I–II 69 %, IV–V 64 %; 1.5 cm plus I–II 29 %, IV–V 45 %. Overall results: excellent-good 66.7 %, fair-poor 33.3 %. I–II results: excellent-good 72 %, fair-poor 28 %

(continued)

Table 5.10 (continued)

Author(s) (cases) (Refs.)	Salter–Harris classifications	Effects on growth
	IV 8	
	V 3	
Roberts (91) [298]	I 28	Shortening of 1.2 cm plus in 30/50 (60 %) evaluated
	II 63	
Neer (17) [304]		Shortening 7/17 (41 %) from 0.5 to 3.5 cm; 5/17 (30 %) 1.5 cm plus
Cassebaum and Patterson [302]		Review of several older studies—growth alterations in 26/55 (40 %). Shortening 2.0 cm plus in 25 %
(iv) *Proximal tibial fracture-separations*		
Shelton and Canale (39) [318]	I 9 (23 %)	Shortening of 1.0–2.5 cm in 7/28 (25 %). All these were I or II fractures, none seen in III–IV lesions. Angulations 5°–7° 8/28 (29 %), also I–II lesions. Only one fracture in entire series in a patient <10 years old
	II 17 (44 %)	
	III 10 (26 %)	
	IV 3 (8 %)	
	V 0	
Burkhardt and Peterson (28) [315]	I 3 (11 %)	Only one of 23 patients was <10 years of age at time of injury; five patients with exceptional injuries (all lawn-mower trauma) had type IV lesions and were <10. Shortening in 5/28 (21 %): I(1), II (1), IV(2), V(2). Angular deformity 7/28 (255) from 12° to 30° I (1), II(1), IV (5)
	II 9 (32 %)	
	III 6 (21 %)	
	IV 8 (29 %)	
	V 2 (7 %)	
Nolan et al. (14) [317]	I 1 (7 %)	No data on overall growth sequelae
	II 6 (40 %)	
	III 3 (20 %)	
	IV 4 (27 %)	
	V 1 (7 %)	
Aitken (14) [46]	I 9 (64 %)	No data on overall growth sequelae
	II	
	III 2 (14 %)	
	IV 2 (22 %)	
(v) *Distal tibial fracture-separations*		
Spiegel et al. (202) [372]	I 36 (18 %)	Growth complications of skeletal importance in entire series (shortening 1 cm; angulation 5°); 26/184 (14 %). Type 1 lesions: 1/28 short; II: 11/66 (17 %) with shortening and/or angulation; III: relatively few complications; IV: one arrest in three cases; V: two, both with premature arrest
	II 91 (45 %)	
	III 49 (24 %)	
	IV 3 (1 %)	
	V 2 (1 %)	
	Triplane 15 (7 %)	Worst complication rate (32 %) in displaced III/IV lesions, Tillaux, triplane, V
	Tillaux 6 (3 %)	
Nolan et al. (90) [317]	I 9 (10 %)	Shortening 1.0–1.6 cm 6/50 (12 % I:0, II:3, III:0, IV:1, and V:2.) Overall results: I good and excellent; V fair and poor; scattered results in II, III, and IV.
	II 52 (58 %)	
	III 14 (16 %)	
	IV 11 (12 %)	
	V 4 (4 %)	

		II	III	IV	V
Excellent	6	7	3	2	1
Good	4	4	2	3	0
Fair	-	5	3	0	1
Poor	-	3	1	3	2

(continued)

Table 5.10 (continued)

Author(s) (cases) (Refs.)	Salter–Harris classifications	Effects on growth
Aitken (21) [47]	I 16 (76 %)	I–II: No deformity; occasionally premature fusion, but no clinically significant shortening
	II	
	III 3 (14 %)	III: No problems
	IV 2 (10 %)	IV: Mild shortening in 1; varus and 1.5 in. shortening in other

Table 5.11 Major lower extremity growth plate fracture-separations

• Proximal femur
– Growth plate fracture-separations of the proximal femoral capital epiphysis (femoral head) are virtually all S–H I injuries. In spite of this category, there is a high incidence of growth arrest due to vascular damage (ischemia, avascular necrosis). Early closed/open reduction with K-wire fixation ±hip spica immobilization (age/size dependent) are needed to improve prognosis
• Distal femur
– Most injuries are S–H I or II but a considerable number of III, IV, and V injuries are also seen. Growth complication rate is high across the spectrum of types I → V owing to relatively extreme force needed to fracture and displace the growth plate and epiphysis and the curved or nonlinear shape of the physis. Careful closed reduction of I, II fractures; metaphyseal to metaphyseal K-wire or screw fixation of large II fragments (to decrease post-injury physeal movement); and anatomic open reduction and epiphyseal to epiphyseal, metaphyseal to metaphyseal internal fixation in III and IV fractures commonly needed to improve long-term prognosis
• Proximal tibia
– Proximal tibial injuries are seen across the S–H spectrum from I → V. Increasing awareness needs to consider fractures of anterior tibial tubercle and tibial spine (with displacement into joint)
– Similar to distal femur, there is increasing need for surgical intervention to minimize growth sequelae and restore function
• Distal tibia
– Growth plate fracture-separations also include the entire spectrum with negative growth sequelae across the categorizations. Many type II and even type I injuries have negative growth sequelae due to chondrocyte crushing at medial nonlinear physeal projection (Kump's bump). Need to consider *triplane fracture* pattern (type II lateral radiographic projection and type III anteroposterior radiographic projection; helpful CT or MR imaging) and *Tillaux* fracture pattern (type III near time of physeal closure)—both of which are better managed with open reduction, internal fixation

associated with major violence and significant displacement. In one series, each of 5 transepiphyseal fractures had dislocation of the femoral head from the acetabulum, all of whom developed avascularity. In a review of 39 fractures in 8 series, Hughes and Beaty noted that approximately half of the fractures were associated with traumatic dislocation of the femoral epiphysis and that it is this factor that predisposes to avascular necrosis [281].

All fracture-separations at this growth plate are Type I (Fig. 5.27a, b). Types II, III, IV, and V injuries have not been described. Significant numbers of complications are associated with these separations, involving avascular necrosis of the femoral head, premature growth plate arrest, and coxa vara even though the Type I injury is generally considered to be benign [283–286]. With each fracture-separation at the proximal capital femoral epiphysis, the question arises initially as to whether one is dealing with a type A or type C situation. The poor prognosis is related to the fact that the proximal femoral growth plate is totally intracapsular and thus has a very vulnerable blood supply. The anatomy of the vessels in relation to the femoral head and neck has been well illustrated by Chung [287]. Speedy but gentle reduction, smooth Kirschner-wire pin fixation, and use of a hip spica are desirable to treat the fracture and minimize the likelihood of negative sequelae. Viability of the femoral head can be determined by bone scan that can be performed even after metallic fixation. Open reduction is generally needed where the head is dislocated.

Certain types of fracture-separations have a more favorable prognosis. Miller reported no avascular necrosis in his study and Davison and Weinstein reported AVN in only 1 of 4 patients [288, 289]. Better results without avascular necrosis are clearly favored by physeal fracture without dislocation of the femoral head from the acetabulum. When dislocation accompanies the fracture, the likelihood of avascular necrosis is extremely high. It also appears that those suffering the fracture younger than 2.5 years of age have a much more favorable prognosis. Forlin et al. reported on 5 children with displaced transepiphyseal fractures of the femoral neck without dislocation [290]. Ages at fracture ranged from 8 to 26 months and three were victims of child abuse. All were treated only with hip spica immobilization with no attempt at closed or open reduction. There were no cases of avascular necrosis. In one patient where diagnosis was delayed for 18 months, nonunion required valgus osteotomy and bone grafting; there was no AVN but premature growth plate closure occurred. In the other patients, two healed with varus, no AVN and open growth plates which corrected the angular deformity over the next few

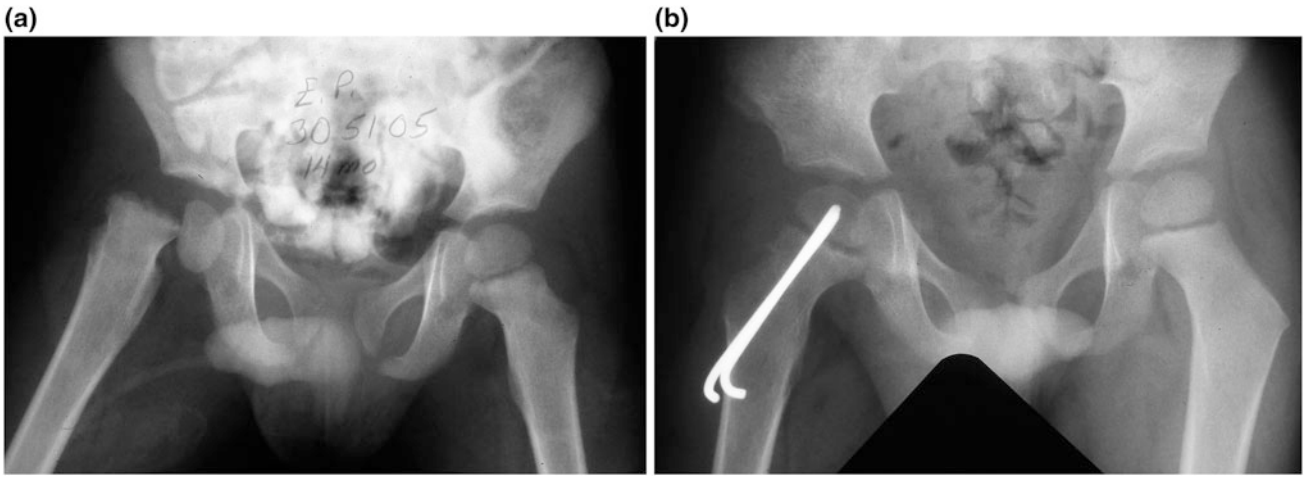


Fig. 5.27 **a** Illustrates a displaced type I proximal femoral capital epiphyseal fracture-separation. **b** Indicates treatment involving open reduction and epiphyseal stabilization using two K-wires and hip spica

years while two healed with no AVN but with premature growth plate closure requiring valgus osteotomy and attention to limb length discrepancy. Gentle treatment initially using only hip spica immobilization favors union without AVN—subsequent growth problems are then manageable to save a functional hip.

Ogden et al. noted that the 5 poor and fair results in 11 patients in his study, by which is meant coxa vara and premature physeal closure, all occurred in children who were more than 2 years old at injury [291]. Treatment is characterized by the need for immediate reduction. Gentle closed reduction can be attempted but if unsuccessful, immediate resort to open reduction is necessary. Post-reduction stabilization is also essential owing to lack of any meaningful periosteal sleeve. Fixation is by smooth K-wires and hip spica in those with growth remaining. All those in the slipped capital femoral epiphysis age group >11 or 12 years of age can be fixed with cannulated screws. The complications include avascular necrosis, coxa vara, premature physeal closure, nonunion (very infrequent), and rare instances of chondrolysis.

Transepiphyseal separation of the upper femoral epiphysis has been documented in two children (22 months and 9 years of age) with cerebral palsy and severe epilepsy after violent seizures. Treatment by closed reduction and 2 K-wires in the younger child and a large fragment cancellous AO screw in the older have led to healing without AVN [292].

5.7.9.1 Neonatal Proximal Femoral Physeal Separation

There are several reports of Type I epiphyseal separation at the proximal end of the femur in the newborn or early in infancy [291, 293]. The newborn fractures are difficult to diagnose since the ossification centers of both the femoral capital epiphysis and greater trochanteric epiphysis have not appeared. The characteristic presentation is often confused with septic arthritis or osteomyelitis of the proximal femur. There is a marked disinclination to use the hip and the lower extremity lies with external rotation. There is lateral displacement or rotation of the proximal femoral shaft which can be confused with a developmental dislocation of the hip. Ultrasound is of extreme value for diagnosis especially in the newborn period. X-rays become valuable approximately 1 week post-injury when the periosteal new bone formation of the proximal femur can be noted. The fractures, as pointed out by Ogden et al. almost invariably involve the complete physis of the proximal end of the femur which underlies both the femoral head-neck and greater trochanter [291]. A high percentage of these injuries in the newborn are associated with traumatic delivery in particular with either breech or footling presentation. In infancy, it is essential to have a high suspicion of the possibility of child abuse.

Ogden et al. reviewed 8 proximal femoral epiphyseal separations. Five were birth injuries and two were in victims of child abuse at 5 and 9 weeks of age [291]. Six were unilateral and 1 bilateral. In their series, the capital femoral epiphysis remained located in all instances. Six patients were treated with Bryant's traction for 6–15 days following which either hip spica or bilateral abduction splinting was used. Follow-up varied from 3 to 15 years in 5 patients and 22 years in 1. There were no long-term growth deformities noted. Two had a mild varus which normalized within the 1st year of life, and another developed anterior bowing of the femur which persisted at 4 years of age.

An experimental investigation to assess the pattern of disruption was done involving manual trauma applied to 6 neonatal stillborn pelvic-femoral units comprising only

musculoskeletal tissue. In each instance, the hip capsule remained intact. Generally, there was a relatively clean break across the physis of the proximal femur and greater trochanter but proximal to the lesser trochanter. The periosteal sleeve was intact posteriorly. Histologic studies showed the fracture invariably to be a Type I growth plate injury with the fracture line across the entire proximal femoral epiphysis. In two cases, the fracture line passed into the epiphysis splitting the germinal zone away from the epiphyseal blood supply. There was also multiple longitudinal splitting of physeal cell columns. Ogden et al. reviewed many cases, most of which were isolated single reports from 1898 onwards [291]. Half of the babies were subsequently described as being "large-for-dates." The fractures were not only through the physis throughout their entire extent, but were almost invariably at or below the lower parts of the hypertrophic zone. Medial propagation into the epiphysis was seen on occasion as were longitudinal splitting and fragmentation of the physis in the experimental model. The germinal cells, however, were not crushed. The posterior periosteum tended to remain intact but was often elevated for several centimeters from the diaphyseal shaft. The frequency of the injury is decreasing with improved obstetric care. Once beyond the neonatal period of hospitalization, child abuse must be suspected.

5.7.10 Distal Femur

5.7.10.1 Newborn Fractures of the Distal Femoral Epiphysis

Traumatic separations of the distal femoral epiphysis have been described in the newborn. Banagale and Kuhns reviewed 23 cases from the literature (1898–1983) including one of their own and noted that all were Salter–Harris type 1 separations [294]. If we add 5 cases that Riseborough et al. reported, then at least 28 cases have been reported [295]. All were Type I injuries. In 7 instances, the cases were bilateral. Where presentation was documented, 22 of the 25 patients were breech with only three vertex. Diagnosis was frequently delayed as concern about swelling and disuse of the limb often centered about septic arthritis, osteomyelitis, paralysis, or lymphedema. The diagnosis frequently came to light only when sequential radiographs showed abundant callus owing to the extensive periosteal elevation in association with the fracture. In spite of this, virtually no negative sequelae occurred. With gentle reduction and splinting, the fractures healed uneventfully. The distal femoral physis in the newborn is less sharply angled centrally than in the older patient and the thickness of the physeal and epiphyseal cartilage is relatively greater in relation to the secondary center bone, both features serving to minimize growth arrest problems. There was occasional angular deformity in particular where diagnosis was unappreciated or late although this had sufficient time to remodel. Shortening was not a problem.

5.7.10.2 Distal Femoral Fracture-Separations Overview

Five types of pathoanatomic pattern occur but the large majority are Type II. The type distribution in 5 major reviews (203 cases) up to 1981 was Type I-15.4 %, Type II-71.6 %, Type III-4.3 %, Type IV-5.8 %, and Type V-2.9 % (Tables 5.10 and 5.11) [45, 296–299]. There is a high incidence of physeal damage, with shortening and angulation occurring in approximately 40 % of cases, even when Type II fractures alone are considered. The Type III and Type IV injuries have a similar rate of problems associated with them. The fairly high incidence of growth plate problems involving angular deformity or shortening or both after distal femoral fracture-separations has been noted in many studies [295–307]. A meta-analysis including studies from 1950 to 2007 assessed 564 fractures with a documented growth disturbance in 291, a rate of 52 % [306]. Significant growth disturbance was defined as a leg length discrepancy equal to or >1.5 cm and/or 5° of varus/valgus deformity. Each of the major SH gradings had relatively high growth disturbances: 36 % of SH1 fractures, 58 % in SH2, 49 % in SH3, and 64 % in SH4. Displacement favored development of growth disturbance which occurred in 65 % with displacement and 31 % without displacement. Growth disturbances occurred both in those treated without internal fixation (58 %) and those treated with internal fixation (63 %). These problems can occur with Type I, II, III, or IV injuries (Fig. 5.28a–q). Bylander et al. concluded that the "Salter–Harris classification is of minor value in predicting growth disturbance after injury to the growth plates of the distal femur and proximal tibia" [301]. The extracapsular blood supply to the distal femur is extensive and there is little concern about a type C injury, although as noted previously the epiphyseal vascular state post-injury is not yet amenable to direct assessment in terms of focal diminution. The major consideration, however, is whether the fracture is associated with the type A, B_1, or B_2 categorizations. The Type II fracture at the epiphysis predisposes to crushing and fissuring of the nontransverse growth plate in association with the great force required for separation. Displacement tends to shear the central and peripheral epiphyseal growth plate regions, frequently causing longitudinal growth plate fracture and communication between metaphyseal and epiphyseal circulations, which allows formation of a bone bridge. In Type II injuries, stabilization of the generally large metaphyseal fragment to the metaphysis using AO compression screws is designed to minimize post-fracture micro-motion that might further damage the epiphyseal plate. The Type II distal femoral injury may conform to the type A pattern, but the B_2 pattern often prevails.

In the Type III injury, either the type A or B_2 phenomena can occur. Which type occurs depends on the transverse level of physeal fracture. If the transverse fracture is at the metaphyseal level, the likelihood of epiphyseal and metaphyseal communication is increased unless reduction is anatomic. Torg et al. reported specifically on 6 Type III fractures of the medial femoral condyle which they had seen over a several year period [307]. The injury was due to a valgus force applied to the knee. In 5 of their 6 cases, the fracture was nondisplaced, and there was often a considerable period of time prior to its being appreciated as a fracture. They stress the importance of the need for cross-table lateral X-rays in suspicious cases of knee injury in an effort to detect fat within the joint fluid and confirm existence of an intra-articular fracture. Oblique and tunnel views were also helpful. Owing to the undisplaced nature of most of their cases and the fact that the age at occurrence was between 14 and 16 years, there were virtually no negative sequelae. Treatment was with a cylinder cast. All the injuries were football or soccer related and in 4 of the 6, the initial routine radiograph did not allow for the diagnosis. It was the stress radiographs and oblique radiographs that clarified the picture although currently stress films are not recommended. At present CT or MR imaging help clarify fracture levels. Lippert et al. found that CT or MRI revealed displacement much better than plain radiographs which significantly underestimated displacement in this particular fracture [308]. In 6 cases having both studies displacement was 0.42 mm by plain radiographs and 2.7 mm by CT or MRI.

Thompson et al. reviewed 30 consecutive fractures of the distal femoral epiphysis [309]. There were 24 Type II injuries, 2 Type III, and 4 Type IV. Growth-related complications were far more frequent in displaced than in nondisplaced fractures. They noted 18 patients (60 %) with excellent results, 8 fair (27 %), and 4 poor (13 %). A fair result had a limb length discrepancy of 1–2 cm and angular deformity of 5°–10°, while a poor result had >2 cm of limb length discrepancy and >10° of angulation. When considering only the displaced fractures, the quality of the result diminished with 48 % excellent, 35 % fair, and 17 % poor. The poorest results were in the group that demonstrated >50 % initial fracture displacement which correlates with the more extensive trauma than in non—or minimally displaced fractures. They noted that 47 % of patients developed lower extremity length discrepancies with 4 < 1 cm, 6 from 1 to 2 cm, and 4 > 2 cm. The lower extremity length discrepancy was not related to the Salter–Harris classification, to the use of internal fixation, or to the chronologic age. They recommended that displaced fracture-separations were best treated with early, gentle anatomic reduction under general anesthesia with open reduction if needed. Following reduction, internal fixation with percutaneous Steinmann pin fixation was helpful to minimize risk of the displacement. A large percentage of long leg casts used following fracture reduction without internal fixation led to some displacement.

More recent studies show similar findings. Arkader et al. studied 73 distal femoral fracture-separation of which 59 % (43 of 73) were type II injuries [310]. A similar distribution of types I to V as in multiple earlier series was found; 24.5, 59, 5.5, 9.5, and 1.5 %, respectively. Displacement occurred in 59 % of these. The overall complication rate in all 73 patients was 40 %. There was a significantly higher incidence of complications among displaced fractures, which is most likely an indication of the greater amount of trauma damaging the physis (compared with nondisplaced fractures). The incidence of complications was 29.4 % in 18 type I patients and 33.3 % in 42 type II patients. There was a growth arrest in 27.4 % of all patients and 55 % of these needed surgical intervention. Osteotomy with or without epiphyseodesis was needed in some. There was a higher incidence of growth complications when the physis was further violated by transphyseal pinning [310]. The authors recommended internal fixation for all displaced fractures, even for those with minimal change. Garrett et al. however while also finding a high percentage of growth disturbances with the distal femoral fractures found that percutaneous smooth pins across the physis were not statistically associated with growth arrest [311].

Eid and Hafez showed a similar pattern and findings in 151 cases [312]. The average age at the injury was 12.3 years. The juvenile age group was most affected with complications. SH II injuries were most common (43 %) and also showed many complications. Segal and Shrader reported two cases of entrapped periosteum at the physeal fracture sites in SH II injuries of the distal femur [313]. Preoperative MR imaging demonstrated the finding. Even with open reduction of the physeal injury with removal of the soft tissue premature physeal arrest occurred in both cases. Liu et al. performed a detailed study of the undulations of the normal distal femoral physis [314]. This anatomic feature is a primary factor associated with physeal damage even in type I and II S–H patterns. The major undulations within the epiphysis, affecting the plane of the physis, were a central ridge, lateral ridge, and medial peak. The height and surface area of each undulation decreased with increasing age, most dramatically in the central ridge.

The B_1 pattern is generally present prior to reduction in Type IV fractures. There is relatively little crushing at the time of Type IV injury and accurate repositioning by open operation can convert a B_1 injury to type A. In the displaced Type III and IV lesions, accurate anatomic reduction and AO compression screw fixation closely reappose the articular cartilage surfaces, epiphyseal bone to epiphyseal bone, growth plate to growth plate, and metaphyseal bone to metaphyseal bone, thus minimizing the likelihood of eventual growth arrest and deformity.

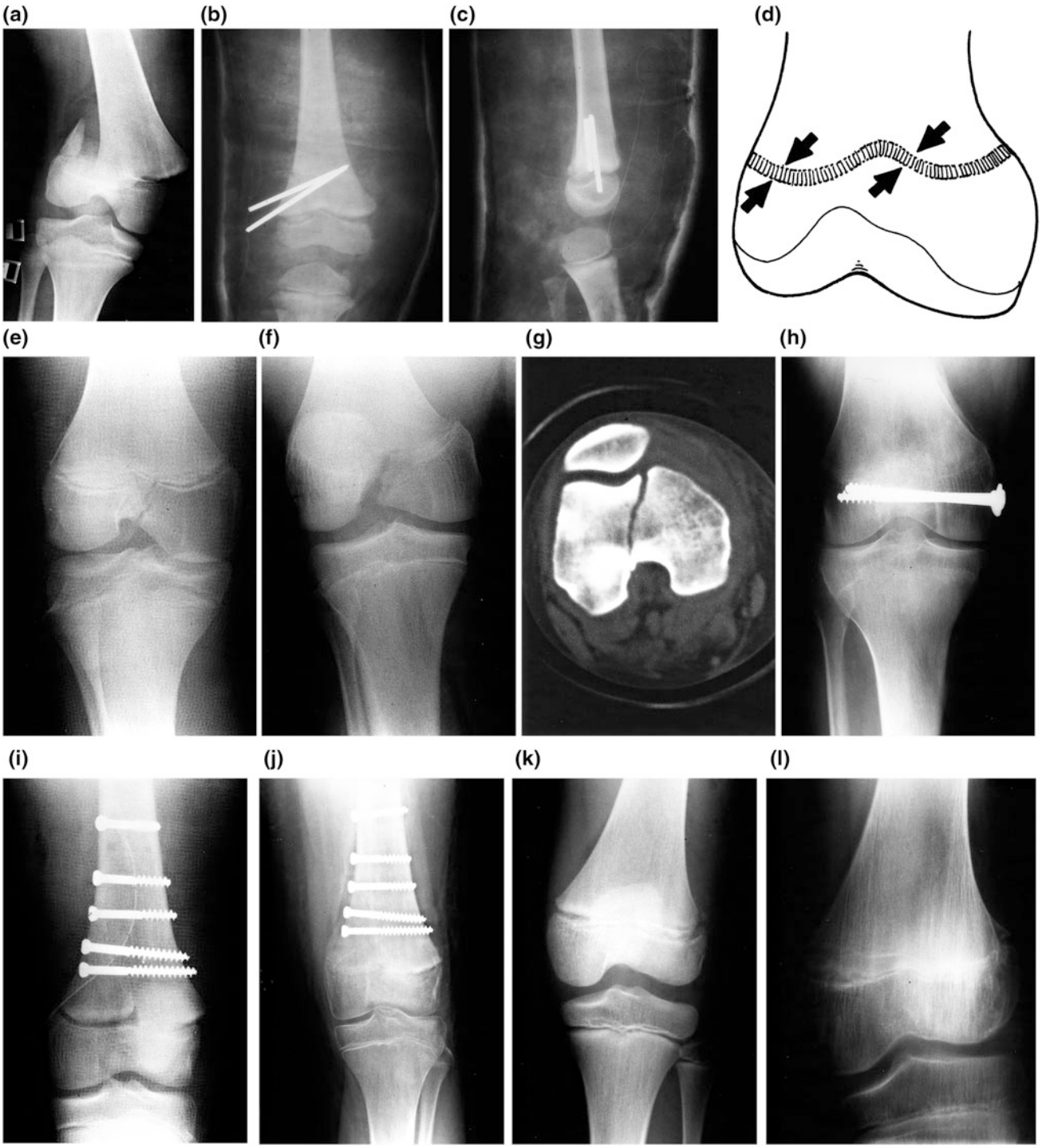


Fig. 5.28 (continued)

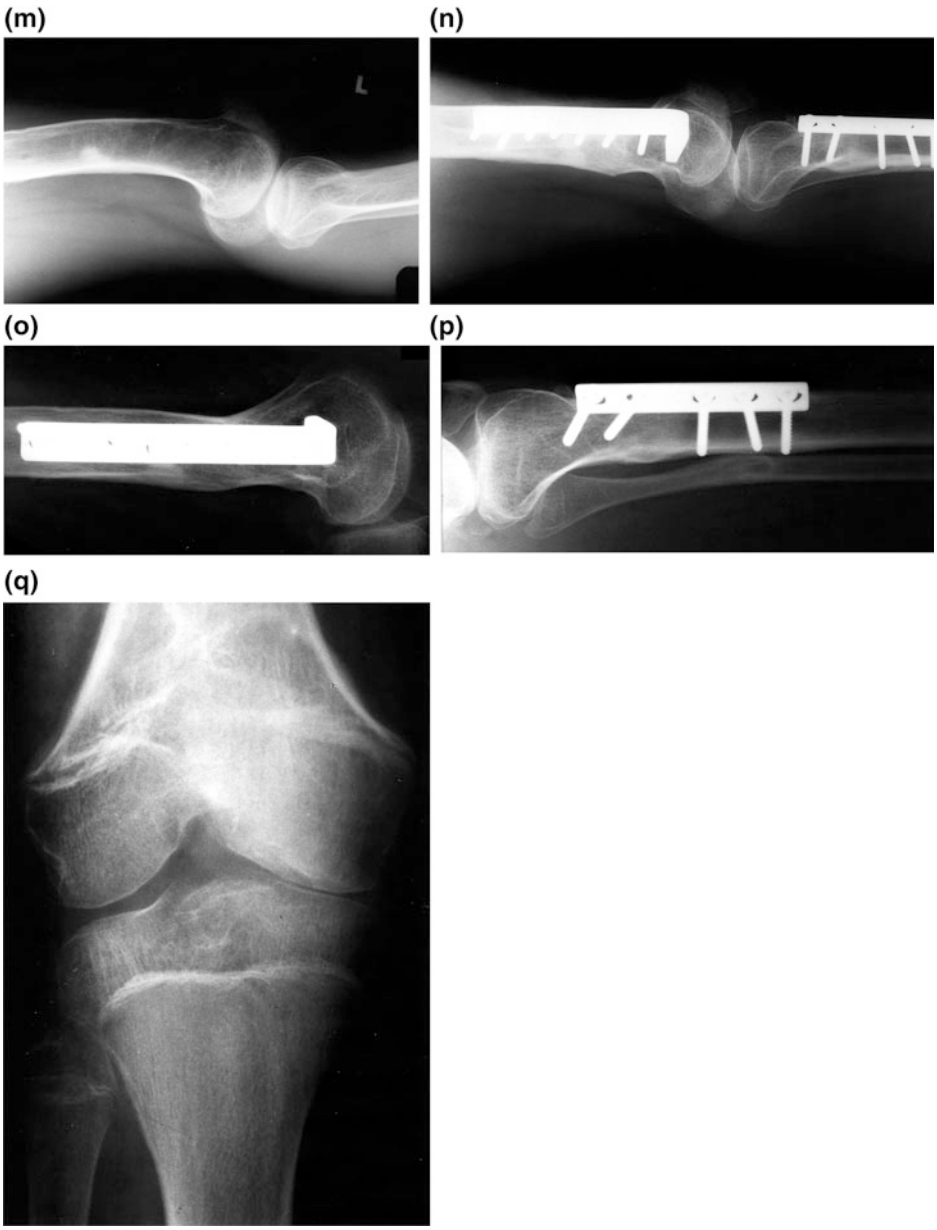


Fig. 5.28 (continued)

5.7.10.3 Growth Problems in Large Series of Distal Femoral Physeal Fracture-Separations

Riseborough et al. studied the results following 66 distal femoral physeal fracture-separations [295]. Sixteen of the patients were seen initially at the authors' hospital. Of those who were referred secondarily, many already had growth problems and the complications listed, while accurate, are not necessarily a true reflection of the frequency following such fractures. Lower extremity length discrepancies in excess of 2.4 cm or leading to contralateral distal femoral physeal arrest occurred in 37 patients (56 %), and angular deformity of more than 5° or requiring osteotomy occurred in 17 patients (26 %). The radiographic sign of central arrest occurred in 13 patients (20 %) and was associated primarily with Type I and Type II injuries. This sign had excellent predictive value for the development of limb length discrepancy. Growth problems correlated well with the severity of trauma and were seen in each of the Salter–Harris types. Fractures in the juvenile age group (2–11 year old) were almost invariably caused by severe trauma and had the poorest prognosis; 19 (83 %) of the 23 injuries in juvenile

patients resulted in growth problems. Fractures in the adolescent age group (11 year olds and older) were caused by less extensive trauma being associated most often with sports injuries; eighteen (50 %) of the 36 adolescents had growth problems. Birth fractures and those in the first 2 years of life were associated with mild growth disturbances on occasion but did not lead to severe growth problems in any of the 7 patients. It was felt that the final results would be improved by anatomical reduction and greater use of internal fixation in Type II, Type III, and IV injuries. The management of these patients after healing of the fracture was not considered to be sufficiently intensive, as 19 patients had a length discrepancy of 2.4 cm or more persisting at skeletal maturity. To a certain extent some growth plate damage is determined at time of injury; questions remain as to which treatments improve prognosis and which may actually worsen it.

a. Fracture Profile. There were 47 boys and 19 girls, a 2.5-to-1 male predominance. The left femur was involved in 38 patients and the right, in 28 (1.4 to 1). Forty-seven of the fractures classified by the system of Salter and Harris were Type I-7, Type II-25, Type III-7, Type IV-6, and Type V-2. The type was uncertain for 19 fractures (initial radiographs were no longer available for assessment or patients were seen initially in other hospitals without documentation). Ages at time of fracture ranged from birth to 16 years 6 months. Five birth fractures and two fractures in the 2nd year of life accounted for 10 % of the injuries; 23 fractures in the juvenile age range (2 years and 3 months old to 10 years and 11 months old) accounted for 35 %; and 36 fractures in the adolescent age range (11 years old or more) accounted for 55 % injuries. The average age at fracture was 10.8 years for boys and 9.8 years for girls.
b. Mechanism of Injury. Three of the 5 birth fractures were associated with breech delivery. Fractures in juvenile patients were associated with much more severe trauma than those in adolescents. Of the 23 children in the juvenile age group, 3 fell from a window, 14 were hit by an automobile, 3 were crushed by a heavy object, 1 sustained gunshot wounds, and only two had a sports-related accident. Twenty-four of the injuries in the adolescents were sports or play-related, 11 were automobile or truck-related, and 1 injury resulted from a fall.
c. Closed and Open Fractures. Sixty fractures were closed and six were open. The open injuries comprised 4 of the 6 Type IV injuries, one Type V fracture, and one fracture whose type was unknown. None of the Type-I, II, or III injuries were open.
d. Methods of Treatment. In the three Type I birth injuries, reduction with traction in extension was not used because it was thought that remodeling would correct any deformities that were not controlled by lower extremity splinting. A victim of child abuse at the age of 1 year and 4 months was treated with a long leg plaster splint. Two of the three older patients with a Type I lesion (12 years and 5 months old, 12 years and 6 months old, and 12 years and 10 months old) had closed reduction and plaster-cast immobilization, and 1 had an open reduction with Kirschner-wire pinning and plaster-cast immobilization. Each of the three latter patients retained the reduction. Twenty of the 25 Type II lesions had closed reduction with cast immobilization, 2 required no reduction, and 3 had closed reduction with percutaneous Kirschner-wire or Steinmann pinning of the large

◀ **Fig. 5.28** Radiographic appearances, treatments, and sequelae following distal femoral epiphyseal growth plate fracture-separations are illustrated. **a** Shows how the lateral metaphyseal region of the femur can crush the central physis in a displaced type II fracture-separation of the distal femur (**b, c**). Operative stabilization seeks to minimize continuing post-fracture physeal damage by allowing healing to occur in a stable environment. **d** Illustrates how the epiphysis moving laterally can impinge on physeal tissue. **e** Shows a type III minimally displaced fracture-separation of the distal femoral epiphysis. AP and lateral radiographs were unrevealing but the oblique film showed the separation. **f** Is a tomographic radiograph showing with greater clarity epiphyseal bone and articular cartilage interruption and displacement. **g** Shows a CT image from a radiologically similar case. **h** Shows anatomic reconstitution following open reduction and internal fixation using an intraepiphyseal AO compression screw. The injury occurred close to skeletal maturity and no growth sequelae followed. **i, j** Massive direct trauma to the distal femur in a skiing injury resulted in a markedly displaced long metaphyseal fragment and transverse physeal fractures involving both medial and lateral components. The knee was treated with open reduction and internal fixation using multiple compression screws across the metaphyseal fragments, while the epiphyseal reduction also held with a long leg cast (**i**). Anatomic healing occurred but was associated with virtual immediate complete transphyseal fusion (**j**). **k** An undisplaced type I fracture-separation of the distal femur in an 8-year-old girl is shown in association with a midshaft diaphyseal fracture on the same side. The diaphyseal injury healed without difficulty in traction followed by casting. No specific attention was paid to the distal femoral fracture. Within 1 year of injury, it became apparent that there was a distal femoral growth plate focal arrest occurring. **l** A tomogram shows the focal lateral physeal arrest with physeal narrowing to disappearance, increased bone density, angular deformity, and a growth arrest line passing obliquely into the area of the bone bridge. Surgical procedures followed involving varus osteotomy and attempted bone bridge resection. **m** A lateral radiograph 6 years later at skeletal maturity shows a flexion deformity of the distal femur, due to premature posterior physeal closure and an extension deformity of the proximal tibia due to unrecognized tibial tubercle area fracture with premature closure. **n–p** Realignment of the lower extremity was achieved with an extension osteotomy of the distal femur and a flexion osteotomy of the proximal tibia (**n**). The corrected positions of the distal femur (**o**) and proximal tibia (**p**) are highlighted. Length equality was achieved at skeletal maturity but required an ipsilateral femoral lengthening and contralateral diaphyseal shortening. **q** A premature central physeal growth plate closure has caused a characteristic fishtail deformity of the distal femur

metaphyseal fragment under radiographic control. In one patient, closed reduction was supplemented with several days of skeletal traction. Of the patients in whom percutaneous pinning was not done, a long leg cast was used for 14, of whom 2 lost some position, and a hip spica cast was used for 8 patients, of whom one lost position. One of the 7 Type III fractures did not require reduction. Six had closed reduction, 4 of which were anatomical and remained so. The position accepted after reduction remained unchanged in 6 patients in whom a long leg cast was used and in the 1 patient in whom a hip spica was used. Three of the six Type IV lesions had open reduction and fixation with Kirschner wires while the other three, two of which were open and required debridement, were reduced by closed manipulation. One of these required open reduction 5 weeks later. One of the two Type V fractures required closed reduction; both were treated in a long leg cast.

e. Findings and Conclusions. The most important factors associated with growth arrest were age at injury and severity of injury rather than the pathoanatomical type. None of the 5 birth fractures, all of which were Type I or Type II lesions, led to significant growth arrest. All angular deformities corrected with growth even when no specific attempts at reduction were made. A review of 6 similar patients also documented the occurrence of such injuries with breech presentation, the uneventful healing, and the tendency for length discrepancies and angular deformities to resolve completely or with minimum discrepancy persisting [48]. Virtually all of the lesions in patients in the juvenile age group, however, were associated with massive trauma. This, rather than the specific pattern of injury, correlated with high levels of growth arrest and deformity. This association of significant problems with severity of injury and displacement has previously been noted in physeal fracture-separations and has led to the proposal for consideration and investigation of such injuries on a pathophysiological basis. The majority of the fractures in this series occurred in patients in the adolescent age group, from 11 years old to skeletal maturity. Although a considerable number of these patients also had growth arrest problems, the proportion was not as great as in the juvenile group. Most of the injuries were sports-related which usually implies a lesser degree of trauma.

Eighty-three percent of the juvenile patients compared with 50 % of the adolescent patients had a length discrepancy or angular deformity. In terms of the pathophysiological classification, the greater the trauma, the more severe the injury the physis receives, especially damage to the blood supply and physeal cartilage that is not evident radiographically. The majority of injuries that subsequently resulted in difficulty were in patients in the juvenile age group. In these children, the periosteal and perichondrial sheath is quite thick, and its disruption implies massive trauma. In the adolescent age group, the perichondrial and periosteal sheath is thinner and is closer in thickness and strength to that of an adult, and relatively few of these patients had growth arrest problems. The mechanism of fracture in the two age groups indicates that the amount of trauma required to disrupt the plate was relatively less in the older patients. In association with a lesser amount of trauma, one can postulate less crushing of the cartilage plate and less vascular disruption. The principle that high-speed trauma produces more problems in terms of soft tissue damage and length of healing than relatively minor, low speed trauma in adult diaphyseal fractures appears to apply equally well to physeal fracture-separations in childhood. In addition, the closer the patient is to skeletal maturity the less the sequelae to growth damage would be.

This study documented the central arrest phenomenon that occurred in 20 % of the patients. Transphyseal bone continuity was seen across the middle of the growth plate, with the radiolucency that persisted medially and laterally representing apparently normal growth plate cartilage. The central arrest phenomenon was ominous, however, in that following its appearance in all patients either complete radiographic fusion occurred in a matter of months or the central arrest persisted with little or no further contribution of the physis to femoral length. Of the 8 central arrest signs in patients whose fracture type was known from the beginning, 6 were in Type I and Type II lesions.

It has been demonstrated in the rabbit that extensive damage to the central area of the physis results in marked interference with growth. It has also been shown, in a physeal fracture model in the distal end of the femur in rats, that with Aitken Type I lesions (Salter–Harris Type II) the fracture line involves the hypertrophic cartilage zone of the physis except in the central region, where the defect extends more deeply into the zone of resting cartilage cells and sometimes into the bone plate of the epiphysis [87]. The central arrest phenomenon is attributable to a similar fracture path in the human femur.

Several forms of treatment were used in this series, although the basic principle of obtaining and maintaining as anatomical a reduction as possible was adhered to. Closed or open reduction should be firm but gentle so as not to aggravate the damage of the physis. There is little advantage in achieving perfect radiographic reduction if the force used to do so causes excessive physeal damage. Many of the patients in this series had immobilization with a long leg cast

rather than a hip spica. The results, however, did not demonstrate problems with long leg casts in the Type I and Type II lesions. Of the 16 patients who wore a long cast, only two lost some position, whereas of the 7 who wore a hip spica cast, 1 lost position. If the patient is short or has an obese or muscular thigh, hip spica treatment is safer, but in a child who is relatively tall and thin, immobilization in a long cast with appropriate flexion and molding forces appears to be adequate. Close monitoring is required. In three patients in whom a large metaphyseal fragment was associated with a Type II fracture-separation, either Steinmann pin or Kirschner-wire fixation of the metaphyseal fragment to the metaphysis was performed after closed reduction. This makes subsequent displacement even less likely and allows the use of a long leg cast with a greater margin of safety. In the Type-III and Type-IV lesions, gentle anatomical reduction by closed or open means and Kirschner-wire or cancellous screw fixation appears to be essential, as the possibility of growth arrest and discontinuity of the articular surface increases in the absence of anatomical reduction. The purpose of operative intervention is fourfold: to restore articular surface continuity, to relate epiphyseal bone only to epiphyseal bone, to restore physeal continuity, and to relate metaphyseal bone to metaphyseal bone. In Type III fractures, internal fixation can pass from the epiphyseal fragment to the main body of the epiphysis without traversing the physis. Similarly, in Type IV lesions, following accurate reduction internal fixation passing from metaphyseal fragment to metaphyseal fragment is warranted. Epiphyseal fragment fixation to the adjacent epiphysis can also be added.

The study highlighted certain problems in management after healing of the fracture. Nineteen patients had a lower extremity length discrepancy of 2.4 cm or more at skeletal maturity, and 8 of them had a contralateral epiphyseal arrest in an attempt to limit the discrepancy. These results would have been improved by earlier investigation and management. In many patients, the discrepancy problems either were not recognized or were seen and treated too late. Computed tomography scans are of great value in delineating the presence and extent of bone bridges. Earlier noninvasive vascular studies might help to determine the extrinsic physeal blood supply and possible intra-osseous communications between epiphyseal and metaphyseal compartments. Magnetic resonance imaging plays an increasing role in management schemes to assess transphyseal bone bridge formation in the early weeks and months post-injury.

Partial inhibition of growth, referred to by Neer as "deceleration of growth", can occur following a physeal lesion. Isolated instances of growth stimulation after fracture-separation also have been reported; the case of one such patient was documented in this series. The importance of following such patients to skeletal maturity even if the physis remains radiographically open following healing is evident.

If total growth arrest is found to have occurred, one can readily calculate the eventual limb discrepancy from femoral and tibial length charts and growth remaining charts. If the projected length discrepancy is <5.0 cm contralateral distal femoral epiphyseal arrest is recommended contralateral distal femoral physeal arrest. Such a procedure will not correct any discrepancy that has already occurred but will prevent it from increasing. If further reduction of the length discrepancy is required, contralateral proximal tibial arrest can be done. This procedure was not resorted to often enough or early enough in this series. If it appears that the ultimate discrepancy will be >5.0 cm, one should consider the option of diaphyseal lengthening of the involved limb.

Early demonstration of partial arrest can help to prevent or minimize angular deformity by alerting the surgeon either to complete the arrest across the width of the plate or to attempt to resect the bone bridge and interpose a biological or prosthetic implant to allow growth to continue. Not all angular deformities are due to growth arrest phenomena. Certain Type I and Type II fractures, if imperfectly reduced, may result in a varus or valgus malunion. CT scans or MRI are important in demonstrating bone bridges or narrowing of the plate. Sufficiently small bone bridges yield to cartilage growth and elongate with continuing activity of the plate; larger bridges, however, lead to growth arrest. Techniques have been developed for resection of osseous bridges and implantation of fat or other materials to block the invasion of vascular mesenchymal tissue and reformation of such bridges. These will be described in Chap. 6.

5.7.11 Proximal Tibia

5.7.11.1 Proximal Tibial Growth Plate

Growth plate fracture-separations of the linear horizontal proximal tibial physis are rare but when they occur a considerable number of patients develop growth arrest problems with Type II, III, or IV injuries (Fig. 5.19a, b) [46, 301, 315–318]. All 5 types of pathoanatomic fracture pattern occur. A compilation of 95 cases from 4 major reviews showed Type I-13.6 %, Type II-43.2 %, Type III-22.1 %, Type IV-18.9 %, and Type V-3.2 % (Tables 5.10 and 5.11) [46, 315, 317, 318]. Approximately 20 % of patients develop partial or complete growth arrest with problems occurring following each of the fracture-separation patterns. Except for major machine-type trauma, proximal tibial fracture-separations tend not to occur in those <10 years of age.

Shelton and Canale noted shortening of 1.0–2.5 cm in 7/28 (25 %), all Type I and II [318]. Angulation from 5° to 7° was also frequent 8/28, (29 %) and again was limited to the Type I and II lesions. Burkhardt and Peterson had similar results [315]. The growth plate is extracapsular and has an excellent blood supply. The slight irregularity of plate shape in the transverse plane, the anterior and inferior epiphyseal projection (tibial apophysis), and the extreme amount of force needed to cause fracture-separation can induce considerable growth plate crushing, allowing the epiphyseal and metaphyseal circulations to interrelate and form a bone bridge (type B_2), although the majority of lesions still yield a type A situation with no growth arrest. A widened physis post-reduction leads to concern about a D_1 situation with a periosteal flap interposed between the fragments. It is important to assess the tibial tubercle carefully as premature fusion of this region can lead to subsequent hyperextension deformities. Figure 5.6a, b, illustrate how MR imaging can reveal unsuspected adjacent bone fractures.

Thompson and Gesler described a rare proximal tibial epiphyseal fracture occurring in a 7-month-old female with apparent child abuse [111]. Closed reduction was ineffective in holding alignment and open reduction and internal fixation were used at which time it was noted there had been infolding of the pes anserinus and periosteum. There was post-repair tibia valga owing to asymmetrical physeal overgrowth even though reduction had been anatomic. This was subsequently corrected with osteotomy within 1 year of injury. The proximal tibial and fibula varus osteotomy realigned the limbs well, but a mild valgus of 12° recurred which remained nonprogressive over the subsequent 3 years.

5.7.11.2 Tibial Spine Fractures

Tibial spine fractures are intraepiphyseal fractures in children which do not involve the epiphyseal growth plate or physis. The terms tibial spine fracture and tibial eminence fracture have been used interchangeably. The tibial eminence is the region of the proximal tibia with two elevations of bone and cartilage; the medial-anterior eminence or spine is the point of insertion of the anterior cruciate ligament as it attaches to the proximal tibia. The lateral-posterior spine has no attachments to it. The large majority of avulsion fractures affect the anterior tibial spine. Tibial spine fractures are included in Ogden's classification as Type VII [63, 64]. They occur at the point of attachment of the anterior cruciate ligament and thus are the childhood analog of ruptures of the anterior cruciate ligament in adults. Owing to the strength of the ligaments in the childhood age group, an injury which would produce a cruciate tear in the adult avulses a segment of cartilage and bone at the point of insertion in the growing child. With stress, the incompletely ossified tibial eminence in the child fails before the ligament. The failure occurs through the cancellous bone beneath the subchondral plate. The cruciate functional integrity is compromised and the fracture, if sufficiently large, can actually encroach onto the weight-bearing portion of the articular surface of the tibia in particular the region of the medial tibial plateau.

The classification of Meyers and McKeever continues to be used widely; Type I is non-displaced, Type II partially displaced or hinged with the posterior segment remaining intact, and Type III fully displaced [115, 319] (Fig. 5.29). Zaricznyj extended the classification to Type IV which includes comminution of the tibial spine fracture [320].

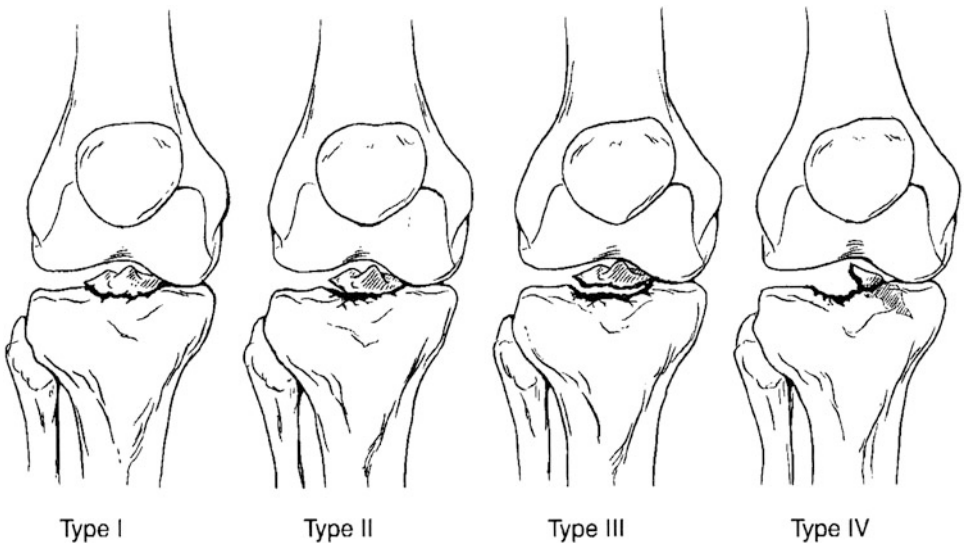


Fig. 5.29 Classification of anterior tibial spine fractures is shown. (Reprinted with permission from Edwards and Grana, Physeal fractures about the knee. J Am Acad Orthop Surg. 1995;3:63–69. Copyright 1995 Wolters Kluwer Health)

Anterior cruciate ligament laxity has been documented in follow-up studies of these injuries. Even though the ligament itself is intact, if the insertion pulls free and heals in a nonanatomic position, the cruciate laxity can be diagnosed. For displaced type III fractures the anterior horn of the lateral meniscus often remains attached to the avulsed fragment preventing closed reduction [321–323].

Wiley and Baxter reported on 82 patients with fractures of the tibial spine in an 8 year period with 45 available for long range assessment [324]. The average age at occurrence was 11 years with the range from 8 to 16 years. There was a 4:1 male predominance. There were 8 Type I, 13 Type II, and 24 Type III injuries. Forty-two involved the anterior tibial spine and only three involved the posterior tibial spine. Type I injuries were treated with cast immobilization with the knee in slight flexion following joint aspiration. All healed uneventfully and resulted in minimal residual laxity. In the Type I and Type II injuries treated only with simple immobilization, no difference in laxity between injured and uninjured knees was noted at final examination. In the Type II and Type III injuries treated with closed reduction compared with the 16 Type III lesions treated with open reduction, no meaningful difference was documented in terms of the final knee stability test. The authors concluded that "fractures of the intercondylar eminence of the tibia in children can result in a measurable degree of cruciate ligament laxity…. however, the patients are generally asymptomatic. An anatomic reduction of the fracture by arthrotomy does not prevent the cruciate laxity or the loss of full knee extension. Open reduction should be reserved for the completely displaced fracture, particularly the inverted fragment so that a bony surface opposes the fracture bed." The authors concluded that the overall prognosis for fracture of the intercondylar eminence of the tibia was "remarkably good, even when the fracture fragment is completely displaced."

Gronkvist et al. assessed 53 cases of anterior tibial spine fractures in patients <15 years of age at the time of injury [325]. Forty-one patients returned for long-term follow-up. They found a substantial number of patients with residual symptoms and instabilities. They documented 5 Type I cases. All these had good results with conservative cast treatment. Fourteen Type II injuries were assessed and the large majority of these had closed reduction followed by casting and all with the exception of two were without symptoms at long-term follow-up. There were 20 Type III fractures with 10 described ultimately as being without symptoms while 10 others were symptomatic at follow-up. Almost all of the Type III cases had open reduction with many also undergoing osteosynthesis as well as casting. Even though the anterior cruciate ligament was not torn, there was a concern that it may have been stretched and elongated as well as associated with the anterior tibial spine fracture. This was particularly felt to be the case in those >10 years of age at injury. They concluded that residual symptoms and clinical instabilities were detected at follow-up in 11 of 32 fractures. The symptoms were most marked in severely displaced Type III fractures in those initially 10 years of age or greater at the time of injury. Their major concern in treatment was to obtain full reduction of the fracture fragment by hyperextension after aspiration. They were unable to demonstrate in their series, however, "any beneficial effects of open reduction with or without wire fixation." They did not regard this as a contraindication to open reduction in selected cases, but as an example rather of incomplete surgical technique. They even considered the need to countersink the bone fragment to compensate for ACL elongation.

Smith reached similar conclusions [326]. He assessed 21 cases of whom 15 were available for detailed follow-up. The three with Type I or Type II fractures had closed treatment and 12 with Type III fractures had open reduction and internal fixation. He found anterior cruciate ligament laxity at long-term follow-up in a large number of cases. Smith also concluded that there was some stretching or elongation of the anterior cruciate ligament even though it remained intact and the chondro-osseous fracture bore the brunt of the displacement.

Experimental study by Noyes et al. demonstrated that prior to fracture of the tibial spine, the anterior cruciate ligament elongated >50 % even though it maintained its continuity [327]. Of their 15 patients, 7 were free of symptoms but 8 had varying degrees of pain with associated muscle atrophy and all had some evidence of anterior cruciate ligament laxity.

Willis et al. assessed 97 patients of whom 50 had a detailed study at least 2 years post-injury [328]. There were 8 Type I injures, 42 Type II injuries, and 47 Type III injuries. The vast majority of Type I fractures were treated with a long leg cast in 20° of flexion alone. Virtually all the Type II patients were treated with closed reduction, aspiration, and long leg casting. The Type III injuries were treated with closed reduction and aspiration plus casting alone, or in equal numbers, open reduction and internal fixation. They too concluded that no treatment method was measurably superior to another with closed reduction methods just as effective as open reduction in terms of eventual knee stability. They concluded that anterior tibial eminence fractures should be treated by closed reduction and immobilization in extension. Arthroscopy could be used to insure adequate reduction of the fragment and open reduction and internal fixation should be reserved for irreducible tibial eminence fracture. The long-term prognosis was guarded because of persistent ACL laxity. In virtually all studies, even those with good or excellent results, ligamentous laxity was defined but in many instances had not yet resulted in any clinical symptoms.

Janarv et al. reported on 61 children with anterior tibial spine fractures showing excellent subjective reports with 87 % good or excellent and 13 % fair [329]. In the entire series, there were 8 Type I injuries, 28 Type II, and 25 Type III. All Type I injuries were treated in cast only. There were 7 closed reductions in the Type II group with the rest being treated with cast alone. In the Type III group, 9 were treated in cast alone, closed reduction was done in 3, open reduction in 3, and open reduction and internal fixation in 10. They concluded that "ATS fracture in childhood seems to be a relatively benign injury in the long term." In Type I fractures, immobilization alone was sufficient. In Type II fractures, they recommended closed reduction by hyperextension followed by casting. In Type III fractures, they recommended open anatomical reduction and stable internal fixation both to insure optimal repositioning as well as to allow assessment of possible underlying meniscal or osteochondral injuries.

McLennan assessed 10 patients with Type III intercondylar eminence fracture with 6 years of follow-up by repeat arthroscopy based on recurring symptoms [330]. He noted long-term morbidity of extension loss, chondromalacia, quadriceps weakness, and ligamentous instability in Type III fractures. He felt that loss of reduction was common after closed reduction and that open reduction and internal fixation, appropriate tensioning of the cruciate mechanism, and aggressive rehabilitation were essential.

Treatment techniques. When long leg casting alone is used the recommended position of the knee varies in reports from full extension to slight flexion of 10° or to flexion of 20° but never beyond that amount. Six to eight weeks of immobilization are usually sufficient. When closed reduction is indicated the mechanism involves full extension or even hyperextension of the knee followed by casting in the position that maintains the reduction, which may even be slight hyperextension. If the type II fracture cannot be reduced closed, if reduction is lost, or for the completely displaced type III fracture open reduction or arthroscopic reduction is warranted almost always then followed by internal fixation. Older techniques used open arthrotomy for reduction and K-wire fixation. Current recommended approaches use arthroscopic reduction with either intraepiphyseal cannulated lag screw (3.5 mm) fixation [321, 331] or intraepiphyseal suture (number 1 Vicryl) fixation [321, 332]. The intraepiphyseal techniques described appear preferable to transepiphyseal screw or suture fixation [333]. Postoperative care varies greatly but is important for optimal results. These usually include (i) post-cast protection in knee immobilization devices, often allowing for graded increases in range of motion, (ii) muscle strengthening and range of motion exercises, and (iii) progressive increase in weight bearing. Excellent results were reported by Mah et al. in the arthroscopy-suture technique for type III fractures [334].

5.7.11.3 Avulsion Fractures of the Tibial Tuberosity

The Watson-Jones classification of tibial tubercle avulsion fractures allowed for good awareness of this injury [335] (Fig. 5.30a). He classified the disorders into three major categories, Types I, II, and III, based on the extent of involvement of the proximal tibial epiphysis as well as the degree of displacement of the fracture fragments. The Type I injury is an avulsion of the small separate ossification fragment of the distal portion of the tuberosity which may be displaced dorsally and proximally. In Type II injuries the entire segment formed by the tibial tuberosity epiphysis is hinged and displaced proximally with the angulation axis at the level of the proximal tibial epiphysis without being completely fractured at its proximal base. In Type III injuries, the fracture line extends into the proximal tibial epiphysis and passes through the articular surface into the joint and thus represents a true Salter–Harris Type III fracture-separation. The fractures occur in the narrow range of 13–16 years of age. Slight modifications of this classification were made by Ogden et al. (Table 5.12 and Fig. 5.30b) who described two variants for each type, Type IA (incomplete separation from the metaphysis) and B (complete separation), Type IIA (non-comminuted) and B (comminuted), and Type IIIA (non-comminuted) and B (comminuted) [336]. A type IV variant is now recognized where the tibial tubercle fracture continues posteriorly along the proximal tibial physis with presence of a posterior–inferior metaphyseal fracture extension (Fig. 5.30c). A small subset of the type IV fractures have an additional fracture line through the epiphysis as well. Those with only the posterior metaphyseal split are referred to as type IV-A and those with both metaphyseal and epiphyseal extension as type IV-B. The initial description of this tibial tubercle fracture was by Ryu and Debenham [337]. It is now recognized more often; Brey et al. recognized the type IV pattern is 15/53 (28 %) of tibial tuberosity fractures [338] and Pace et al. described 24 type IV fractures in a large series of 130 tibial tubercle fractures in children and adolescents for an incidence of 19 % [339]. The lesion is in effect a type II Salter–Harris fracture but warrants separate recognition as an extension of a tibial tubercle fracture. Closed reduction is warranted in Type I and II injuries but only if hinge displacement is noted. Long leg or cylinder cast is used for 4–6 weeks but the patient must be followed closely with knee radiographs as displacement can occur. If it does, open reduction and internal fixation are needed. Open reduction is done if bone fragment repositioning cannot be achieved or held [340, 341]. Anatomic reduction must be considered the primary objective in Type III and Type IV fractures and most Type III and Type IV injuries are treated with open reduction and internal fixation. The bone fragment is held with one or two cancellous compression

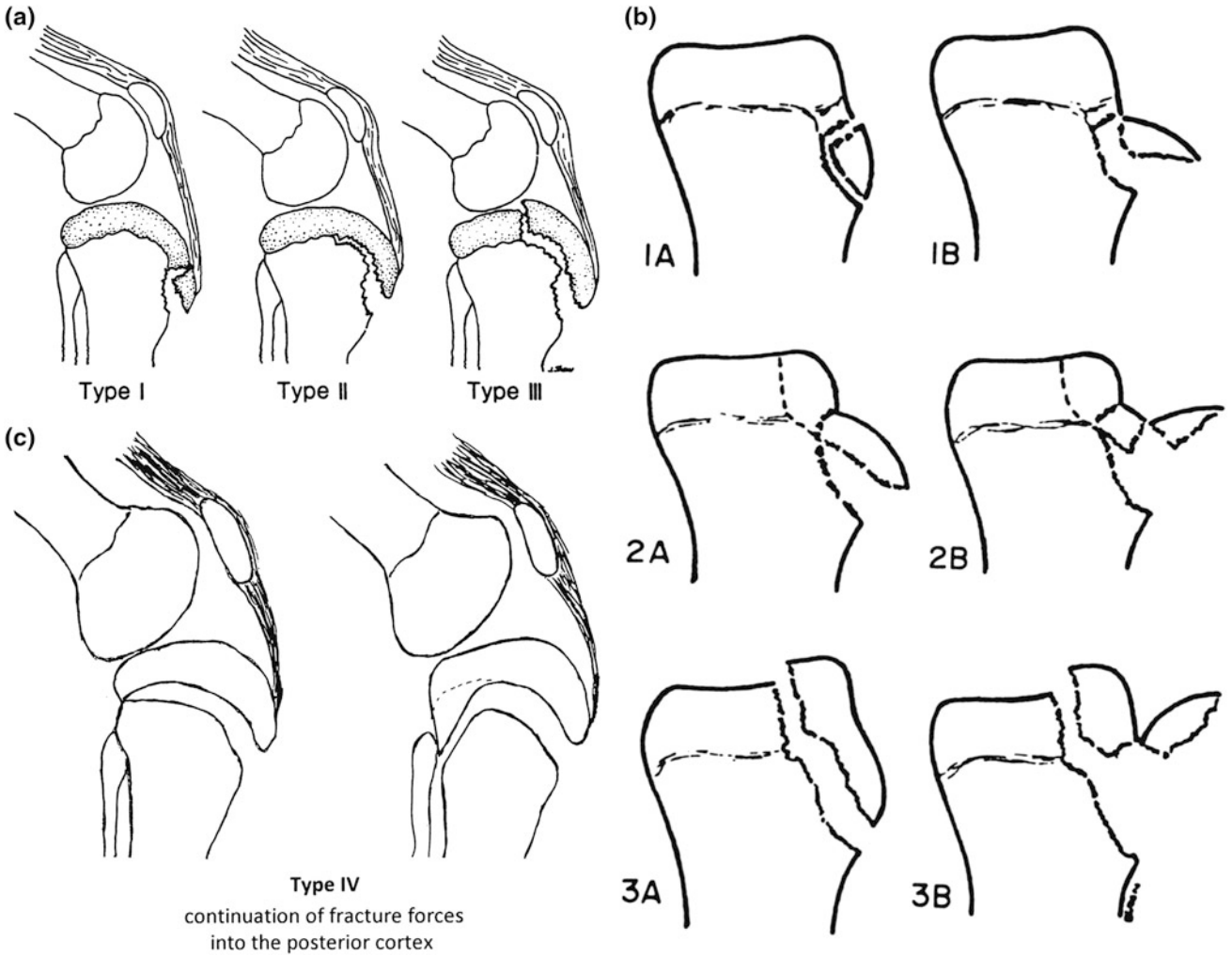


Fig. 5.30 The Watson-Jones (**a**) [346], Ogden (**b**) [336], and Ryu and Debenham (**c**) classifications for tibial tubercle fractures of childhood are shown. (Reprinted with permission from Christie and Dvonch, Tibial tubercle avulsion fractures in adolescents. J Pediatr Orthop. 1981;1:391–394. Copyright 1981 Wolters Kluwer Health and with permission from Edwards and Grana, Physeal fractures about the knee. J Am Acad Orthop Surg. 1995;3:63–69. Copyright 1995 Wolters Kluwer Health)

screws, the periosteum is repaired, arthrotomy is done to inspect the menisci and confirm joint surface anatomic reduction, and patellar tendon repair is stabilized by tension band wiring [341]. Anatomic reduction and healing without loss of position are considered to be highly desirable with these fractures. There is now increased use of internal fixation after closed or open reduction; this is done for any displacement in cast and as a primary intervention in Type III and Type IV lesions. Some groups treat all fractures with ORIF [342]. In a series of 24 types IV fractures, all were treated with open reduction and internal fixation [339]. Cancellous compression screws are used commonly but associated plate fixation is sometimes needed for larger fragment stabilization.

CT scans are valuable to look for type III and IV extensions and to assess degree of displacement for surgical planning. Forceful trauma causes many of the higher grade injuries and reports of incipient or developed compartment syndromes are not infrequently encountered. There tends to be relatively little deformity due to growth arrest since the age of occurrence is late, around the time that the physis itself is closing and the anterior tibial tubercle is fusing to the anterior tibial metaphysis.

Gaudier and Bouret in 1905 demonstrated good awareness of this injury [340]. The type III fracture was well known, with involvement also of the proximal tibial epiphysis and fracture into the tibial plate and articular joint surface. Open reduction and wire/staple fixation were reported. Henard and Bobo reviewed cases in the literature from 1935 to 1980 comprising 76 fractures in 72 patients [343]. The male/female ratio was 4.5/1.0. Most Type III fractures were observed in 15–17 year old patients whereas Type I and II

Table 5.12 Ogden et al. classification of tibial tuberosity fractures[a]

Type IA	There is only minimal displacement of the fractured tibial tuberosity
Type IB	There is greater displacement of the tibial tuberosity although it remains hinged proximally rather than fully displaced
Type IIA	The fracture line is more extensive involving not only the tibial tubercle, but the adjacent anterior and inferior part of the secondary ossification center of the proximal tibia. The fracture is hinged proximally
Type IIB	There is comminution of the fragment although hinging persists proximally
Type IIIA	The fracture involves the tibial tuberosity but crosses the proximal tibial growth plate to pass through the secondary ossification center and the articular surface into the joint
Type IIIB	The same fracture pathway occurs but the tuberosity fragment is comminuted

[a]From Ogden et al. (Ref. [336])

fractures were most often noted from 12 to 14 years of age. For this reason, virtually no reports of growth disturbance of the proximal tibial epiphysis such as genu recurvatum and lower extremity length discrepancies have been reported even after the severe intra-articular Type III fractures. Bolesta and Fitch recorded a typical profile with 16 cases, all in boys, at an average age of 15.2 years (range 10–17 years) of whom 4 had underlying Osgood-Schlatter disease [344]. There were 3 1B, 6 3A, and 7 3B lesions. All were treated successfully with open reduction and internal fixation. Hand et al. described 7 cases, all in males, ages 14–16 years with 1 type I and 6 type III injuries [345]. Each of the type III lesions had open reduction and internal fixation with screws, pins or wires. All healed uneventfully. In 8 cases, reported by Christie and Dvonch, there was no growth discrepancy or angular deformity in either Type I, II or III injuries [346]. The average age of occurrence in that study was 15 years. Chow et al. updated literature reports in 1990 to 150 fractures in 145 patients [347]. They reported on 16 patients with final results good in all patients with full ranges of motion, good strength and no growth sequelae. Age of involvement was at an average of 13.3 years (range 10–16 years) with a 13:3 (4.3 to 1) male/female ratio. Driessnack and Marcus reported a displaced fracture of an unossified tibial tubercle in 12-year-old boy treated with good early result by suturing through adjacent bone and periosteum [348]. Pace et al. in their study of 130 fractures treated operatively found 24 type II, 76 type III and 24 type IV with 6 not classifiable [339].

After extensive lower extremity trauma in the first decade of life prior to ossification of the tibial tubercle and in association with femoral and/or tibial diaphyseal or even distal femoral physeal fractures there can be nonrecognized proximal tibial tubercle area trauma which only presents 2–3 years later as anterior physeal growth arrest with slowly developing and usually severe genu recurvatum. Pappas et al. and Aitken have alluded to such occurrences [46, 349].

5.7.12 Distal Tibia

5.7.12.1 Distal Tibia Fracture-Separations

The distal tibia is the second most common site for growth plate fracture-separation, after the distal radius. Slightly more than 50 % of distal tibial fracture-separations are of the Type II pattern, but all 5 types are represented (Tables 5.10 and 5.11). This profile of S–H type distribution remains unchanged in two recent very large studies of distal tibial physeal fractures [350, 351]. Displaced type I fractures rarely occur even in large series [350] while other series consider the fracture to exist based on clinical examination but with a negative X-ray leading them to exclude that group from their statistical analysis [351]. In a study of 225 cases by Seel et al. fracture distribution was S–H I 0.4 %, S–H II 57 %, S–H III 22 %, and S–H IV 20 % with no S–H V identified [350]. Study of 195 cases by Schurz et al. showed S–H II 58 %, S–H III 34 % and S–H IV 8 % with no S–H V [351]. Two specific subtypes of fracture at this physis are recognized widely—the adolescent Tillaux fracture, a Type III pattern involving the lateral half of the distal tibial epiphysis, and the triplane fracture which is classified in most series as a type IV fracture since radiographs in the anteroposterior projection show a Type III lesion and in the lateral projection a Type II lesion. These two fractures are referred to as transitional fractures of the distal tibia since they occur exclusively at the end of the adolescent period when the physis is undergoing its unique pattern of closure and final maturation [129]. In the study by Seel et al. there were a total of 94 type III and IV fractures of which 43 (46 %) were Tillaux or triplane [350]. Cooperman et al. also described the triplane fracture [352].

(a) *CT imaging for distal tibial growth plate fractures.* It is clear that CT imaging provides excellent visualization for the often multiplanar distal tibial growth plate fractures. A study specifically comparing plain (conventional) radiographic assessments of distal tibial growth plate fractures with CT assessments in a relatively large group of adolescent patients shows the considerably higher accuracy provided by CT imaging [353]. The study evaluated 33 patients at a mean age of 14 $\pm$ 2 years in whom both studies were done. The fractures were classified as S–H I to V or triplane I–III. The overall accuracy of plain radiographs (compared with CT) was 82 % for fractures involving the

metaphysis, 64 % for separation at the articular surface, 61 % for ridge formation at the articular surface and 79 % for subluxation. CT classification of SH types differed from plain radiographic classification in 10/33 cases (30 %) with the highest misclassification rate in S–H type III. With triplane fractures plain radiographs were incorrect in 5/7 (71 %) cases. Types I and II fractures were accurately diagnosed by both methods but the authors showed that S–H types III and IV and triplane fractures (including number of fragments) were much more accurately diagnosed by CT. Concerns about the much higher radiation exposure with CT imaging compared to plain radiographs have led many to use magnetic resonance imaging for clearer three-dimensional imaging of complex ankle (and other site) fractures of the growth plates [354, 355]. A balance needs to be determined assessing the therapeutic value of the more precise information provided by the CT imaging with long-term problems of radiation exposure.

(b) *Growth Arrest Problems*. Ten to 40 % of distal tibial growth plate injuries have growth complications. The range of growth problems is variable in several studies for a few reasons. Closer analyses are being done more recently finding a higher number of problems. Some series concentrate on problematic types of fracture so the number of growth problems is understandably increased. Finally, many of the distal tibial injuries occur close to or at the time of closure of the epiphysis so that even if growth problems occur, they may not reach clinical significance. Most Type I lesions result in good to excellent healing, and most Type V lesions lead to fair to poor results. Detailed reports of types II, III and IV lesions show a scattering of results with fairly uniform distribution between excellent, good, fair and poor in each type [71, 72]. The frequency, variable patterns and growth arrest problems of distal tibial fracture-separations were well illustrated in detailed presentations by Giuliani and Bartl [356, 357]. Bartl reviewed 235 cases seen over 25 years. Pure epiphyseal separation accounted for 37.5 % (S–H Type I), separation with diaphyseal fracture 35.8 % (S–H Type II), separation with epiphyseal fracture 12.8 % (S–H Type III), and separation with both epiphyseal and diaphyseal fractures 14.2 % (S–H IV). Of particular interest are the line drawings of radiographs from dozens of cases in both projections showing the variable patterns of fracture with the pathoanatomic gradings [357]. Distal tibial fracture-separations lead to the second highest frequency of bone bridge formation after the distal femur [358]. Chadwick and Bentley reported growth retardation in 8 of 28 (26.8 %) distal tibial epiphyseal injuries [359]. Dotter and McHolick reported an 18 % incidence of negative growth sequelae [360]. One of the reasons for this occurrence is the medial physeal irregularity jutting into the metaphysis which is frequently damaged allowing for transphyseal vessel communication and bone formation. This local anatomic feature has been called Kump's bump or Poland's bump by some in reference to previous descriptions of it [361]. Growth arrests can be seen with each of Type II, III, and IV injuries, with especially high complication rates in types III and IV [317, 352, 362–372]. Growth plate convexity as seen in the lateral radiograph, and the proximal deviation of a localized segment of the plate in its medial one-third as seen in the anteroposterior radiograph, can result in B_2 injuries by predisposition to crushing of the plate with Type I and II displacements. In radiologic Type III lesions, transverse fractures that histologically are at the metaphyseal level and Type IV injuries with considerable crushing can lead to epiphyseal–metaphyseal bone union, B_2 pathophysiologic type, especially if anatomic reduction is not achieved. The types of fracture-separation at the distal tibia and their realtion to age are shown in Table 5.13 [372].

Reports on distal tibial fracture-separations have noted the growth arrest problems and the evidence for diminished problems with accurate open reduction and internal fixation. A detailed study of 55 distal tibial and fibular epiphyseal fractures indicated that important prognostic features regarding subsequent growth arrest were the type of treatment, degree of displacement, and age at injury, whereas the Salter–Harris classification system alone "could not significantly predict the growth pattern" [365, 368]. Spiegel et al. followed 184 distal tibial and fibular epiphyseal fractures and defined low-risk and high-risk groups regarding growth deformity (shortening, angular deformity, joint incongruity).

Table 5.13 Epiphyseal growth plate fracture-separations at distal tibia-fibula (based on average age at occurrence)

10.5 years	Type II fibula	[7 patients]
10.6 years	Type I tibia	[36]
11.4 years	Type IV tibia	[3]
11.5 years	Type III tibia (medial)	[43]
12.1 years	Type I fibula	[18]
12.5 years	Type II tibia	[91]
13.3 years	Triplane tibia	[15]
13.3 years	Tillaux tibia	[6]
13.6 years	Type III tibia	[6]

Wide age variations per fracture are seen but the average values drift upwards based on these fracture types; derived from Spiegel et al. JBJS Am 1978;60A:1046–1050

The low-risk group had 89 patients with only 6.7 % having growth problems and was composed of all type I tibial fractures, types III/IV tibial fractures with <2 mm of displacement and all type I/II fibula fractures. The high-risk group consisted of 28 patients with 32 % having growth problems and was composed of type III/IV tibial fractures with 2 mm or more of displacement, juvenile Tillaux fractures, triplane fractures and type V (comminuted) fractures. An intermediate group of relatively unpredictable results involved only type II tibial fractures with 66 patients having 16.7 % complications [372]. Both tomography and CT scanning have been extremely helpful in defining more clearly the actual pattern of fracture within epiphyseal and metaphyseal bone [127, 129, 372, 373]. MR imaging studies demonstrate early transphyseal vessel communication between epiphysis and metaphysis [72, 120, 121]. Hynes and O'Brien have shown that careful examination of plain radiographs following fracture repair to assess growth arrest or disturbance lines can help define the likelihood of future problems [374].

Cutler et al. studied 62 distal tibial physeal fractures [375]. Type II injuries accounted for 47 % of the fractures (mean age 13.4 years), type III 34 % (mean age 12.9 years), type IV 6 % (mean age 14 years), and triplanar 13 % (mean age 14.4 years). Their study assessed the value of CT imaging for diagnosing the exact fracture pattern and guiding screw placement for internal fixation which they defined as being perpendicular to the fracture and at its midpoint.

Leary et al. in a paper published in 2009 reviewed 124 physeal fractures of the distal tibia allowing for a current overview of all the types of fractures [376]. The review assessed patients treated from 1998 to 2006. The mean follow-up was only 57 (8–400) weeks but patients were assessed until symmetric growth was noted for a minimum of 1 year or until closure of the growth plates was documented radiographically. Type of fracture pattern was I-4 (3 %), II-40 (32 %), III-20 (16 %), IV-11 (9 %), Triplane 23 (19 %), and Tillaux-26 (21 %). PPC (premature physeal closure) of a problematic nature was seen in 12.1 % of the entire series with none in type I, 25 % of the type II fractures, 10 % of the type III, 18 % of the type IV, 4 % of the triplane and none of the Tillaux (owing to late age of occurrence). Considering all cases of PPC, 67 % were in type II fractures, 13 % in type IV and 7 % in triplane. The rate of PPC by mechanism of injury was sports 8 % (7/85), fall 6 % (2/32) and motor vehicle accidents (6/7) 86 %. There was no association between the PPC and the number of reductions attempted or the extent of any residual gap but there was a correlation with the extent of initial displacement.

Barmada et al. studied 92 patients treated for distal tibial physeal fractures [377]. The overall premature physeal closure (PPC) rate was 27.2 % [377]. PPC occurred across the spectrum of disorders but predisposing factors were indentified. Salter–Harris III and IV fractures had a 38 % PPC rate, types I and II a 36 % rate and triplane 21 %. They noted that "more anatomic reductions resulted in statistically significant decreases in PPC rates". A residual physeal gap >3 mm following reduction on radiographs in type I and II fractures increased the PPC to 60 % compared to 17 % with no gap. Open reduction in 5 cases of type II injury with a residual gap showed entrapped periosteum in each case. Anatomic reduction decreased growth arrest problems, especially by removing interposed soft tissue in type I and II injuries.

Seel et al. showed premature physeal closure (PPC) in 11 % of cases with sufficient documentation [350]. This occurred in each of the II, III, and IV types. They found no significant difference in the mean initial fracture displacement between those with or without PPC and also no mean residual fracture displacement [350].

Schurz et al. found only 8 % with an average or poor result [351]. Of 195 patients, 125 (64 %) were treated conservatively and 70 (36 %) had closed or open reduction and screw or K-wire fixation. They interpreted their results as underlining the "requirement to achieve an absolute anatomical reduction in all planes in every patient by closed or open procedures." They felt that "no fracture displacement can be tolerated" [351].

An example of a type III fracture-separation of the distal tibia is shown in Fig. 5.32a–c.

5.7.12.2 Pattern of Closure of Distal Tibial Physis

Many of the unique fracture patterns of the distal tibial epiphysis relate to the fact that there is not uniform closure of the physis toward the end of skeletal growth but rather medial plate closure occurring prior to lateral closure. The normal fusion pattern in the distal tibial epiphysis has been documented well by MacNealy et al. (Fig. 5.31) [378]. Closure occurs initially at the medial-central portion adjacent to the region of localized proximal deviation of the physis into the adjacent metaphysis (Kump's bump) and then involves the entire medial segment. The earliest closure thus occurs throughout the entire medial segment and is a little more prominent anteriorly than posteriorly. The pattern of closure then moves in a lateral direction, but the entire time to full fusion can take up to 18 months. For a considerable period of time, therefore, the medial physis is closed while the lateral physis is open. Ogden and McCarthy also studied the pattern of growth plate maturation at the distal tibia [291]. They too noted closure from medial to lateral sides over an extended several month period of time; the physiologic epiphyseal arrest began medially over the malleolus and then extended laterally. As a general finding, central and medial closure is seen beginning at 12.5 years, completion of medial closure is noted at 13 years, closure moving to the lateral segments at 13.5 years, and complete closure at 14 years.

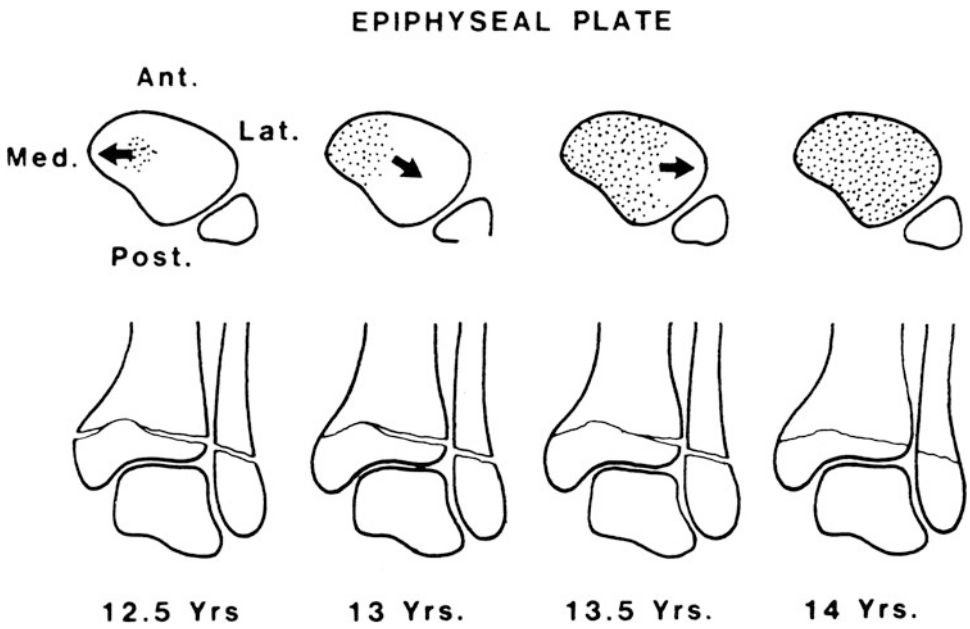


Fig. 5.31 The normal pattern of closure of the distal tibial physis is shown. The dotted areas represent closure on the upper or transverse sections. Closure progresses from medial to lateral sides. (Reprinted from Ref. [378]). (Reprinted with permission from MacNealy et al. Injuries of the distal tibial epiphysis: systematic radiographic evaluation. AJR. 1982;138:683–689. Copyright 1982 The American Roentgen Ray Society)

5.7.12.3 Transitional Fractures

Von Laer has discussed the transitional fractures, the bi-plane fracture or the juvenile fracture of Tillaux and the triplane fracture, and feels that the injuries are caused by external rotation and eversion [129]. The occurrence of a particular type depends on the maturity of the physis and not on the mechanism of trauma. In his study of the two groups the average age of females was 13.3 years (range 11–15 years) and of males 14.7 years (12–16 years). In both types the more lateral the epiphyseal fracture line was the more frequently the medial physis was closed. Dias and Giegerich also felt that, in both types of transitional fracture, the pattern of distal tibial physeal closure strongly influenced the type of fracture in the adolescent with external rotation injuries of the foot in relation to the leg [379].

(a) *Juvenile Fracture of Tillaux*: The juvenile or adolescent fracture of Tillaux is a Type III epiphyseal fracture-separation occurring at the distal tibia during the time frame that the distal medial tibial physis has closed while the lateral segment remains open (Fig. 5.32). Von Laer refers to this injury as a bi-plane fracture. CT scans confirm an epiphyseal component only with no metaphyseal involvement. Tillaux performed adult cadaveric experiments in which he found that the tibial fragment of bone was produced by an avulsion force from the pull of the intact anterior inferior tibial-fibular ligament [380]. This fracture is referred to by some as the juvenile or adolescent fracture of Tillaux. More specifically it is an avulsion fracture of the anterolateral portion of the distal tibial epiphysis caused by the pull of the intact anterior inferior tibial-fibular or anterior syndesmotic ligament sustained during an external rotation injury to the foot. The displacement of the fragment is either lateral or anterolateral. Kleiger and Mankin reported a large series of patients with this injury and many subsequent reports have appeared [381]. In the large majority of instances, closed reduction is successful but open reduction and AO screw fixation of the displaced fragment help lead to anatomic positioning and excellent results. Growth arrest is not a problem since fusion of the physis is already occurring and indeed the medial half has already fused. These injuries are relatively rare because of the limited time frame during which they can occur. Stefanich and Lozman described 5 cases [382], Dias and Tachdjian 3 in a series of 71 ankle fractures [383], Karrholm et al. reported 17 in 361 cases of distal tibial injury [365], and Molster et al. reported on 6 fractures [384]. This fracture represents one of the few which is more common in girls. Rang has indicated that the majority of these fractures are so minimally displaced that no reduction is required and short leg casting is appropriate [55]. Long-term studies, however, do show some instances of articular incongruity such that open reduction and internal fixation is readily resorted to. Internal fixation using a compression screw is warranted wherever the degree of displacement is 2 mm or greater on any radiographic projection. CT scans are helpful in providing clearer resolution.

(b) *Distal Tibial Triplane Epiphyseal Fracture-Separation*: The triplane fracture also owes its pattern to the unusual configuration of the distal tibial growth plate and, more

Fig. 5.32 A Tillaux juvenile distal tibial fracture-separation is seen. This pattern occurs where the medial physis has closed while the lateral remains open

importantly, the variability of its closure across the transverse diameter. It is essentially a type IV fracture-separation and as such, almost invariably requires open reduction and internal fixation for optimal results. In its simplest description, it appears like a type III fracture on the anteroposterior ankle radiograph and like a type II fracture on the lateral (Fig. 5.33a, b). Von Laer has shown that the epiphyseal fracture line in bi-plane or triplane fractures can be intra-malleolar, medial, central or lateral as far as the anterior syndesmosis [129]. The wandering fracture line has sagittal, transverse (horizontal), and coronal (frontal) components. Marmor defined the components of this fracture in 1970 [385] although Bartl had alluded to it in 1957 [357, 385]. Lynn described two cases and was the earliest to coin the term "triplanar fracture" [386]. The triplane fracture is characteristically composed of two,three, and occasionally four fragments with or without fibular fractures. According to Cooperman et al. the two-fragment triplane fracture has the tibial shaft, medial malleolus, and anteromedial portion of the epiphysis as one fragment with the second fragment consisting of the remainder of the metaphysis, lateral epiphysis, and attached fibula (Fig. 5.33a) [352]. In the three-fragment triplane fracture, the pattern is similar, but the anterolateral epiphyseal segment is free rather than lying attached to the distal tibial regions. Fragment 1 is rectangular and represents the anterolateral quadrant of the distal tibial epiphysis; fragment two consists of the medial and posterior portions of the epiphysis in addition to a posterior metaphyseal spike; and fragment 3 is the tibial metaphysis (Fig. 5.33b). A four fragment distal triplane fracture has also been described on occasion. The fourth fragment is the medial tibial epiphyseal segment separated along the physis as well as by the intra-articular component [372, 373, 387].

Clement and Worlock showed that the triplane fracture can occur when the distal tibial physis is still completely open [388].

CT scanning is most important for clear delineation of these injuries. Ertl et al. diagnosed 11 three-fragment and only 4 two-fragment fractures using CT, tomography, and observation at open reduction while a group of examiners having no knowledge of these findings and viewing only the plain radiographs diagnosed 11 two-fragment and 4 three-fragment patterns [389]. Owing to the occurrence of this fracture near the end of skeletal growth angular deformity and limb length discrepancy are not clinical problems [362]; of 13 patients with a triplane fracture studied, none had growth arrest problems. Open reduction and internal fixation are done to restore joint surface anatomy.

Karrholm et al. described ankle fractures of the distal tibial epiphysis as comprising 4 stages: juvenile Tillaux fracture comprising stages 1 and 2; stage 3 a triplane fracture without a fibula fracture; and stage 4 a triplane fracture with either two, three, or four fragments along with a fibula fracture [363]. Dias and Tachdjian felt that the mechanism of injury was pure external rotation of the foot without either pronation or supination [383]. Most observers feel that the juvenile Tillaux fracture is produced by the same mechanism of injury as the triplane form with the mechanism being supination-eversion.

Studies of increasing numbers of patients have clarified treatment approaches. The results in general with this fracture are now very good to excellent. Growth-related problems are extremely rare because of the relatively late age of occurrence in relation to the time of skeletal maturity. The prognosis is thus dependent on the accuracy of the reduction. Both closed and open methods have been used widely and excellent results in general are reported. In an extensive review of the literature by Rapariz et al. the distributions of closed and surgical treatment were noted [390]. If one adds their series plus that of Landin et al. in a total of 217 cases reported 133 had either no need for reduction or closed reduction only and 84 had operative intervention with open reduction and internal fixation [371]. A consensus is clearly building for an approach which can be stated as follows: CT imaging is most helpful for defining not only the pattern of

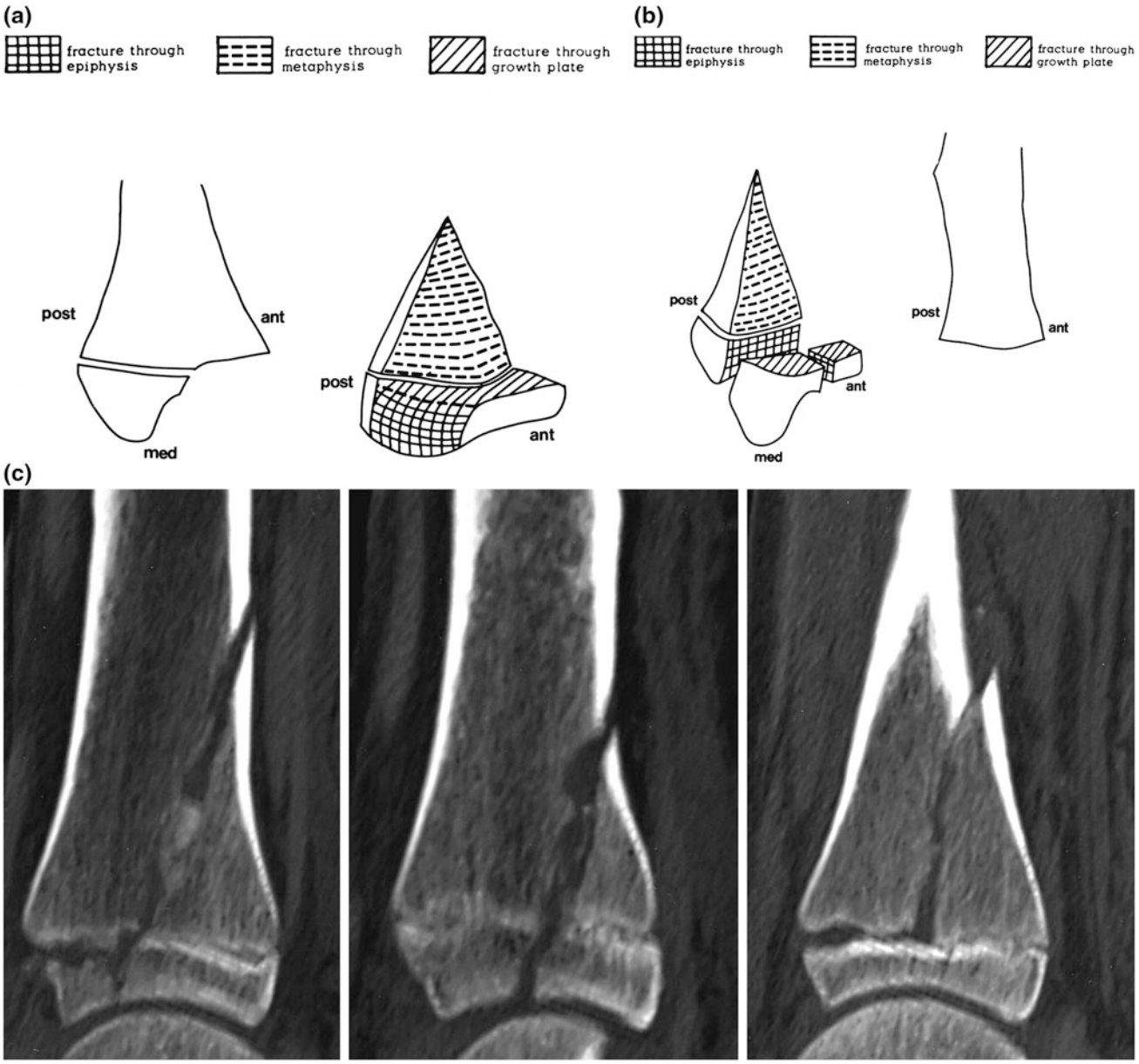


Fig. 5.33 The triplane fracture of the distal tibia appears as a type III fracture on the anteroposterior radiograph and a type II fracture on the lateral radiograph. Since it passes from articular cartilage through epiphysis, physis and metaphysis it is, in three-dimensional considerations, a type IV fracture. **a** Illustrates a two-part triplane injury and **b** a three-part injury. **c** Shows the value of CT imaging in defining the fracture pattern for the triplane injury. Three sagittal plane images from the same ankle post-injury show: at *left*, the type IV and type III patterns; in middle, a type IV configuration; and at *right*, a type II pattern. [a and b reprinted from Ref. 378]. (Reprinted with permission from MacNealy et al. Injuries of the distal tibial epiphysis: systematic radiographic evaluation. AJR. 1982;138:683–689. Copyright 1982 The American Roentgen Ray Society)

fracture and the degree of displacement, but the number of fragments (Fig. 5.33c). Plain films can be misleading in this regard. If there is no displacement, a long leg cast is appropriate. Closed reduction can be attempted in those situations with displacement. It is important to get anatomic or near anatomic reduction, however, with long-term studies showing that displacement of 2 mm or more in any projection can predispose to late arthritic changes. If closed reduction does not meet these criteria or if displacement occurs in the first few weeks of immobilization, then open reduction and internal fixation using epiphyseal and metaphyseal compression screws are warranted. Kim et al. stress the importance of anatomic reduction with the triplane and Tillaux fractures [391]. Excellent results were achieved in 14

cases (11 triplane, 3 Tillaux) with closed reduction held with percutaneous K-wires in 6 and open reduction maintained with cannulated screw fixation. As the results with anatomic reduction appear long standing, there should be little to no reluctance to resort to open reduction and internal fixation with these injuries. Initial studies showed excellent results with both closed and open reduction. When studies progress, however, beyond 5 years, those ankles with >2 mm displacement begin to show early degenerative changes. Since this is an intra-articular fracture with the intra-articular component in the central regions well within the major weight-bearing areas, the importance of anatomic reduction is evident. In a long-term follow-up of 35 patients with a triplane fracture where the mean follow-up was 5 years 2 months (range 24–162 months) there was no pain in 35, normal walking in 35, full job performance in 35, anatomically perfect radiographs in 33 of 35 (94 %), and full ankle joint function in 31 of 35 (88 %). There was no varus or valgus deformity, no limb length discrepancy, and only an external rotation deformity >10 % in 3 of 35 (8 %) [371].

Cummings has reported two patients with deltoid ligament ruptures and syndesmotic disruptions associated with triplane fractures [392]. The fibula was broken in both cases (one 12-year-old boy and one 12-year-old girl.) Syndesmotic screws were part of the repair process along with exploration and repositioning of the deltoid ligament medially.

5.7.12.4 Studies Focussing on Specific S–H Distal Tibia Injuries

(a) *Type III Fracture of Medial Malleolus with Intra-articular Osteochondral Fragment*: Beaty and Linton presented an interesting case in which a medial malleolar type III distal tibial epiphyseal fracture in a 9 year old girl was found associated with an intra-articular osteochondral fragment [393]. This was seen on an oblique plane radiograph and by tomography. Open reduction served not only to realign the physis and articular surface but to excise the osteochondral fragment.

(b) *Type IV Fractures of the Classic Pattern*: Type IV fracture-separations of the distal tibial epiphysis of the classic or uni-planar pattern can occur. Virtually all of these will involve the medial malleolus. There is a tendency for these injuries to be difficult to diagnose on plain radiographs. Cass and Peterson noted that in 18 ankles with a fracture involving the medial malleolus, extension of the fracture into the metaphysis could often be appreciated only on oblique radiographs or with tomography and CT scanning [362]. In 9 of 18 tibias with a fracture of the medial malleolus, premature partial closure of the distal physis occurred. This led to angular deformity or limb length discrepancy sufficient to require epiphyseal arrest, osteotomy, or bone bridge excision. There was a marked tendency for the classic type IV fracture-separations to occur in a younger and often much younger age group than the triplane fractures. They are also due to inversion and crush injuries and thus damage the physeal cartilage to a greater extent. Because of the tendency toward displacement and the high incidence of growth-related problems, the recommendation is for a perfect anatomic reduction which generally implies open reduction and internal fixation.

(c) *Late Results in Distal Tibial Physeal Fracture-Separations with an Intra-Articular Component*: Landin et al. studied a subset of patients with childhood distal tibial physeal fractures to assess patients with physeal injuries and an intra-articular component [371]. They thus separated for study 78 patients from 373 who had Salter–Harris lesions Types III and IV of the medial malleolus, Tillaux fractures (Salter–Harris III of the anterolateral part of the distal tibial epiphysis), and triplane fractures. The patients had all been treated during a time frame in which there was an awareness of the fact that these injuries were in a relatively high-risk category and thus either accurate closed reduction or open reduction and internal fixation were carefully utilized. The results in general were quite favorable. Part of this was due to the accurate repositioning and part to the fact that most fractures occurred at an age when the remaining growth potential of the physis was small such that premature growth arrest was not clinically significant. In addition, most of the injuries were caused by low energy trauma. They concluded that the intra-articular component of the fracture should be reduced exactly preferably with open reduction and internal fixation if needed. The majority of symptomatic ankles had had a Tillaux or triplane fracture. The distribution of fractures numerically showed 14 type III lesions of the medial malleolus, 6 type IV lesions of the medial malleolus, 17 Tillaux fractures, and 28 triplane fractures.

Nenopoulos et al. studied distal tibial physeal and epiphyseal injuries with intra-articular involvement, which refers to SH type III and IV and triplane injuries [394]. Their long-term follow-up from 2 to 13 years with an average of 7–9 years showed a relatively favorable outcome considering that 72 % had nonoperative and 28 % operative treatment. Residual varus of 10°–15° occurred in 4.

Cottalorda et al. also concentrated on the type III (30 cases) and IV (18 cases) medial malleolar fractures [395]. Surgery to restore anatomy was done in all 48. Mean follow-up was only 3 years and 3 months but 28 were skeletally mature at final assessment. The long-term outcome was good in 45, fair in 2 and poor (6° varus deformity) in 1. They interpreted their favorable results compared to other series as based on operative intervention to restore normal anatomy in essentially all patients since they opted for surgery with displacement of 1 mm or greater. Arthrotomy was always done to assess intra-articular reduction and most osteosynthesis/stabilization was with epiphyseal lag screw for cancellous bone or screw fixation with a washer to give better reduction and compression than K-wires. They indicated that "the value of the open reduction is a direct visual reduction of the fracture, rather than removal of the interposed tissue".

Further support for anatomical reduction (almost always open) and screw fixation in SH-III/IV fractures of the medial malleolus was provided by Petratos et al. [396]. This particular type of physeal fracture and its potential to lead to growth arrest was defined by McFarland in 1931 [397]. The study showed a 35 % premature growth arrest but the group of patients operated within 1 day of injury had a markedly improved outcome. Five of 6 children with operation delayed beyond 24 h developed premature arrest. A further predisposition to growth arrest was the extent of initial displacement. The authors advised operative treatment of S–H III/IV fractures involving the medial malleolus with initial displacement >1 mm. They strongly advised against closed reduction preoperatively and recommended surgery within 24 h of injury.

(d) *S–H II fractures; detailed assessment*:

(i) San Diego study. Russo et al. presented a detailed study of the growth responses to S–H II fractures of the distal tibia [398]. They reviewed a large series of 96 fractures. They assessed premature physeal closure (PPC) in relation to post-reduction displacement (residual displacement) and the methods used to treat that. All patients had initial treatment with closed reduction in the emergency department. Results showed a high rate of PPC of 43 % overall; the greater the displacement and the more extensive the surgical intervention the greater the PPC rate. Patients with <2 mm of post-reduction displacement had only a nonweight-bearing long leg cast (29 % PPC/7 % subsequent procedure-epiphysiodesis, osteotomy); 2–4 mm displacement treated with long leg cast (33 % PPC/15 % subsequent procedure); 2–4 mm displacement treated with open reduction internal fixation (ORIF) (46 % PPC/18 % second procedure); and > 4 mm displacement with ORIF (55 % PPC/23 % second procedure). Statistical analysis showed no differences in PPC or secondary procedures between groups, but also no improvement in results with more aggressive intervention. In those with 2–4 mm of post-reduction displacement none of age, sex, injury mechanism, time to fracture management, number of reduction attempts or operative treatment significantly influenced PPC. The authors concluded that for the displaced S–H II distal tibial fracture surgical fixation with anatomic reduction and removal of interposed periosteal tissue did not reduce the incidence of PPC and might increase the need for subsequent surgeries.

(ii) Rohmiller et al. found a premature physeal closure rate of 40 % in type I and II fractures of the distal tibial epiphysis. The most important determinant of premature fusion was fracture displacement post-reduction [399]. They studied 91 patients and found growth disturbances in 29 % with conservative treatment, 50 % with closed reduction alone, 36 % with closed reduction and k-wires, and 41 % after open reduction. They recommended anatomic reduction to decrease risk of premature fusion whether obtained by closed or, if necessary, open reduction. Pronation-abduction injuries were more likely to cause growth problems than supination injuries [399].

(iii) Overview by Kraus and Kaiser. Kraus and Kaiser did a literature review of S–H I/II injuries of the distal tibia, which they refer to as epiphyseal separation, in an effort to determine resulting growth disturbances [400]. They found great variability in reports on this injury and set about to determine why this occurs. The variability extended to management approaches as well. Poor results with both closed and open reduction, in terms of subsequent growth disturbances, led to the assumption (or recognition) that growth sequelae might be determined at the time of injury and also possibly made more likely by operative intervention. Their article published in 2008 essentially anticipated some of the findings described by Russo et al. in 2013, also reviewing type II injuries. Kraus and Kaiser reviewed the literature in detail and recognized two major deficiencies: a low number of cases in each article and a tendency to not distinguish between physeal

separations (S–H I/II) and physeal fractures, including the transitional fractures (S–H III/IV). They found a large variability in study methods in the relatively few papers available such that a reasonable statistical meta-analysis was not even possible. Textbooks and the older investigations prior to 1990 referred to growth complications only in the 5–15 % range whereas more current studies put the range from 36 to 50 %. Factors considered by many authors, without uniformity of results, concerned (i) mechanism of injury, (ii) primary displacement and persisting displacement after reduction, and (iii) nature of treatment (closed reduction, open reduction, type of stabilization, removal of interposed periosteum). They refer to several works in the current German literature stressing risks to operative intervention for this particular fracture [401, 402]. They point out that only 2 of 19 referenced papers were not affected by methodological limitations (those of Rohmiller et al. [399] and Barmada et al. [377]). The authors feel that a prospective study would be needed to overcome the limitations of current understanding and a 20-institution study involving three countries is underway.

(e) *Case Illustrations of Two Type III Medial Fracture-Separations*: A case of growth arrest following a type III distal tibial medial epiphyseal fracture-separation and its management is illustrated in Fig. 5.34a–k. Figure 5.35a–c illustrates a fracture treated by open reduction and AO compression screw fixation which healed uneventfully.

5.7.13 Proximal and Distal Fibula

Proximal fibula growth plate fractures are rare and unless associated with massive open trauma do not lead to growth problems. Havranek reported on 6 fractures all caused by automobiles injuring pedestrians [403]. There were four girls and two boys involved at an average age of 11.9 years (range 9.5–15.3 years). Fracture types were type II, 3; type III, 1; and type IV, two but all healed uneventfully. One of the 6 had open reduction and wire fixation; the rest were treated in cylinder casts. The distal fibula is frequently the site of undisplaced Type I fractures, with types II to V virtually never seen. Isolated Type I lesions, type A by the pathophysiologic classification, all appear to heal uneventfully without growth arrest. Distal fibula fractures associated with fracture-separations of the distal tibia occasionally develop premature fusion. Isolated distal fibula physeal fracture-separations have been diagnosed more commonly than statistical studies indicate. Owing to the generally benign nature of the injury they are virtually all treated on an outpatient basis, often symptomatically only, without specific delineation of whether the distal fibular discomfort is a sprain, an epiphyseal type I fracture or an adjacent metaphyseal injury. There is a tendency to diagnose a type I fracture if tenderness is localized clinically by palpation at the level of fibular growth plate. Since most radiographs show no displacement and follow-up X-rays are usually not taken that diagnosis is not definite. In an interesting report, Boutis et al. prospectively performed MRI studies on presumed type I distal fibula growth plate fractures [404]. None of the 18 patients had evidence of fibular growth plate injury on the MR imaging. Fourteen (78 %) had evidence of ligamentous sprains, 11 (61 %) had bony contusions, and 1 (6 %) had a subtle fibular avulsion fracture. All returned to full weight bearing by 4 weeks. Management of the injury would not change but the overdiagnosis of type I injuries is probably very common.

5.7.14 Growth Patterns Following Distal Tibial and Fibular Growth Plate Fracture-Separations Using Roentgen Stereophotogrammetry

Karrholm and associates performed a series of detailed studies involving mechanism of injury and growth pattern after epiphyseal growth plate ankle injuries in children [363–368]. They utilized the roentgen stereo-photogrammetric technique to assess growth. This method involved placing spherical tantalum balls within the bones and subsequently following the positional relationships between each radiographically with time. At operation or after fracture healing, spherical tantalum balls 0.5 mm in diameter were inserted either at the time of open surgery or percutaneously under local anesthesia. On the fractured side, 3–5 balls were inserted at each side of the growth plate in the distal tibia with 1 ball inserted on each side of the growth plate in the distal fibula on both sides as well as in the distal tibia on the intact side. Patients were followed with radiographic examination 1–3 weeks after implantation of markers and then 1 month later. Subsequent exams were performed at intervals of 3–6 months during the 1st year, 6–12 months in the second and later years if follow-up was indicated. Standardized radiographic technique was used following which the films were evaluated in a precision instrument for aerial photogrammetry. This method allowed for detailed studies of the relative extensiveness of growth of the distal tibial and fibular epiphyses in relation to the normal side. The second aspect of the work by Karrholm and associates involved assessment of growth pattern in relation to the mechanism of injury. They utilized schemes for interpreting

(a)
(b)
(c)
(d)
(e)
(f)
(g)
(h)
3M
6M
9M
(i)
(j)
(k)

adult ankle fracture mechanisms and applied them for the first time to childhood fractures. They related the growth pattern to supination-eversion injuries, supination-adduction injuries, as well as pronation-abduction and pronation-eversion. They were able to define 5 types of growth pattern following injury. These involved normal growth, initial growth stimulation of varying time length, initial and temporary growth retardation, initial and permanent growth retardation, and initial and permanent growth arrest. The roentgen stereo-photogrammetric method in conjunction with the anatomic-traumatological classification permitted early determination of the growth pattern with high accuracy and demonstrated growth disturbance months before it would be evident from plain radiographs. Their summary showed that prediction of a specific growth pattern could be made only with low accuracy but separation of the growth patterns into two groups—one with symmetrical growth, initial and temporary growth retardation, and growth stimulation, and the other with progressive growth retardation and growth arrest could be made. In 67 % of cases, when they compared the predicted outcome with the actual result, correct classification was made. They felt that the Salter–Harris classification alone could not significantly predict the growth pattern.

5.7.15 Ligament Damage Following Distal Femoral and Proximal Tibial Physeal Fractures

Bertin and Goble performed a retrospective study of 29 cases of physeal fracture about the knee to assess the degree of ligament stability [405]. The average age at injury for the distal femoral fractures was 12 years 5 months, and the average age at injury in the proximal tibial fractures was 14 years 4 months. Follow-up was at a mean of 66 months post-fracture. They found that 6 of 16 patients with distal femoral fractures and 8 of 13 patients with proximal tibial fractures had associated ligamentous laxity to static testing at follow-up evaluation. This represented an incidence of 48 %. They concluded that physeal fracture does not preclude ligament damage and that ligamentous assessments, while difficult, should be part of initial assessments as well as post-healing assessments and rehabilitation programs [405].

5.8 Traumatic Damage to Growth Plates by Pathologic, Chronic Repetitive, and Indirect Effects

5.8.1 Pathologic Epiphyseal Growth Plate Fracture-Separations

5.8.1.1 Myelomeningocele

Pathologic epiphyseal growth plate fracture-separations are seen in patients with myelomeningocele. These have been likened to a Charcot neuroarthropathy disorder in which repeated damage to a physeal region is allowed to continue since the patient has insufficient ability to appreciate pain and continues to use the affected limb. There have been several studies documenting the occurrence of epiphyseal growth plate fracture-separation in patients with myelomeningocele, stressing in particular the often negative sequelae. One of the earliest descriptions in the English literature is the paper by Gillies and Hartung in 1938 [406].

Gyepes et al. drew clear attention to the entity of marked skeletal changes at the metaphyseal-physeal junctions of the lower extremities in meningomyelocele patients who remained ambulatory [407]. The characteristic radiographic changes involved (i) widened cartilaginous epiphyseal plates; (ii) irregular, dense, slightly widened metaphyses; and (iii) subperiosteal metaphyseal-diaphyseal new bone formation. To this list can be added (iv) minimal to absent epiphyseal displacement; (v) prolonged healing time; and (vi) a high incidence of premature growth plate fusion. Repetitive trauma with continuing mobility and limited immobilization were felt to be the keys to the pathogenesis of the clinical and radiologic findings. Muscular paralysis alone does not lead to these changes since they are never seen in such disorders as poliomyelitis or muscular dystrophies where sensation remains intact. It is the insensitivity to pain which leads to a Charcot-type neuroarthropathy. The radiologic changes will regress once appropriate and relatively prolonged immobilization is instituted. Not infrequently, biopsy of the metaphyseal region has been undertaken with the suspicion that the disorder represented either an osteomyelitis or a sarcomatous process. In the paper by Soutter, a bone marrow metaphyseal biopsy was performed immediately adjacent to the physis and the marrow space was found to be occupied by callus and evidence of healing fractures [408].

◀ **Fig. 5.34** A sequence of radiographs and MR images show growth arrest following a type III fracture-separation of the distal tibial medial epiphysis. **a** Is an anteroposterior radiograph with no evidence of injury but the oblique view (**b**) clearly shows the minimally displaced type III fracture-separation. Treatment was by long leg cast with no reduction (**c, d**). At 3 months post-injury the physis is irregular but no definitive bone bridge is seen (**e**). By 6 months mild varus tilt of the distal tibia is seen along with medial tibial physeal closure. Note the distal tibial growth arrest line angling toward the medial bone bridge (**f**). By 9 months the varus tilt is more marked (**g**). MR imaging defines the medial bone bridge with marrow signal continuity across the physis between epiphyseal and metaphyseal bone (**h**). Distal tibial-fibular valgus osteotomy with completion of physeal closure led to restoration of normal alignment at skeletal maturity (**i–k**)

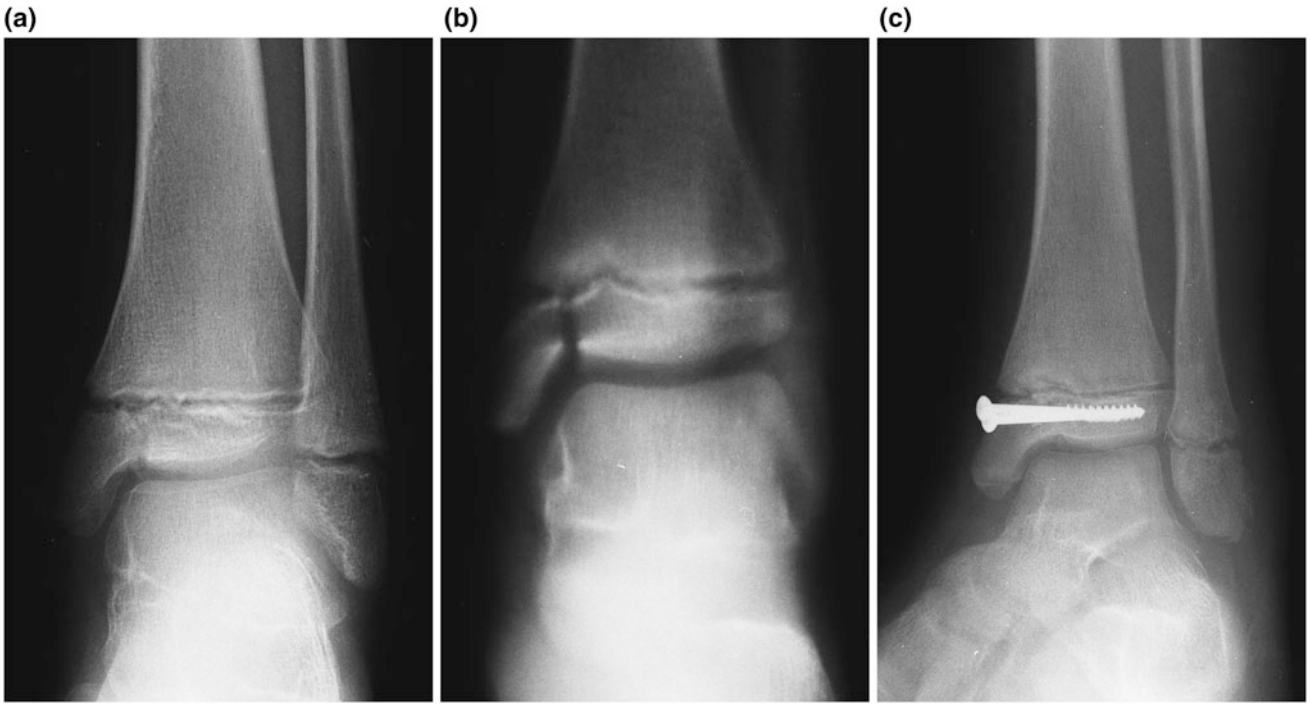


Fig. 5.35 **a** Anteroposterior ankle radiographs demonstrate a type III fracture-separation of the distal medial tibial epiphysis in an 11-year-old male. The degree of displacement is difficult to determine. **b** A tomogram of the distal tibial epiphysis shows the clear cut separation of the epiphyseal fragment from the adjacent epiphysis. The question is raised as to whether the transverse fracture line passes through the hypertrophic zone, which is less worrisome, or is present within the outer reaches of the metaphysis, a more worrisome situation as illustrated in Fig. 5.15. The normal medial physeal irregularity referred to by some as Kump's bump is seen clearly by tomography. **c** Shows treatment of a similar fracture by intraepiphyseal AO compression screw to restore articular continuity

Wenger et al. reviewed 244 patients with spina bifida and documented a 23 % incidence of at least one fracture of a lower limb including 8 epiphyseal fractures (2.8 %) [409]. The pattern outlined in their study was similar to previous and subsequent papers. The majority of epiphyseal fractures were either of the Type I or Type II variety. The characteristic findings involved a widening of the radiolucent area of the involved physis, irregularity of the metaphyseal layer of bone, absent to only minimal displacement of the epiphysis, and a prominent metaphyseal periosteal reaction which often led to the concern about an osteomyelitis or neoplastic condition such as osteosarcoma, Ewing's sarcoma, or leukemia. The fractures described are all involving the lower extremities because of the nature of the meningomyelocele lesion sparing the upper extremities. Each of the four major lower extremity physes can be affected involving the proximal and distal femur and proximal and distal tibia. The clinical signs involve swelling and redness about the joint region, although discomfort is minimal. Premature closure of the involved physis occurred in 5 of 9 patients. Since the fractures occur generally in those <12 years of age and often early in the first decade, such injuries often lead to significant lower extremity length discrepancies which complicate an already problematic situation. The fractures are generally late in being diagnosed and tend to take much longer to heal than their counterparts in an otherwise normal child. Because of the delay in union and the high degree of complication, immobilization in a solid cast for a 2 month period is almost always the recommendation of the various studies.

Kumar et al. described five physeal fracture-separations in 16 patients with myelomeningocele [410]. Four of these involved a distal tibial physis and one the proximal tibial physis. There was no clear-cut history of trauma. X-rays revealed an increase in the width of the physis and an irregularity at the physeal-metaphyseal bone junction. The physeal fractures were most common in the lower lumbar level ambulatory group. Healing was much slower in the physeal injuries than in diaphyseal or metaphyseal fractures, the injury should be well protected in a cast for a period of 8–12 weeks, and weight bearing should not be allowed until early signs of union were clear.

Lock and Aronson described seven epiphyseal growth plate fractures in a large group of myelomeningocele patients [411]. All metaphyseal and diaphyseal fractures healed satisfactorily whereas the seven fractures that

involved the physeal plate were a major problem with three showing delayed union and two premature growth arrest. Four of the fractures were Type I and three were Type II.

Roberts et al. reported five physeal growth plate fracture-separation in four children with myelomeningocele and also noted physeal widening as a prime radiologic indicator of the disorder [412]. Each of the injuries was undisplaced and there was no periosteal new bone formation indicating early diagnosis. Protection from further trauma resulted in rapid clinical resolution. They felt, however, that with early diagnosis, the period of immobilization could be shorter than previous studies had indicated and usually a 4 week period was sufficient.

Fromm et al. studied a large number of patients with myelomeningocele, assessing 82 children out of a group of 947 who sustained a total of 224 fractures [413]. Amongst these were 3 distal femoral epiphyseal separations (1.4 %), 3 proximal tibial epiphyseal separations (1.4 %), and 6 distal tibial epiphyseal separations (2.7 %). In 1 of the 3 cases at the distal femoral epiphysis, there was premature closure of the epiphyseal growth plate, with premature closure also occurring in one of three proximal tibial and two of six distal tibial fracture-separations.

Edvardsen pointed out the frequency of physeal damage in patients with myelomeningocele [414]. He noted the broadening and loosening of the physis due to repetitive trauma. He observed six physeal disorders in 50 children from 2 to 7 years of age. Since the observations were frequently made by chance without history either of trauma or discomfort, the number seen probably under-represented those that occurred. Physeal regions of patients with myelomeningocele could be traumatized during daily walking activities and in association with therapy such as passive joint movements.

Quilis reported 3 cases of fracture-separation of the epiphysis, 1 of which suffered premature closure of the growth plate [415]. The radiographic appearance of these fractures in the epiphyseal and metaphyseal regions can be confused with many disorders including osteomyelitis, bone sarcoma, bone syphilis, scurvy, neurotropic joints, and the battered child syndrome.

Multiple case reports of the occurrence of the lesion with its characteristic finding of widening of the epiphyseal line and abundant periosteal reaction with new bone formation were made by Soutter [408] and Golding [416]. Golding commented on the similarity of the findings to a Charcot joint. The epiphyseal line was much wider than normal, there was irregularity of bone appearance in the metaphysis adjacent to the widened physis and periosteal elevation led to considerable new bone formation in the metaphyseal region. Physeal slippage was almost always minimal in extent.

Rodgers et al. reviewed 19 chronic physeal fractures in 13 patients with myelodysplasia. In only 3 cases could the injury be ascribed to a traumatic event [417]. Many of the patients had extreme delay in diagnosis. The commonest site was the distal tibia in ten followed by the distal femur in four, proximal femur in three, and proximal tibia in two. All patients were treated with prolonged immobilization averaging 5.8 months (range 3–18 months) using either braces or casts. Four of the fractures required operative fixation. All injuries had healed at 4.8 years follow-up but in 4 of the fractures growth plate premature fusion was noted.

In each of the many studies reported, fractures are most commonly seen in the distal femur, proximal tibia, and distal tibia with some also occurring in the proximal femur in higher lesions. In occasional instances, several growth plate fracture-separations occur in the same patient. It is thus important to follow patients with myelomeningocele carefully, especially when excessive walking or physical therapy treatments lead to swelling in the joint regions. If an epiphyseal fracture-separation is noted, it would be wise to radiograph each of the physeal areas of the lower extremities to make certain that other injuries had not occurred.

5.8.1.2 Other Pathologic Disorders

Epiphyseal growth plate fracture-separations of a pathologic nature are rare except in myelomeningocele or neurologic disorders similar to them in which there is continuing motor function in the presence of absent or markedly diminished sensation. In most reports of epiphyseal slipping there is no clear history of trauma and the disorder is generally attributed to repetitive low grade trauma either with walking or therapy in which slippage occurs but with normal pain sensation not being present continuing activity leads to worsening injury.

Epiphyseal separations in spastic cerebral palsy were reported in four severely affected patients by Aroojis et al. [418]. There were 9 epiphyseal separations of the distal femur and proximal humerus in the 4 patients which the authors also attributed to associated scurvy (Vitamin C deficiency). Rapid healing occurred with splinting and vitamin C treatment [418].

Epiphyseal slipping in relation to other disorders is seen most frequently with slipped capital femoral epiphysis. The two other pathologic entities which can be associated with slipped epiphyses in areas other than the proximal femur are renal osteodystrophy and rare instances of scurvy.

5.8.1.3 Premature Physeal Closure Following Seemingly Unrelated Fractures of the Ipsilateral Diaphysis and Metaphysis

There is increasing recognition of the occurrence of premature physeal fusion following seemingly unrelated diaphyseal or metaphyseal fractures on the same side. The large majority of patients are 11–14 years of age. The limb length

discrepancy is often significant since follow-up generally was discontinued with repair and rehabilitation of the shaft fracture and there was no awareness by the treating physician of any physeal injury. In the patients to be reported below from several series a total of 19 patients with premature physeal closure are described of whom 8 were males and 11 females. The mean age at occurrence in the males was 11 years 10 months (range 10–14 years) and the mean age in the girls was 11 years (9–12 years of age). In the entire series the mean age at occurrence was 11 years 5 months (range 9–14 years).

Morton and Starr described asymmetrical closure of the upper tibial epiphysis following fracture of the distal third of the tibial shaft without apparent injury to the epiphysis [419]. The affected epiphyses closed prematurely resulting in progressive hyperextension deformity of the knee. One patient was an 11-year-old girl and the other a 13-year-old boy. As part of their treatment, both had proximal tibial K-wires placed but the wires were not near the tibial tubercle being described as 1 and 1½ inches or greater distal to the tubercle. The deformity became evident in the 2nd year following injury and in both instances was major in relation to shortening and angular deformity. The authors describe the fractures of the lower third of the tibia as being severe although the course of treatment had seemed unremarkable. They also referred to a case of Smillie in a young girl who suffered an open fracture of the tibial shaft complicated in a late stage of recovery by a supracondylar fracture of the femur and then discovery sometime later of a genu recurvatum caused by closure of the anterior portion of the upper tibial epiphysis.

Hunter and Hensinger described multiple premature growth arrests on the ipsilateral side in an 11-year-old girl who with major trauma suffered a comminuted spiral fracture of the proximal third of the shaft of the right femur [420]. She was ultimately treated in a hip spica for 5½ months. During the year following the injury, she was noted to have early closure of all epiphyseal plates of the right lower extremity proximal and distal femur, proximal, and distal tibia, and proximal fibula except for the distal fibula. The growth arrest lines indicated that the closure had occurred shortly after the original injury. The closure phenomenon was so marked that premature fusion of the epiphysis of the greater trochanter and of the iliac crest also occurred. Eighteen months following injury, the right lower extremity was 5 cm shorter than the left.

Abram and Thompson noted marked wrist deformity after premature closure of the distal radial physis following what appears to have been an uncomplicated torus fracture of the distal radial metaphysis in a 10-year-old girl [173].

Hresko and Kasser described 7 patients with long bone diaphyseal fractures who subsequently developed premature physeal closure around the knee [421]. In each instance, the growth deformity was marked. There were two femoral neck fractures, two femoral subtrochanteric fractures, a femoral diaphyseal fracture, and two tibiofibular diaphyseal fractures. Skeletal traction (which can cause premature epiphyseal arrest if the pin is placed directly into a physeal area) was used for only three patients, two of whom had physeal arrests in the bone other than the one where the traction pin was placed while in the other the traction pin was shown clearly by X-ray to be well distal to the proximal tibial physis where eventual fusion occurred.

Beals described 3 patients who experienced the premature complete physeal closure of the ipsilateral limb following diaphyseal fracture [422]. In each instance, clinically significant length discrepancy occurred. A 14-year-old boy suffered a subtrochanteric fracture of the left femur with subsequent premature closure of the ipsilateral distal femoral and proximal tibial physes. A scanogram at age 20 documented 4.5 cm of lower extremity length discrepancy. An 11-year 10 months old girl suffered a fracture of the distal right femur followed by ipsilateral proximal tibial physeal closure with the right tibia 1.6 cm short 6 months post-fracture. An 11-year 3-month-old boy suffered fractures of the distal right femur and mid-right tibia and experienced premature closure of the proximal femoral physis and the proximal distal tibial physes. Closure of the distal femoral physis was due to direct trauma. Twenty-one months after the fracture, scanograms demonstrated 8.8 cm shortening of the right limb.

Bowler et al. described two cases of premature closure of the anterior portion of the proximal tibial physis with associated genu recurvatum in a 12 year old boy and an 11 year old boy, both of whom suffered right femoral shaft fractures [423]. Proximal tibial osteotomies were required in both.

Paul et al. reported a 9-year-old girl with a displaced fracture of the distal third of the radius and ulna [424]. Treatment by closed reduction under general anesthesia appeared unremarkable and healing was uneventful. Three years later, she presented with 5 cm shortening of the ulna and evidence of a complete arrest of the distal ulna epiphysis.

Aminian and Schoenecker described two fractures of the distal radius with no evidence to suspect involvement of the distal radial physis which lead to subsequent complete arrest of the adjacent growth plate [240]. Injury occurred in a 12-year-old girl treated with closed reduction and in an 11 year old girl treated with casting without reduction for a torus fracture of the distal radius and a fracture of the ulnar styloid process. The 12-year-old girl presented 2 years later with a markedly prominent distal ulna due to premature partial closure of the distal radial physis. The 11-year-old girl presented 2 years later with progressive prominence of the distal ulna and radiographic evidence of a premature growth arrest of the distal radius. Both eventually required corrective surgery.

Although the phenomenon is increasingly well documented, it still remains relatively rare and unfortunately no definitive understanding of the pathophysiology is available. The possibility exists that the physis is injured in an undetectable way at the time of diaphyseal or metaphyseal fracture, but this alone would appear to be insufficient cause. The age at occurrence of the phenomenon is quite narrow with a mean occurrence at 11 years and virtually all patients between 10 and 13 years of age. It is known that long bone fractures speed up the overall development of the involved bone presumably in relation to the increased vascularity of the entire bone associated with the reparative response. The fact that this phenomenon occurs during the growth spurt at a time when relatively little growth is remaining might make the physeal regions vulnerable to premature closure.

5.8.1.4 Physeal Separation Due to Stress Injury Caused by Chronic Repetitive Activity

Over the past few decades, the widespread participation of children and adolescents with open growth plates in intensive athletic training programs, especially where chronic repetitive exercises are done, has led to the causation of a syndrome which appears compatible with an undisplaced stress separation of the overused physeal area. Caine et al. have reviewed physeal injuries in childhood and youth sports in excellent detail, concentrating in particular on the chronic repetitive physeal injuries [425]. It is the children and adolescents who participate in only one sport on a 12-month rather than a seasonal schedule who are most prone to these injuries. These are most common at the distal radial physis and distal ulnar physis in gymnasts, at the proximal humerus in baseball pitchers and at distal femur and proximal tibia in many sports. An early report by Adams defined the abnormality in the proximal humeral epiphysis of 5 boys involved in baseball pitching with extensive activity [426]. He considered the disorder to be an osteochondrosis but the symptoms and radiographic descriptions appear compatible with a physeal separation. Of the 5 boys described, two were 13 years old, one 14 years old, and two 15 years old. In North America, the disorder is commonly referred to as the little league shoulder syndrome. The principal clinical finding was pain in the shoulder at the end of a hard throwing motion. X-rays showed a characteristic widening of the proximal humeral physis and demineralization and fragmentation adjacent to the physis without evidence of avascular bone necrosis. The discomfort quietened almost immediately with rest and avoidance of activity and the X-ray shortly regained normal structure. Comparative X-ray studies of both shoulders showed demineralization and marked widening of the epiphyseal line in the pitching arm. The symptoms were relieved and the X-ray became normal over the few months following discontinuation of the activity.

Dotter reported a case in a 12-year-old pitcher with similar shoulder symptoms and X-ray changes, and he diagnosed the lesion as a fracture through the epiphyseal cartilage plate [427]. Cahill et al. reported 6 cases of stress fracture of the proximal humeral epiphyseal plate in 11- and 12-year-old male baseball pitchers [428]. Symptoms were as described above with pain and inability to perform. X-ray changes showed widening of the epiphyseal line with metaphyseal bone fragmentation and irregularity.

Many cases have been presented (see Caine et al. [425]) including a large series of 23 by Carson and Gasser [429].

Stress fracture through the distal femoral epiphysis in athletes was reported by Godshall et al. with two cases [430]. Chronic, strenuous, and repetitive exercise in relation to sports led to the disorder in two males 14 and 15 years of age. The 14-year-old had pain in his knee for several months on an intermittent basis with acute worsening immediately prior to his assessment. The physis in particular of the distal lateral femur was widened and a diagnosis of stress fracture of the physis was made. This healed uneventfully with rest using crutches for 3 weeks and decreased physical activity for 3 months. Follow-up X-rays showed complete healing of the stress fracture through the epiphyseal line. In the second case, pain developed over a 4-week period in the knee region. X-rays also showed widening of the distal femoral epiphyseal line. Crutch use and diminution of activity for 12 weeks led to complete healing of the physis radiographically. In neither case did premature physeal fusion occur with resumption of more controlled activity. The proximal tibial physis may be the site of abnormality and on occasion both physes are involved. Laor et al. have used MR imaging to further define the entity [431].

Most reported cases have involved the distal radial physis in gymnasts. Roy et al. reported 21 cases involving stress changes of the distal radial epiphysis in young gymnasts [245]. The X-ray changes appear consistent with undisplaced stress fractures of the distal radial physis. In this series, no residual growth-related problems were observed. Treatment involved wrist immobilization until the symptoms disappeared followed by increased rest and gradual reinstitution of activity at a less intensive level. In their series, 11 had radiographic changes and in these recovery took at least 3 months; in a second group, 10 had similar symptoms but no radiographic changes and recovered within an average of 4 weeks. The mean age at time of diagnosis was 12 years with a range from 10 to 17. Nineteen of the 21 were female. The amount of activity was extensive and in the 21 patients, 17 worked out at least 6 h/day, 6 days/week. The characteristic radiographic findings of nondisplaced physeal separation in relation to repetitive stress are: widening of the

growth plate of the distal radial epiphysis, particularly on the radial and volar aspects; cystic changes usually of the metaphyseal aspect of the epiphyseal plate associated with an increase of irregularity in the physeal- metaphyseal bone margin; and occasional haziness within the usually radiolucent area of the epiphyseal plate.

Fliegel reported 3 cases of stress-induced widening of the distal radial growth plate in adolescent athletes [243]. Characteristic radiographic features were again seen involving irregular widening of the growth plate, irregular metaphyseal borders along with flaring of the metaphysis, and on occasion, subperiosteal new bone formation. Symptoms resolved with diminished activity although radiographic changes took anywhere from 9 to 24 months to fully resolve. In relatively advanced cases, there is also a tendency to sclerosis of the adjacent metaphysis. Fliegel's cases were in a 14-year-old girl, 14-year-old boy, and 14.5-year-old boy. In two of the instances, X-rays returned to normal with rest, but in one, there were some changes of residual deformity of the metaphyseal area and relative shortening of the radius.

Similar stress injury findings of the distal radial growth plate were found in 21 cases by Carter and Aldrich [244]. In their group, there were 17 boys (average age 13.5 years) and 5 girls (average age 14 years). Characteristic radiographic findings again involved widening of the distal radial growth plate, particularly on its volar aspect; haziness of the growth plate due to irregularity of the border between the cartilage and the metaphyseal zone; and an increase in the transverse diameter of the metaphysis. The ulnar growth plate can also be irregular. With rest, the haziness and widening of the growth plate resolve, although some irregular metaphyseal scalloping may persist.

There is increasing recognition that these injuries at the distal radius can lead to premature growth arrest with clinically significant wrist deformity.

Physeal injury due to repetitive stress occurs in areas of most rapid growth where the hypertrophic zone is felt to be most vulnerable. When increased activity is super-added, the physeal separation without displacement occurs. The physis is widened as there is interruption of the normal mineralization process in the metaphysis.

5.8.1.5 Genu Recurvatum After Skeletal Traction Involving Inadvertent Placement of the Proximal Tibial K-Wire Through the Tibial Tubercle Physeal Area

When using skeletal traction, care must be taken not to place the wire near or through a physis. Skeletal wires through or immediately adjacent to physes can be shown to induce premature bone fusion. The most common area for this complication to occur is the proximal tibia where the K-wire is usually placed well distant to the transverse proximal tibial physis but on occasion somewhat anteriorly and thus in the region of the distal extension of the tibial tubercle physis [432, 433].

5.9 Management of Negative Sequelae of Growth Plate Fracture-Separations

5.9.1 General Considerations

Even with improved diagnosis and treatment of growth plate fracture-separations, some injuries will develop growth plate damage and negative growth sequelae. It is important to make efforts to determine how much of any growth plate damage is determined by the injury itself and how much by delay in treatment or the treatment itself. Use of the pathophysiologic approach to supplement the pathoanatomic diagnosis should be helpful. Greater application of the more detailed pathoanatomic categorizations of Ogden and Peterson should be used. Amongst the measures to be taken to minimize damage are: (i) a high level of awareness and recognition of nondisplaced fractures and their treatment by cast immobilization for a minimum of 3 weeks; (ii) gentle closed or open reduction of type II fractures with metaphyseal fragment-metaphysis screw/K-wire fixation to minimize post-reduction instability, and (iii) open anatomic reduction and internal fixation for type III and IV intra-articular injuries with even minimal (2 mm or greater) displacement. Once growth plate damage has occurred transphyseal bone bridge formation serves as a tether which causes either complete or partial cessation of growth. There are 3 possible major sequelae to a growth plate fracture-separation: shortening; angular deformity, and joint surface incongruity (Fig. 5.11). If there is complete cessation of growth shortening without angular deformity occurs. If there is only partial or focal bone bridge formation there is usually some shortening but the major problem relates to angular deformity as the rest of the growth plate continues to function. Shortening alone is a characteristic either of massive complete bone bridge formation or of central bone bridge formation >50 % of the diameter of the physis. Angular deformity is characterized by bone bridge formation adjacent to the periphery of the plate. Management of the bone bridge and of the sequelae is divided into two time periods, early and late. By late we refer to the situation in which a bone bridge has formed and negative growth sequelae have occurred involving shortening, angular deformity, or joint surface incongruity. The use of the term early refers to the demonstration of a transphyseal bone bridge within the first several months after fracture but prior to the onset of any clinically detectable shortening or

angulation. Articular surface irregularity is a problem from the moment it occurs. Management techniques are described in great detail in Chap. 6. Approaches to growth plate damage have also been outlined in the literature [117, 358, 434]. General outlines are discussed below.

5.9.2 Management of Early Bone Bridge Formation

MR imaging techniques are increasingly able to show the formation of bone bridges early in their evolution within a few months of growth plate fracture. Not all bone bridges are sufficiently large to cause tethering, however. It is known by both clinical and experimental investigations that not all bone bridges are sufficiently extensive to lead to growth plate arrest. The growth force generated by the physis is extremely great and with many small bridges such as those with 10 % involvement of the entire physis or less the affected physis can grow away from or stretch out the bone bridge such that no clinical sequelae follow [117, 358, 435]. Owing to the sensitivity of the MR imaging technique it is extremely important to beware of this phenomenon and not to operate prematurely for a small physeal bridge which might not cause an arrest. At present it is advisable to follow the patient sufficiently closely that some documentation of actual growth arrest involving slight shortening or early angular deformity is present before transphyseal resection is performed.

Once a bone bridge has been defined as clinically problematic even in the early phases, two possible treatment approaches can be taken. Transphyseal chondrodiatasis even without formal excision of the bridge may be sufficiently effective to allow for this approach. If not one can perform early transphyseal bone bridge resection and interposition of fat or other tissues.

5.9.3 Management of Late Sequelae of Bone Bridges. Bone Bridge Excision, Physeal Interposition Materials and Transphyseal Chondrodiatasis

Management of the late sequelae includes management of the bone bridge, the angular deformity and any shortening. Management of the bone bridge is dependent on several considerations: the position of the bone bridge, the amount of physeal cartilage replaced by the bone bridge, and the amount of growth remaining in the affected physis. If it is felt that growth is worth preserving then bone bridge resection can be considered. The general rule for effective resection of a bone bridge is that it involves only one quarter of the affected growth plate or less. CT scans and MR imaging are used increasingly for more accurate definition of the extent of the bone bridge. If angular deformity has occurred osteotomy to correct that deformity as well as bone bridge resection is needed. Bone bridge resection and interposition tissues are discussed in Chap. 6.

If it is determined that insufficient growth is remaining to warrant physeal excision or if the growth plate involvement is too extensive to expect growth to continue following excision, then complete physeal closure is performed surgically to eliminate the chance of worsening angular deformity. Osteotomy is performed to correct angular deformity. One can then either accept the degree of shortening that will occur or elect to perform a physeal arrest on the contralateral side to prevent worsening limb length discrepancy. If there is already a significant limb length discrepancy then the contralateral physis might have to be fused to prevent worsening of the length discrepancy as well as fusion of an additional physis to allow for correction of the discrepancy which has already occurred. If physeal closure will lead to length discrepancies >5 cm, the option of limb lengthening can be considered.

On occasion the bone bridge can be excised followed by interposition of a material designed to prevent recurrence or a procedure to regain length using transphyseal chondrodiatasis. Experimental investigations into bone bridge resections, interposition materials and transphyseal lengthening are discussed in detail in Chap. 6.

Langenskiold created defects in rabbit growth plates and demonstrated that fat placed in the defect prevented bone bridge formation as it kept the epiphyseal and metaphyseal vessels separate [436]. This procedure has been used clinically with many excellent results [358, 436, 437]. Peterson and Mallet have used methyl methacrylate to bridge the physeal defect but the method has not gained clinical applicability [358, 438]. Many other investigators have confirmed the occurrence of bone bridges with epiphyseal–metaphyseal circulatory communication, generally in the process of describing the effects of various interposition materials in preventing vascular mingling and bone formation. These works include those of Osterman using fat, deep-frozen hyaline rib cartilage, and bone wax [439]; Bright using silastic [440]; Eulert [441] and Lennox et al. [442] using cartilage plugs; and Olin et al. [443] using oriented iliac crest apophyseal cartilage transplants.

Laboratory investigations show possible future clinical promise for vascularized growth plate transplants [444, 445] and tissue culture growth of chondrocytes prior to their placement into focal defects [446].

Another response to a developing growth plate bone bridge involves use of chondrodiatasis in which pins are placed on either side of the growth plate and gentle distraction applied with an external fixator to pull apart the bone bridge tissue and allow an interposition tissue to reform

[447, 448]. Caution is warranted, however, based on large animal studies. Fjeld and Steen showed growth retardation after lengthening by epiphyseal distraction with an average reduction in growth potential of each study ranging from 40 to 70 % [449]. At the present time these approaches are not sufficiently refined to allow for widespread use but they are beginning to be used clinically in selected instances.

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Lower Extremity Length Discrepancies

6

6.1 Terminology

Lower extremity length discrepancies refer to differences in length between the two extremities which can be due to some or all of pelvic, femoral, tibial, and foot height differences. The total length differential in the standing position is not dependent solely on the height of the involved bones but can be altered further by unilateral joint dislocation or subluxation, particularly at the hip but also at the sacroiliac or knee joints; by asymmetric femoral–tibial angular deformity; by asymmetric hip, knee, or ankle contractures; and by fixed pelvic obliquity. The term leg length discrepancy is still used commonly to refer to this broad entity but is imprecise. In strict anatomic terminology, leg refers to the segment between the knee and the ankle rather than to the entire extremity. The terms lower limb or lower extremity length discrepancy are more accurate [1, 2].

6.2 Clinically Significant Length Discrepancies

6.2.1 General Guidelines Concerning Extent of Clinically Significant Length Discrepancies

There are no absolute numbers concerning the amount of length differences which require treatment. For most practitioners in this field any discrepancy projected at skeletal maturity to be >2.0–2.5 cm warrants treatment whereas anything under that cannot be expected definitively to have serious negative long-term sequelae. For those wishing to "fine-tune" discrepancy management, there is some evidence that discrepancies as little as 1.25 cm or ½ in. predispose to negative sequelae but discrepancies less than that are rarely treated surgically by even the most ardent practitioners. The negative sequelae of a lower extremity length discrepancy involve (i) an asymmetric appearance, (ii) an awkward gait, (iii) the possibility of osteoarthritis of the hip on the longer side owing to the associated pelvic obliquity and the uncovering of the femoral head associated with this, and (iv) low back pain in association with the compensatory lumbar scoliosis (Fig. 6.1). It is the general experience that those with discrepancies >2.5 cm warrant treatment. In those with projected discrepancies of <2.0 cm, there is no definitive evidence that leaving these discrepancies untreated will lead to long-term degenerative problems. The zone of uncertainty concerning the need for limb equalization is between 2.0 and 2.5 cm shortness. The extent of any discrepancy must also be considered in relation to the individual's total height since the effect of the same discrepancy is relatively more marked in someone 5 ft tall than in another >6 ft tall.

6.2.2 Percentage of Individuals with Equal Limb Lengths

6.2.2.1 Clinical-Radiological Data

Only 25–50 % of people have equal lower extremity lengths. Hasse and Dehner over 100 years ago (1893) reported leg length differences in 68 % of 5,141 soldiers with the left longer than the right in a proportion of 3.3 to 1 [3]. Lower extremity lengths were equal in only 32 %. Edinger and Biedermann documented lower extremity lengths in 351 individuals radiologically [4]. Both extremities were of equal length in 178 (51 %), had <5 mm difference in 27 (8 %), and had discrepancies between 5 and 50 mm in 146 (42 %). The left was longer than the right in a proportion of 3.6 to 1. Rush and Steiner documented 1,000 healthy army recruits referred to the radiology department because of a low back complaint [5] and 100 soldiers without complaint. An anteroposterior radiograph of the lumbosacral spine, pelvis, and proximal femurs in the standing position was made in standardized fashion. The lower edge of the film was parallel to the standing platform such that any differences in the level of the femoral heads indicated a difference in lower extremity length. Length differences were measured in

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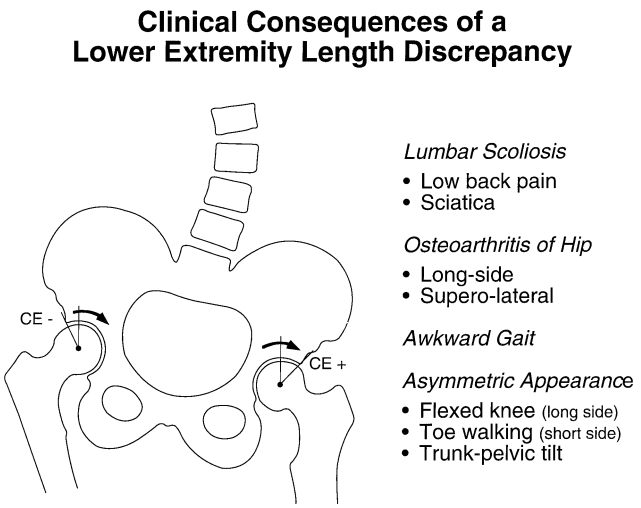


Fig. 6.1 The clinical consequences of a lower extremity length discrepancy are illustrated. Lower extremity length discrepancy with shortness on the *left* is associated with a compensatory lumbar scoliosis, pelvic obliquity, and a relative adduction positioning of the hip on the longer right side. Note the diminution of the CE angle on the longer right side which can predispose to superolateral osteoarthritis

millimeters. The limbs were equal in length in 23 % of the larger mildly symptomatic group and in 29 % of the smaller fully asymptomatic group. Based on this study, only 25 % of individuals had equal lower extremity lengths.

6.2.2.2 Anthropological Data

Anthropological data involving skeletal measurements of paired long bones in man also demonstrate a tendency to increased length of the left femur compared to the right with a left/right predominance also present but less marked in the tibia. Schultz reported on skeletal measurements from 753 human skeletons involving 232 white, 233 American black, 118 North American Indian, 122 Alaskan Eskimo, 41 Chinese, and 7 Australian aboriginal skeletons [6]. On average, the humerus and femur were approximately 8 % shorter in females than in males. The measurements were made to the nearest millimeter. In virtually all studies reported, the right upper extremity is longer than the left, usually in the range of 75 % of cases. This is felt to reflect the right-handed dominance in the human species. Virtually, all studies however, also show the length of the femur and tibia to be longer on the left in those where equal limb lengths are not present. When measurements in 744 individuals were averaged, in all races the left femur was longer than the right in 50 %, the right was longer than the left in 33 %, and both were equal in only 17 %. The left/right predominance was therefore 1.5 to 1. Differences were less marked in the tibia. In 734 individuals, the left was greater than the right in 45 %, the right was greater than the left in 40 %, and the right equaled the left in only 15 %. When both femur and tibia were combined, only 5 % had equal lengths in 727 individuals. The left was longer in 54 % and the right was longer in 41 % with a left/right predominance of 1.3 to 1. These studies were similar to clinical measurements made by Haase and Dehner [3]. Garson measured 70 skeletons noting that the combined femur and tibia lengths were longer on the left in 54.3 % and longer on the right in 35.8 %, with equal lengths being present in 10 % [7]. The combined femoral–tibial differences when the left was longer averaged 4.8 mm and when the right was longer averaged 3.3 mm. In 124 skeletons from Switzerland, Schwerz found the left femur longer in 52 %, the right femur longer in 31 %, and both equal in 17 % [8]. Almost all studies show smaller discrepancies with the tibia. In all racial groups and in both sexes asymmetries favoring the left bone of the lower extremity, in particular in relation to the femur, are much more frequent than those favoring the right. The absolute amounts of discrepancy, however, are small with the series in adult man showing a general average of only 2.5 mm difference in the femurs. The humeral differences were greater, however, averaging 4.1 mm longer on the right. Munter compiled a detailed analysis of 326 (233 male/93 female) adult Anglo-Saxon skeletons although all bones were not available from each skeleton [9]. The mean values for femoral and tibial lengths in his series were also greater on the left side for both males and females. The mean femoral lengths in the male were 2.4 mm greater on the left side for the femur and 4.5 mm longer on the left side for the tibia. In females, the left side was longer for the femur by 4.8 mm and on the tibia the left side was longer by a mean of 1.5 mm. Munter noted from several other series that there was little to no racial variation in side differences or in proportional differences such that data could be pooled for more statistical significance. There is little presentation of absolute data in the Munter study since most of the assessments related to correlative values. All the basic numerical data, however, are presented in the appendix such that the bilateral differences for each individual could be calculated.

6.2.3 Clinical Effects of Lower Extremity Length Discrepancies

Possible negative sequelae of lower extremity length discrepancies have been studied in efforts to relate symptoms to particular amounts of discrepancy (Fig. 6.1). Gurney has written an excellent overview of the subject concentrating on studies attempting to assess the clinical sequelae of various amounts of discrepancy [10]. The major considerations assessed below concern the relationship of lower extremity length discrepancies to hip pain and eventual osteoarthritis of the hip, osteoarthritis of the knee, scoliosis, low back pain

and sciatica, and gait disturbances with associated physiological sequelae.

6.2.3.1 Osteoarthritis of the Hip

Primary osteoarthritis (OA) of the hip is quite common as is osteoarthritis secondary to the major childhood hip abnormalities of developmental dysplasia, Legg–Calve–Perthes disease and slipped capital femoral epiphysis. It is thus very difficult to document with statistical certainty whether a length discrepancy alone is the primary determinant of a hip arthritic condition. Friberg reported that in 254 patients with lower extremity length discrepancies complaining of chronic hip pain, 226 (88.9 %) had the pain on the longer extremity side [11]. In 28 cases (11.1 %), pain was located in the hip on the shorter side.

Morscher has clearly discussed the changes in hip joint mechanics due to leg length discrepancies [12]. He pointed out that studies by Pauwels had shown that a lesser amount of pressure is actually transmitted to the hip joint of the shorter leg owing to the pelvic tilt which serves to increase the area of contact between the femoral head and the acetabulum [13]. There is also truncal shift over the short side further minimizing the effort needed for hip abduction. Conversely, the weight-bearing characteristics of the longer side hip are worsened since there is a decrease in coverage of the femoral head by the acetabulum on the longer side owing to the nature of the pelvic tilt and increased load at the joint on the longer side due both to diminution of the area of contact between the femoral head and the acetabulum and also to the increase in tone necessitated for the hip abductor muscles with increased distance between origin and insertion. He likened the action of a lower extremity length discrepancy on the longer side to a coxa valga deformity. The extent of increased coverage of the femoral head on the short side and decreased coverage on the long side has been documented by Krakovits using a trigonometric series of calculations [14]. When the leg is shortened by 1 cm, the diminution of the CE angle of Wiberg on the longer side is 2.3°; 2 cm shortening = diminution of 4.6°; 3 cm = 6.8°; 4 cm = 9.1°; 5 cm = 11.3°; 6 cm = 13.5°; 7 cm = 15.6°; 8 cm = 17.7°; 9 cm = 19.8°; and 10 cm = 21.8°.

Gofton also supported the contention that stresses imposed on the longer side hip are greater than normal with those on the shorter side reduced [15]. Acetabular pressure on the longer side was concentrated laterally due to the adducted position of the proximal femur leading to superolateral femoral head OA. Gofton and Trueman detected a clear association between the idiopathic superolateral osteoarthritis of the hip and the lower extremity length discrepancy with the hip on the longer side involved in 33 of 36 instances [16]. There were 31 of the 36 cases showing OA on the longer side with discrepancies from 5 mm (3/16 of an inch) and greater with 16 of the 36 having a discrepancy >1.25 cm (½ in.). The differences in lower extremity lengths were determined radiographically with strict application of a standardized standing orthoroentgenographic technique. It was the superolateral variant of osteoarthritis that was particularly related to the length discrepancy. The more global or medial forms of OA were not assessed and none of the patients had clear predisposing causes of OA such as hip subluxation or dislocation or residual evidence of any of the other childhood hip disorders. When measurements alone were considered 4 patients had OA on the shorter side, 3 had OA but were level, and 29 had OA on the longer side. When a correction was made to allow for an estimation of the original prearthritic leg length discrepancy by adding 5 mm or 3/16 of an inch to the side with the OA to represent the amount of articular surface collapse, even more patients were shifted to the group showing length discrepancy with the longer side affected. They concluded that length discrepancy was present in at least 33 of the 36 cases with the longer side developing the OA.

6.2.3.2 Osteoarthritis of the Knee

In a study of 3,026 adults, 50–79 years of age with or at a high risk for knee osteoarthritis, osteoarthritis in the shorter leg was more commonly seen than in the longer [17]. This relationship became more common the greater the discrepancy. Inequality as little as 0.5–1.0 cm increased the risk for osteoarthritis primarily in the shorter leg. Inequality of 1 cm or more was associated with increased odds of having knee radiographic osteoarthritis in the shorter leg (53 vs. 36 %) and inequality of 2 cm or more was associated with even greater odds of having radiographic knee osteoarthritis in the shorter leg (68 vs. 37 %).

6.2.3.3 Scoliosis, Low Back Pain, and Sciatica

The correlation of compensatory lumbar scoliosis with lower extremity length discrepancies has also been studied as have attempts to equate the shortness with increases in lumbar discomfort and sciatica. The relationship between shortening, compensatory scoliosis, and discomfort, however, has been difficult to document. Morscher describes the attempts at correlations well [12]. He noted that Hult found that almost 54 % of patients with lower extremity length discrepancies complained of lumbar pain but that 60 % of patients without such discrepancies had similar complaints [18]. Electromyographic studies by Taillard and Morscher showed that relatively small leg length discrepancies between 1 and 2 cm could lead to a remarkable increase in muscle activity in several muscle groups [19]. The possibility remains therefore that even small discrepancies make it difficult to maintain a complete resting position owing to secondary muscle activations.

Scoliosis: A lower extremity length discrepancy leads to a clinically detectable compensatory lumbar scoliosis in the

standing position with pelvic tilt, low on the shorter side, and the curve convex to the shorter side. With the patient sitting or the short side elevated by standing on blocks, the pelvis levels and the scoliosis corrects. Forward bend in the standing position also eliminates compensatory scoliosis.

The relationship between lumbar scoliosis and lower extremity length discrepancies is not invariably the same. In the large majority of cases, the convexity of the lumbar scoliosis is directed toward the shorter side but in perhaps 10–15 % of cases, the scoliosis is contralateral to that expected on a purely mechanical basis. Morscher indicates that the development of a lumbar scoliosis may be due more to dynamic forces in association with walking rather than static forces as demonstrated in the standing position [12].

Low back pain: The findings in scoliosis due to leg length inequality (discrepancy) have been assessed and are dependent on the age of the patient as well as the extent of the discrepancy and the length of time it remains uncorrected. Papaioannou et al. studied 23 young adults with untreated limb length inequality (1.2–5.2 cm) present since childhood [20]. They used anteroposterior radiographs in the standing position without correction of the discrepancy and after correction with a wooden block. They assessed the Cobb angle, axial rotation of the vertebrae, and pelvic asymmetry. There was no significant pelvic asymmetry. The lateral curve was always convex to the short side (without limb equalization), almost invariably from *L*1 to *L*5, and associated with a definite rotatory deformity. After neutralization of the inequality, the Cobb angle was decreased but not always totally corrected. The lumbar scoliosis with limb length inequality was compensatory and nonprogressive but abnormalities of the Cobb angle and axial rotation are rarely corrected fully with neutralization of the discrepancy.

In a slightly older group of patients with limb inequality (mean age 37 years), the compensatory lumbar scoliosis showed not only lateral bend but also axial rotation of the lumbar vertebrae, compression of the intervertebral disc spaces on the concavity, and pelvic rotation [11]. All of these eventually led to pain with disc and nerve root irritation.

In a comparison of spinal radiographs of patients with chronic low back pain comparing 50 with 1 cm or more of length discrepancy (compensatory scoliosis) and 50 with straight spines (no compensatory scoliosis), asymmetric structural changes in the former group included asymmetric end-plate contours of the lumbar vertebral bodies, wedging of the fifth lumbar vertebra, and lateral traction spurs and osteophytes (especially in those over 40 years of age) [21].

Low back pain itself is quite common and relatively large numbers of patients very carefully studied would be needed to determine whether or not there was an increased prevalence in those with lower extremity length discrepancies alone. In the study by Rush and Steiner involving 1000 army recruits with low back pain and a smaller group of 100 without pain, the percentages of lower extremity length differences in the larger/smaller groups were as follows: 1–5 mm 39.5/38 %; 6–10 mm 22.5/29 %; 11–20 mm 13.3/4 %; and 21 mm +1.7/0 % [5]. The combined patients with length discrepancies 5 mm or less were 62.5/67 % and with length discrepancies 10 mm (1 cm) or less were 85/96 %. It was only beyond the 11 mm discrepancy level that the percentage incidence of back symptoms increased beyond the control range. The length discrepancies were then correlated with the pathological conditions of the spine seen on anteroposterior and lateral radiographs. The radiographic abnormalities were present in the same percentage of patients with equal limb lengths and in those with length discrepancies with 25 % of each group showing changes. The authors concluded that in the symptomatic group it could have been length discrepancy itself with the associated compensatory scoliosis rather than the radiographic abnormalities that was responsible for the symptoms.

Nichols used clinical tape measurements from anterior superior iliac spine to the tip of the medial malleolus to document that 7 % of 1,007 patients without back pain had a length discrepancy of 1.25 cm (½ in.) or more while a limb length discrepancy of 1.25 cm or more was seen in 22 % of 180 airmen complaining of low back pain [22]. In his review of the Rush-Steiner data, he also concluded that a significant difference in the incidence of back pain and a shortened lower extremity could only be seen when the discrepancy was 11 mm or more.

Giles and Taylor studied the relationship of lower extremity length inequality and low back pain in 1,309 patients and a small control group of 50 [23]. The prevalence of length discrepancy of 1 cm or more was more common in patients suffering from low back pain (18.3 % of 1,309) than in the normal population (8 % of 50 controls). Friberg studied the correlation between lower extremity length discrepancy, low back pain and chronic unilateral hip discomfort [11]. The study comprised 1,157 subjects; 653 patients with chronic low back pain with or without sciatica, 254 with chronic unilateral hip pain, and 359 symptom-free army conscripts. In the total series, the lower extremities were of equal length in only 8 % of patients. The left lower extremity was longer than the right by a ratio of 1.4 to 1. There was excellent correlation between an increase in the amount of lower extremity length discrepancy and both back pain and hip discomfort. The incidence of low back pain in the lower extremity length groupings 5.0–9.0 mm, 10.0–14.0 mm, and 15.0 mm or more was 45.3, 18.4, and 11.7 %, respectively, with the numbers of the symptom-free group at the same length discrepancies much less at 27.9, 13.4, and 2.2 %. The ratio of symptomatic to nonsymptomatic back pain patients with limb lengths of 5.0 mm or more was 1.73 to 1; 10.0 mm or more, 1.93 to 1; and 15.0 mm or more,

5.32–1. A discrepancy of 1.5 cm or more therefore clearly appeared to predispose the individual to a relatively high likelihood of back discomfort; the presence of leg length inequality of 1.5 cm or more was 5.32 times more likely in 653 patients with chronic low back pain than in 359 symptom-free soldiers. Friberg also refers to several studies where "the high prevalence of LLI (leg length inequality) in patients with low-back symptoms has been established."

Sciatica: Sciatica predisposed to radiate into the longer side by a ratio of 3.7 to 1 [11], similar to findings in the small series of Redler [24] where in 15 cases of sciatica, it was present on the longer side by a 2 to 1 ratio.

Ten Brinke et al. found that 62 % of 104 patients with a length discrepancy of 1 mm or more had pain radiating to the shorter leg [25].

Back Pain Before and After Length Discrepancy Treatment: The review by Gurney refers to four studies that indicated substantial to complete relief of low back pain in mild-to-moderate length discrepancies with use of a shoe lift on the short side [10]. Friberg also refers to several reports, including his own, of "positive results of the simple and non-invasive shoe-lift under the foot of the short leg" in relieving back pain [11].

Rossvoll et al. assessed back pain in young adult patients before and after subtrochanteric shortening osteotomies of the femur performed after skeletal maturity [26]. There were 22 patients followed for an average of 5 years. The mean preoperative length discrepancy was 3.2 cm with follow-up discrepancy diminished to 0.43 cm. Approximately, half of the patients had relatively serious low back pain prior to surgery with the other half having minimal to no low back pain. The mean ages at operation in the two groups were 25.9 and 20.2 years. The degree of low back pain was felt to be significantly reduced after the operation. Tjernstrom and Rehnberg studied back pain before and after leg lengthening procedures [27]. Before their 100 lengthenings, 18 patients in the age range 15–36 years experienced low back pain but after an average 6 years postoperative follow-up only 6 experienced pain. Bhave et al. also noted improvement of lumbosacral pain after lengthening [28]. Eleven of 18 patients had pain prelengthening for a mean discrepancy of 4.9 cm with none having pain at follow-up after correction to within 1 cm discrepancy.

Asymptomatic Regarding Back Pain with Limb Leg Length Discrepancies: Some studies failed to identify any relationship between low back pain and leg length inequality. Soukka et al. studied 247 males and females 35–54 years of age [29]. There were 53 symptom-free individuals found to have a mean 5.5 ± 4.1 mm shortness, while 78 persons with severe low back pain had a similar mean of 5.3 ± 4.0 mm shortness. Yrjonen et al. followed 96 patients with Legg–Perthes for several decades noting that "leg-length inequality was a common finding but low-back pain was not a significant problem" [30]. Hoikka et al. also noted that leg length inequality and lumbar scoliosis have a poor correlation with low back pain in 100 young or middle-aged adults suffering from chronic low back pain [31]. Gibson et al. found that otherwise healthy young adults with an average of 3 cm of limb length discrepancy perceived no functional effect [32], while Gross evaluated 35 marathon runners and found 7 with limb length discrepancies ≥ 1 cm who reported no effects upon their performance [33].

6.2.3.4 Gait Asymmetry

Kaufman et al. performed detailed gait studies on 20 subjects to determine the magnitude of discrepancies that resulted in gait abnormalities [34]. A limb length inequality >2 cm (3.7 % difference) resulted in gait asymmetry that was greater than that observed in the normal population. Compensatory mechanisms to lengthen the shorter side include downward pelvic obliquity, increasing knee extension in midstance, vaulting, toe walking, and combinations of these. On the longer side, mechanisms include increasing pelvic obliquity, circumduction of the limb, increasing hip or knee flexion, and increasing ankle dorsiflexion. For minimal discrepancies, the foot can also participate with the shorter side foot-supinating (inversion) and the longer side pronating (eversion). This number correlates well with the generally accepted clinical guideline beyond which length discrepancy correction is warranted.

Goel et al. performed gait analysis for discrepancies <2 cm to determine the maximum moments at the hip, knee, and ankle joints [35]. They concluded that a minor length discrepancy of 1.2 cm did not produce meaningful biomechanical changes and that the body was well able to compensate for minor lower extremity length discrepancies up to 2 cm. They studied 10 healthy subjects with equal limb lengths, simulated minor limb length discrepancies using a shoe lift of 1.25 cm, and an additional 10 asymptomatic patients with limb length discrepancies ranging from 1 to 2 cm. Their study "did not find an association between minor limb length discrepancies and predictable changes in lower extremity joint kinetics that might potentially lead to joint abnormalities."

Gurney et al. found a breakpoint in induced artificial limb length discrepancy between 2 and 3 cm studying several parameters in adults on a treadmill [36]. There was a significant increase in oxygen consumption and perceived exertion with 2, 3, and 4 cm discrepancies; a significant increase in heart rate, minute ventilation, and quadriceps activity in the longer limb with 3 and 4 cm discrepancies; and a significant increase in plantar flexor activity in the shorter limb with a 4 cm discrepancy.

White et al. noted that the shorter limb sustained a greater proportion of load and loading rates in those with 1–3 cm

discrepancy [37]. Walsh et al. found that pelvic obliquity was the most common mechanism to compensate for discrepancies up to 2.2 cm with larger discrepancies leading to knee flexion on the longer side for compensation [38]. Bhave et al. studied objective gait parameters in 18 shorter and longer limbs before and after limb lengthening and compared to findings to 20 subjects with no limb length discrepancy [28]. The difference in mean stance times between shorter and longer limbs was 12 % before lengthening and only 2.4 % after lengthening. Length differences were corrected to within 1 cm. The differences between the two limbs in those without discrepancy were 2 %.

Song et al. studied mechanical work during gait of 35 children with true limb length discrepancies by assessing compensatory mechanisms on frontal and sagittal plane videotape [39]. The average discrepancy for the 7 patients with no observable compensatory strategy was 1.64 ± 2.83 cm (2.2 % of the length of the long extremity). For this range of deformity they felt no treatment was necessary. The average discrepancy for the children who used toe-walking as a compensatory strategy was 6.54 ± 2.83 cm (10.4 %). They also found no correlation between limb length discrepancy and pelvic obliquity or abductor muscle strength. The compensatory gait strategies they observed were equinus of the ankle (toe-walking) on the short side, vaulting over the longer limb (at knee and hip), and circumduction of the longer limb.

6.3 Limb Length Determination

6.3.1 Clinical Measurements

Clinical examination of a patient with a lower extremity length discrepancy remains the basic form of assessment. When viewed from the back in the standing position, one looks for a compensatory scoliosis, palpates the levels of the iliac crests, and examines for the levels of the buttock and popliteal creases, the presence of a plantigrade foot, and the thigh and calf circumferences. Children with lower extremity length discrepancies use compensatory mechanisms to maintain an upright alignment. In the standing position with the feet flat and the knees fully extended, a compensatory lumbar scoliosis is seen with the curve convex on the shortened side. With forward bend or in the sitting position, the scoliosis disappears, as there is no longer need for any compensation. A rotatory thoracic or lumbar component is absent with forward bend in a compensatory scoliosis whereas in a structural curve it persists. There is pelvic obliquity with the iliac crest lower on the shortened side. When the child is standing or walking, the discrepancy can be hidden either by flexing the knee on the longer side or by walking with the foot in an equinus position on the shorter side. Assessment of a patient with a lower extremity length discrepancy should check for the range of motion of the ankle as in some of the larger longstanding discrepancies, this equinus posturing can become partially fixed with active dorsiflexion decreased compared to the normal longer side ankle.

To measure the extent of discrepancy, rectangular blocks of known height are placed under the foot on the shortened side with the patient standing in bare feet with hips and knees fully extended. The blocks are positioned until the compensatory scoliosis disappears and the iliac crests can be palpated at the same level. This clinical assessment is essential as it accurately denotes the entire extent of any discrepancy including pelvic, thigh, leg, and foot components.

Another characteristic clinical measurement of lower extremity length discrepancy, done with a tape measure and the patient lying supine, measures the distance from the inferior tip of the anterior superior iliac spine to the inferior tip of the medial malleolus on each side. Jamaluddin et al. have shown in a study of 48 patients that the tape measurement method with a nearest reading of 5 mm is as accurate as computerized tomography (CT) scanograms. [40]. It is important to check that there is no pelvic obliquity, hip or knee contractures, or femoral–tibial angular deformities in the patients being assessed in this way. If these conditions are present, measurement from the umbilicus to the medial malleolus can also be performed to register what is referred to as the apparent limb length discrepancy. Smith has reported a clinical method for determining lower extremity length discrepancy which is particularly valuable in those with hip or knee flexion contractures [41]. The method, referred to as the thigh-leg inspection test, is performed by placing the patient in the supine position with the hips and knees flexed 90°. Determination of the difference in height of the thighs is made by using a flat protractor on the most superior aspect of the knee joint on the longer side and measuring the difference between the protractor and the shortened thigh at the knee. The shortened leg is then measured as the thighs are held parallel. The difference in length of the longer side heel and the shortened heel is measured by placing the protractor on the plantar surface of the longer heel and measuring the distance between it and the shorter heel. This measurement eliminates flexion contractures at the hips, knees, and ankles as a source of error. It also measures the soft tissue component of the lower extremity as well as the bones. The measurement was found to be more reproducible than tape measurements or block measurements in a comparative study of several practitioners in 96 patients with a mean of 5.2 cm length discrepancy. The technique is yet another way of estimating lower extremity

length discrepancies in accurate fashion clinically and bypasses concerns with hip, knee, or ankle flexion contractures. Morscher and Figner have described clinical and radiographic methods of measurement in detail [42].

6.3.2 Segments to Be Considered in Assessing Lower Extremity Length Discrepancies

Lower extremity length discrepancies can involve any or all of four segments: pelvic height, femoral length, tibial length, and foot height. The clinical assessment measuring the length discrepancy with the patient standing on blocks takes each of these four segments into consideration while most of the other length determination modalities do not. The clinical measurement from the anterior superior iliac spine to the medial malleolus eliminates consideration of the foot and only partially addresses the pelvic height; the characteristic radiographic determinations of femoral and tibial length do not consider either the pelvic or the foot regions; and virtually all the limb length determinations and surgical corrections relate to the femur and tibia alone without considering the other two segments. Although the femur and tibia are responsible for the vast majority of the limb height, there can be situations where foot and pelvic abnormalities contribute meaningfully to the length discrepancy. In these situations, specific radiographic determination of their height is important.

6.3.3 Radiographic and Other Imaging Documentation of Lower Extremity Length Discrepancies

At least seven imaging techniques have been used to document the length of the lower extremity bones and the extent of lower extremity length discrepancies. Many of the screening surveys referred to in Sect. 6.2 above documented length discrepancies using standardized standing positions but radiographs of only the lower spine, pelvis, and hips. The relative femoral head positions allowed for length discrepancy measurements but not for absolute femoral/tibial/foot height measurements. The many technical considerations in making accurate radiologic measurements have been detailed [12, 16, 42, 43].

6.3.3.1 Teleoroentgenograms

Teleoroentgenograms are limited to use during the 1st year of life. They refer to a plain X-ray of the entire lower extremity centered over the knee. If taken at a 72 in. height, they are accurate in terms of length owing to the minimal magnification with the small limb. After this age, they are of decreasing accuracy in documenting limb length discrepancies owing to angular distortion (Fig. 6.2a).

6.3.3.2 Orthoroentgenograms

This technique was developed by Green and associates in the late 1940s to document accurately lower extremity length discrepancies [44]. Both femurs and tibias are radiographed in their entirety. A single long X-ray cassette with a single long X-ray sheet is used. Three X-ray machines are built onto the ceiling of a specifically defined chamber 72 in. from the X-ray film. There is one machine to be centered over the hip, one to be centered over the knee, and one to be centered over the ankle. Three radiographs are taken in rapid succession. Studies documented that the magnification factor is under 1 % with this technique. As well as providing extremely accurate length determinations, the film allows for radiographic visualization of the entire bone for indication of structural or angular deformities. This technique is infrequently used today because of concerns about the total amount of radiation exposure with sequential studies (Fig. 6.2b).

6.3.3.3 Scanograms

This is a commonly used technique today for lower extremity length discrepancy documentation. It can be accurate if details of performance are rigidly adhered to although in practice many inaccuracies are seen. Three radiographs are taken similar to the orthoroentgenogram centered over hip, knee, and ankle but spot films only are taken with the intervening femur and tibia diaphyseal segments spared any radiation. A ruler is placed beside the limb and the radiographic projection of the ends of the femurs and tibias over the ruler allows for a measurement at that level. The ruler should be calibrated in millimeters. A major problem with this technique is patient movement during the repositioning of the single machine. This can lead to inaccuracies which if slight cannot be detected by those subsequently reading the radiographs. High levels of quality control are needed to ensure accurate measurement.

6.3.3.4 Computerized Tomography Scans

The CT scan can provide accurate length measurements owing to the high-resolution calibration of the technique. It is difficult to justify the use of this technique for sequential studies due to high levels of radiation exposure but lower dosing can be used to lessen this concern since bone detail is not being assessed.

6.3.3.5 Ultrasonography

Ultrasound can be used to document bone length [45]. It is particularly helpful in the first 2 years of life when cartilage elements compose the bulk of the epiphyses. Although it has not been adopted for widespread use, a recent study in young

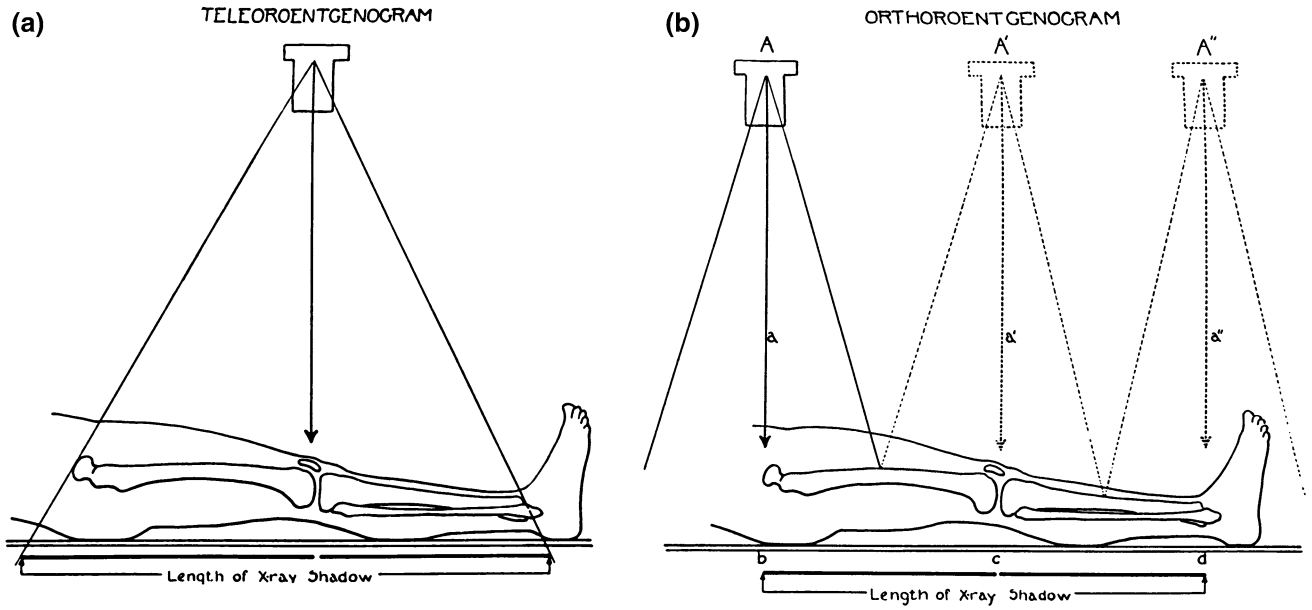


Fig. 6.2 Radiographic measurements used to determine lower extremity lengths. **a** Teleoroentgenogram. A single exposure of the entire lower extremity centered over the knee provides a radiographic image of both the entire femur and the entire tibia and fibula. The longer each bone is, the greater the magnification error owing to the increased divergence of the rays. **b** Orthoroentgenogram. In performing an orthoroentgenogram a single long X-ray cassette is used. Three cameras which can be moved along a track are mounted at a standardized 72 in. distance from the cassette holder. Three radiographs are taken in rapid succession with one camera centered over the hip joint, one over the knee joint, and one over the ankle joint. The perpendicular rays intersect the ends of the bones recording the true length. Each long bone is imaged completely allowing for structural and angular deformity assessments as well

adults showed that a laser-based ultrasound method was extremely accurate compared with radiographic length measurements with the intraclass correlation coefficients (ICC) value for agreement between methods 0.97 [46].

6.3.3.6 Full-Length Standing Anteroposterior Radiographs

Some centers are reintroducing the use of full-length standing anteroposterior radiographs of both lower extremities to assess not only the length discrepancy but also the deformity with one study [47]. Computed radiography is used to assess the images obtained but the study is not a formal CT scan. Sabharwal et al. compared same day full-length standing AP radiographs to scanograms in 111 patients with limb length discrepancy [47]. The age range was wide (9 months to 73 years) with a mean of 18.8 years and 71 % <18 years of age. For the standing AP film, the pelvis was leveled with a shoe lift and one film centered at the knees was taken at a minimum patient-to-tube distance 203 cm. Scanograms were done with the patient supine using 3 separate images centered over hip, knee, and ankle at a patient-to-tube distance of 101 cm. Compared with the scanogram the mean magnification with the standing AP radiographs was 4.6 % (3.3 cm). The radiation dosage is actually as much as 2–3 times higher with the scanograms, although they improve measurement accuracy by decreasing magnification and parallax errors.

6.3.3.7 Magnetic Resonance Imaging

The measuring accuracy of magnetic resonance imaging can also be applied to extremity length determinations [48]. It is extremely accurate (almost exact) in cadaver studies [49]. While not used clinically to any great extent, it can be valuable in specific situations, especially if limiting radiation is a consideration.

6.4 Causes of Lower Extremity Length Discrepancies

A large number of disorders during the growing years can either stimulate or retard the growth of epiphyses unilaterally or asymmetrically such that a lower extremity length discrepancy occurs. Virtually any childhood disorder which affects an epiphysis can lead to stimulation or retardation of growth and possible limb length discrepancy must be considered in relation to overall management. Even disorders which are present throughout the skeleton, such as hereditary multiple exostosis, can affect sides unequally. The causes,

effects, and extent of lower extremity length discrepancies throughout the spectrum of disorders affecting the growing skeleton are listed in Table 6.1.

6.5 Developmental Patterns in Lower Extremity Length Discrepancies

The discrepancies that develop in children are susceptible to considerable change with time, as the involved physes have the potential for increasing the discrepancy, maintaining it at a stable level, or correcting it spontaneously. Not all length discrepancies increase continually with time during the growing years. In a review of lower extremity length discrepancies in 803 children who were followed by at least annual orthoroentgenograms for 5 or more years to skeletal maturity or to time of corrective surgery, it was demonstrated that several patterns of developmental discrepancy can occur [50]. These are dependent on the nature of the conditions causing the discrepancies and on the place and time of their occurrence. They do not refer to changes following bone surgery. Table 6.1 gives a broad categorization of disorders which can be associated with lower extremity length discrepancies, an indication of whether they cause growth retardation or stimulation, and a range of length discrepancies with which they are associated.

6.5.1 Patient Population

Longitudinal data on lower extremity length discrepancy from patients who were followed in the Growth Study Unit at the Children's Hospital, Boston, over a 40-year period (1940–1980) were studied. The patterns of developmental discrepancy that developed were demonstrated by charting the extent of a discrepancy directly against time as represented by the patient's chronologic age [50]. The patterns were also related to skeletal age to show their independence from that parameter. Lower extremity length discrepancies were documented by standard techniques using teleoradiographs for patients who were younger than 5 years of age. Orthoroentgenograms, from which femoral and tibial measurements were made, were used for all the older patients. Skeletal age was determined from posteroanterior radiographs of the left wrist and hand and correlated with the Todd atlas [51] until 1950 and with the Greulich and Pyle atlas [52] thereafter.

For inclusion in the review, an individual had to have been followed by radiographic means at the Growth Study Unit for a minimum of 5 years (or from the onset of disease), either to the time of skeletal maturity or to the time of bone surgery. Virtually all of the patients were assessed annually, and often semi-annually, from the time of onset or detection of the disease to maturity. These patients were followed prospectively because they had an affection in which lower extremity length discrepancy was known to occur, rather than being seen only after a clinically apparent discrepancy had developed. With the exception of the group of patients with a fractured femoral diaphysis, the patients included in this review had to have had a discrepancy of 1.5 cm or more at some time during the period of assessment. The classification does not refer to any change in discrepancy that followed surgical physeal arrest, diaphyseal lengthening, or osteotomy.

The disease entities studied and the number of patients in each group were as follows. There were 18 patients with proximal femoral focal deficiency, 102 with congenital coxa vara and a congenitally short femur (some with associated anomalies of the leg and foot), 17 with Ollier's disease (enchondromatosis), 21 with physeal destruction, 115 with poliomyelitis, 33 with septic arthritis of the hip, 116 with a fractured femoral diaphysis, 29 with a hemangioma, 17 with neurofibromatosis, 46 with hemiparetic cerebral palsy, 113 with hemiatrophy or hemihypertrophy (anisomelia), 36 with juvenile rheumatoid arthritis, and 140 with Legg–Perthes disease. The distribution of pattern types, the average discrepancy in cm, and the range of discrepancies before surgery were assessed for each group.

6.5.2 Classification of Developmental Patterns in Lower Extremity Length Discrepancies

Type I, upward slope pattern: The lower extremity length discrepancy develops and increases continually with time, at the same proportionate rate.

Type II, upward slope–deceleration pattern: The lower extremity length discrepancy increases at a constant rate for a variable period of time, and then shows a diminishing rate of increase independent of skeletal maturation.

Type III, upward slope–plateau pattern: The discrepancy first increases with time, but then stabilizes and remains unchanged throughout the remaining period of growth.

Type IIIA, downward slope–plateau pattern: The discrepancy decreases with time, but then stabilizes and remains unchanged throughout the period of growth.

Type IIIB, plateau pattern: The discrepancy, detected initially after it has developed, remains unchanged throughout the remaining period of growth.

Type IV, upward slope–plateau–upward slope pattern: The discrepancy first increases, then stabilizes for a variable but considerable period of time, and then increases again toward the end of the growth period.

Table 6.1 Causes, effects, and extent of lower extremity length discrepancies

		Stimulation				Retardation			
		A	B	C	D	A	B	C	D
1. Femoral disorders	Proximal femoral focal deficiency							✓	✓
	Coxa vara					✓	✓	✓	
	Congenital short femur					✓	✓	✓	
	Developmental dysplasia of the hip								
	• Subluxated hip					✓			
	• Dislocated hip					✓	✓		
	• Avascular necrosis					✓	✓	✓	
	Legg–Calve–Perthes disease					✓	✓		
	Slipped capital femoral epiphysis					✓	✓		
	Status post varus osteotomy					✓	✓		
2. Tibial and fibular disorders	Congenital short tibia (Fibular hemimelia)					✓	✓	✓	
	Tibial agenesis (Tibial hemimelia)								✓
	Pseudoarthrosis of tibia (Anterolateral Bowing) ± neurofibromatosis					✓	✓	✓	
	Posteromedial tibial bowing					✓	✓		
	Blount's disease (Tibia Vara)					✓	✓		
3. Foot disorders	Club foot					✓			
4. Trauma	Epiphyseal growth plate Fracture/Separations					✓	✓	✓	✓
	Diaphyseal fractures								
	• Healing with shortening or overgrowth	✓	✓			✓	✓		
	• Loss of bone mass						✓	✓	✓
5. Infection	Syphilis (femur/tibia)								
	Septic arthritis								
	• Hip or knee	✓				✓	✓	✓	
	Meningococcal septicemia					✓	✓	✓	
	Femoral/Tibial osteomyelitis (metaphyseal-diaphyseal)	✓	✓						
	Tuberculosis								
	• Hip or knee	✓				✓	✓		
	• Femoral/Tibial shaft	✓				✓			
6. Prolonged unilateral immobilization/9–12 + months	Tuberculosis					✓	✓		
	CDH, etc.					✓	✓		
7. Neuromuscular disorders	Poliomyelitis					✓	✓	✓	
	Cerebral Palsy-hemiparesis					✓	✓		
	Peripheral nerve injury (Unilateral); Sciatic nerve paralysis					✓	✓	✓	
	Myelomeningocele					✓	✓		
	Arthrogryposis					✓	✓		
	Diastematomyelia					✓	✓		
8. Vascular disorders	Vascular malformations	✓	✓	✓					
	• Klippel–Trenaunay	✓	✓	✓					
	• Parkes Weber	✓	✓	✓					
	• Proteus	✓	✓	✓					
	• Beckwith–Wiedemann	✓	✓						
	Hemangioma (Newer terminology)	✓							
	Cutis Marmorata Telangiectatica Congenita	✓	✓			✓	✓		
	Following use of neonatal umbilical or femoral catheters	✓	✓			✓	✓	✓	

(continued)

Table 6.1 (continued)

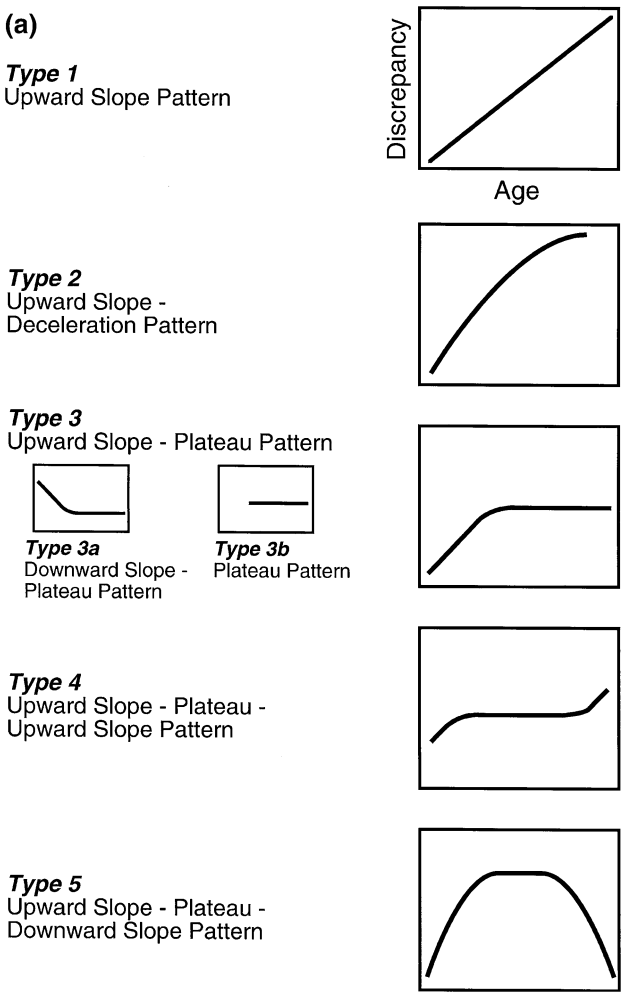
		Stimulation				Retardation			
		A	B	C	D	A	B	C	D
	Synovial hemangioma (knee)								
	Arteriovenous aneurysms (traumatic)	✓	✓						
9. Hemihypertrophy, with connective tissue abnormalities	Cerebrovascular malformations	✓	✓						
	Lipomatosis	✓	✓						
	Lymphedema	✓	✓						
	Lymphangioma	✓	✓						
	Neurofibromatosis	✓	✓			✓	✓		
	Silver–Russell syndrome	✓	✓						
	Malignant tumors: Wilm's, adrenal, carcinoma, hepatic carcinoma	✓	✓						
10. Hemiatrophy	Otherwise normal appearing limb					✓	✓		
11. Inflammatory Disorders	Juvenile rheumatoid arthritis	✓	✓			✓	✓		
	Scleroderma								
12. Hematologic Disorders	Hemophilia	✓	✓			✓	✓		
	Thalassemia					✓	✓		
13. Tumors/Focal bone lesions lesions	Benign lesions								
	• Fibrous dysplasia								
	• Unicameral bone cyst					✓	✓	✓	
	• Aneurysmal bone cyst					✓	✓	✓	
	• Osteoid osteoma	✓	✓						
	• Caffey's disease	✓	✓			✓	✓		
	Malignant tumors								
	• Resection with growth plate damage					✓	✓	✓	✓
	• Resection with loss of bone mass					✓	✓	✓	✓
	• Radiation-induced physeal arrest					✓	✓	✓	
14. Skeletal dysplasia (Asymmetric Lengths)	Hereditary multiple exostoses	✓	✓			✓	✓		
	Ollier's enchondromatosis					✓	✓	✓	✓
	Stippled epiphyses (Chondrodysplasia Punctata)					✓	✓		
	Dysplasia epiphysealis hemimelica					✓	✓		
	Melorheostosis					✓	✓	✓	
	Camptomelic dwarfism					✓	✓		
	Congenital banding (Streeter Syndrome)					✓	✓	✓	
15. Bone diseases with high incidence of asymmetric deformities	Osteogenesis imperfecta					✓	✓	✓	
	Rickets					✓	✓		
	Renal osteodystrophy					✓	✓		
	Vitamin a intoxication of infancy					✓	✓		
	Scurvy (lack of vitamin C)					✓	✓		
16. External causes	Burns					✓	✓	✓	
	Frostbite					✓	✓		

Code A = 0–2 cm; *B* = 2–5 cm; *C* = 5–15 cm; *D* = 15 cm+

Type V, upward slope–plateau–downward slope pattern: The discrepancy increases with time, stabilizes, and then decreases in the absence of surgery.

The classification is illustrated in Fig. 6.3a and an indication of the various patterns in various disorders is outlined in Fig. 6.3b.

(a)



(b)

Distribution of Developmental Patterns in the Various Diseases in Eight Hundred and Three Patients

Condition	No. of Patients	Pattern Type I	II	III	IV	V
Proximal femoral focal deficiency	18	18	0	0	0	0
Congenitally short femur, including congenital coxa vara (with some associated leg and foot anomalies)	102	65	29	8	0	0
Ollier's disease	17	17	0	0	0	0
Destroyed epiphyseal growth plates	21	21	0	0	0	0
Poliomyelitis	115	64	25	17	9	0
Septic arthritis (hip)	33	14	4	12	3	0
Fractured femoral shaft	116	0	8	108*	0	0
Cerebral palsy (hemiparetic)	46	15	5	24†	0	2
Anisomelia						
Hemihypertrophy	86	48	20	18	0	0
Hemiatrophy	27	17	4	6	0	0
Hemangiomas	29	9	8	10	1	1
Neurofibromatosis	17	11	2	3	0	1
Juvenile rheumatoid arthritis	36	7	0	16	0	13
Legg-Perthes disease	140	21	8	52	10	49

* Both type-III and type-IIIA discrepancies.
† Many of these discrepancies were detected in the plateau phase (type IIIB).

Fig. 6.3 **a** The developmental pattern classification showing types I–V. (Reprinted with permission from Shapiro F, Developmental patterns in lower extremity length discrepancies. J Bone Joint Surg Am 1982;64A:639–651) **b** The distribution of patterns in several of the more frequent length discrepancy categories is shown

6.6 Lower Extremity Length Discrepancies in Specific Disease Entities: Pathoanatomy, Pathophysiology, Developmental Patterns, Ranges of Discrepancies

In this section, we incorporate information from the study reported in the article Developmental Patterns in Lower Extremity Length Discrepancies [50] and information from the extensive literature on the entire range of disorders that can lead to length differences. The focus is on the pathoanatomy and pathophysiology of the disorders themselves and particularly on the pattern of discrepancy development and the extent of the discrepancies in the specific diseases. In most instances, the ranges of length discrepancy values are provided. Some studies refer to percentage shortening, in relation to the normal side. Reference of the Green-Anderson tables can then indicate the range of values in absolute terms.

6.6.1 Terminology of Congenital Limb Deficiencies

Congenital limb deficiencies are among the commonest causes of lower extremity length discrepancies. We will refer to the commonest and most severe types; but in reality, they represent part of a spectrum of disorders affecting appendicular development in both upper and lower extremities. Extensive efforts have been made over the past few decades to develop encompassing classifications for these disorders but they are so variable and the terminology used has been so awkward that there has been no universal agreement on ways to refer to them. As a result, individual terms from differing classifications have come to be used commonly and on occasion different terms are used to refer to the same disorder.

6.6.1.1 Frantz and O'Rahilly

The classification of Frantz and O'Rahilly is an all encompassing approach which divides congenital skeletal limb deficiencies into terminal, where there are no unaffected parts distal to and in line with the deficient portion, or intercalary, where the middle portion of a proximodistal series of limb components is deficient but the proximal and distal portions are present [53]. Each of these two main groups then may be either transverse, where the defect extends transversely across the entire width of the limb, or longitudinal, where only the preaxial or postaxial portion is absent (hence the deficiency is longitudinal). Among the terms used in the classification are amelia, absence of the limb; hemimelia, absence of a large part of a limb; phocomelia, a flipper-like limb with a hand or foot attached more or less directly to the trunk; acheiria, absence of a hand; apodia, absence of a foot; adactylia, absence of a digit including the associated metacarpal or metatarsal; and aphalangia, absence of one or more phalanges. Hemimelia may be complete or partial. The term paraxial hemimelia indicates that either the preaxial or the postaxial portion of the distal half of the limb is involved. The anatomical term preaxial refers to the border of a limb on which either the thumb or the big toe is situated and the term postaxial refers to the opposite border. The preaxial paraxial hemimelias are therefore either radial or tibial and the postaxial paraxial hemimelias are ulnar or fibular. The various subtypes of paraxial hemimelia are named after the absent portion; radial hemimelia refers to a deficiency of the radius. The terminology of congenital skeletal limb deficiencies is shown Fig. 6.4a.

6.6.1.2 Dysmelia

Henkel and Willert proposed a differing approach to classification of the congenital malformations which they felt outlined more accurately the teratological sequence [54]. The term dysmelia is used to refer to limb malformations varying from mild hypoplasia to partial and total aplasia of the tubular bones of the extremities and even to complete nonformation of the extremity. They arrange the abnormalities according to their degree of severity to form a teratological sequence linked by a common morphological pattern and enabling subtle variations to be included and to represent the abnormalities throughout an entire limb. The approach addresses three questions: (1) Which region of the limb and which skeletal elements are affected? (2) In which manner are they affected—by hypoplasia, partial aplasia, or total aplasia? and (3) Have the affected skeletal elements also undergone fusion or synostosis? There are five main types of any teratological sequence of dysmelia: (1) distal form of ectromelia (ectromelia refers to involvement of the radius or tibia with their peripheral rays); (2) axial form of ectromelia; (3) proximal form of ectromelia; (4) phocomelia (abnormalities where no remnants of long bones are seen between the limb girdle and the hand or foot); and (5) amelia (total loss of an extremity). The classification of malformations was derived from a survey of 693 deformed limbs (Fig. 6.4bi–iii). This approach would seem to offer the best correlation with gene and molecular abnormalities as they are increasingly defined in relation to limb development.

6.6.1.3 International Terminology for the Classification of Congenital Limb Deficiencies

The International Society for Prosthetics and Orthotics organized a working group to propose a terminology for limb deficiencies which would be accepted internationally [55]. They utilized both the system of Frantz and O'Rahilly

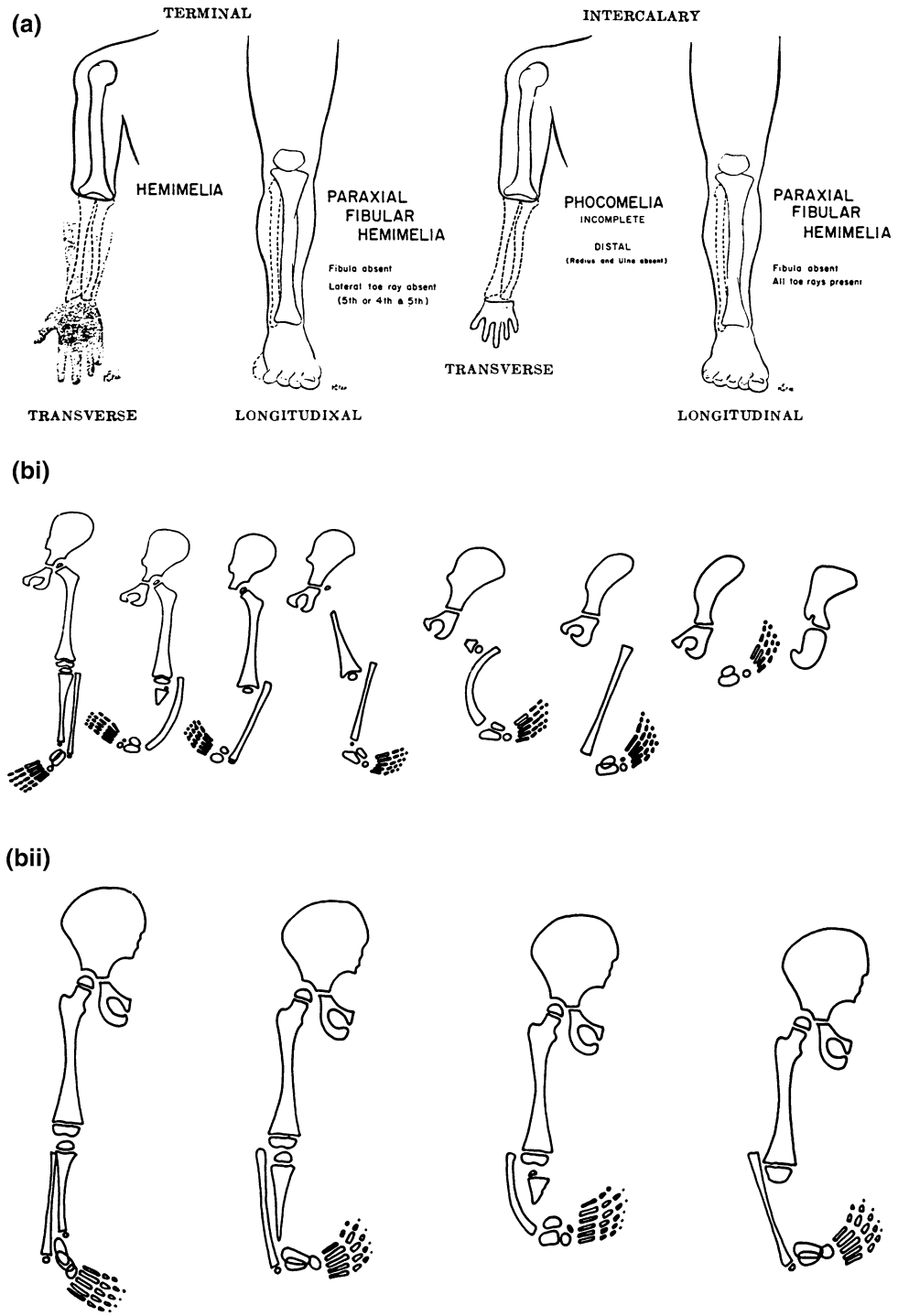


Fig. 6.4 Classifications of congenital skeletal limb deficiencies are illustrated. **a** The classification of Frantz and O'Rahilly is shown in 4a. The terms terminal, intercalary, transverse, and longitudinal are illustrated. (Reprinted with permission from Frantz and O'Rahilly, Congenital skeletal limb deficiencies. J Bone Joint Surg Am 1961;43A:1202–1224). **bi–iii** The classification of Henkel and Willert is shown in this figure **bi–iii**. **bi** The teratological sequence of dysmelia of the lower extremities is shown. **bii** Sequential changes of the tibia are shown in a series of cases. The femur is relatively normal throughout. **biii** Sequential changes of the femur are shown with relative normalcy of the tibia, fibula and foot regions (Reprinted with permission from Henkel and Willert, Dysmelia: a classification and a pattern of malformation in a group of congenital defects of the limbs. J Bone Joint Surg Br 1969;51B:399–414)

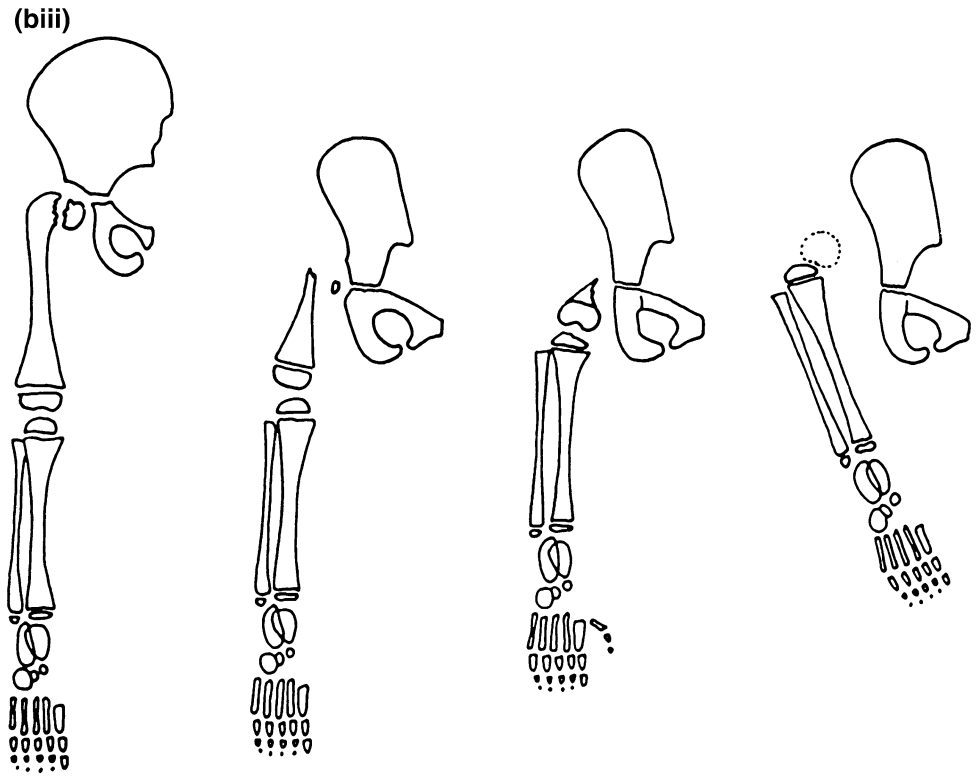


Fig. 6.4 (continued)

and that of Henkel and Willert along with other terminologies in efforts to reach agreement.

There is still no unanimity of opinion concerning descriptive terms for this wide array of disorders, although with appropriate clinical and radiologic descriptions there is rarely any doubt as to which entity is being discussed. Even after adoption of any uniform terminology, it would take several years before the studies and the literature are all conformed to a standard. It remains essential for those involved with these disorders to have a general understanding of the differing classifications used. In the next sections, the commonest terms will be referred to.

6.6.2 Congenital Abnormalities of the Femur

Congenital abnormalities of the femur encompass a spectrum of disorders from those in which the femur is completely absent to those in which it is present, structurally normal and only somewhat smaller than that on the opposite side. These can be classified into four broad groups including proximal femoral focal deficiency, coxa vara with congenital short femur, congenital short femur with diaphyseal bowing, and anisomelia in which the femur is normally shaped but smaller than that on the opposite side.

6.6.2.1 Proximal Femoral Focal Deficiency

In each of the 18 patients with proximal femoral focal deficiency, severe progressive shortening of the type I pattern occurred [50]. In types A and B, proximal femoral focal deficiency as defined by Aitken, the proximal part of the femur is intrinsically maldeveloped, with no effective capability for normal reconstitution even though the acetabulum and femoral head are present [56]. In types C and D, the proximal structures are even more markedly abnormal, with no visible ossified head and the tapered diaphysis displaced proximal to the shallow, often unrecognizable acetabulum (Fig. 6.5a). Severe growth sequelae in this class of femoral developmental abnormalities are well known [57]. Proximal femoral focal deficiency resulted in an average of 27 cm of shortening, with some lower limbs having as much as a 45-cm discrepancy. The range of femoral shortening averaged 60 % (range 40–80 %) compared with the normal side. In patients classified as having type A, B, or C deficiency, the shortening averaged 57 %, and in type D it averaged 80 %. Tibial shortening averaged 7.6 % (range 0–37 %) and fibular shortening averaged 28 % (range 0–100 %) in all types. This condition caused the most severe discrepancies seen in the series and presents an extremely difficult management problem. Accurate prediction of the final discrepancy is possible from the early years of life in patients with this condition, however, owing to the invariable type I pattern.

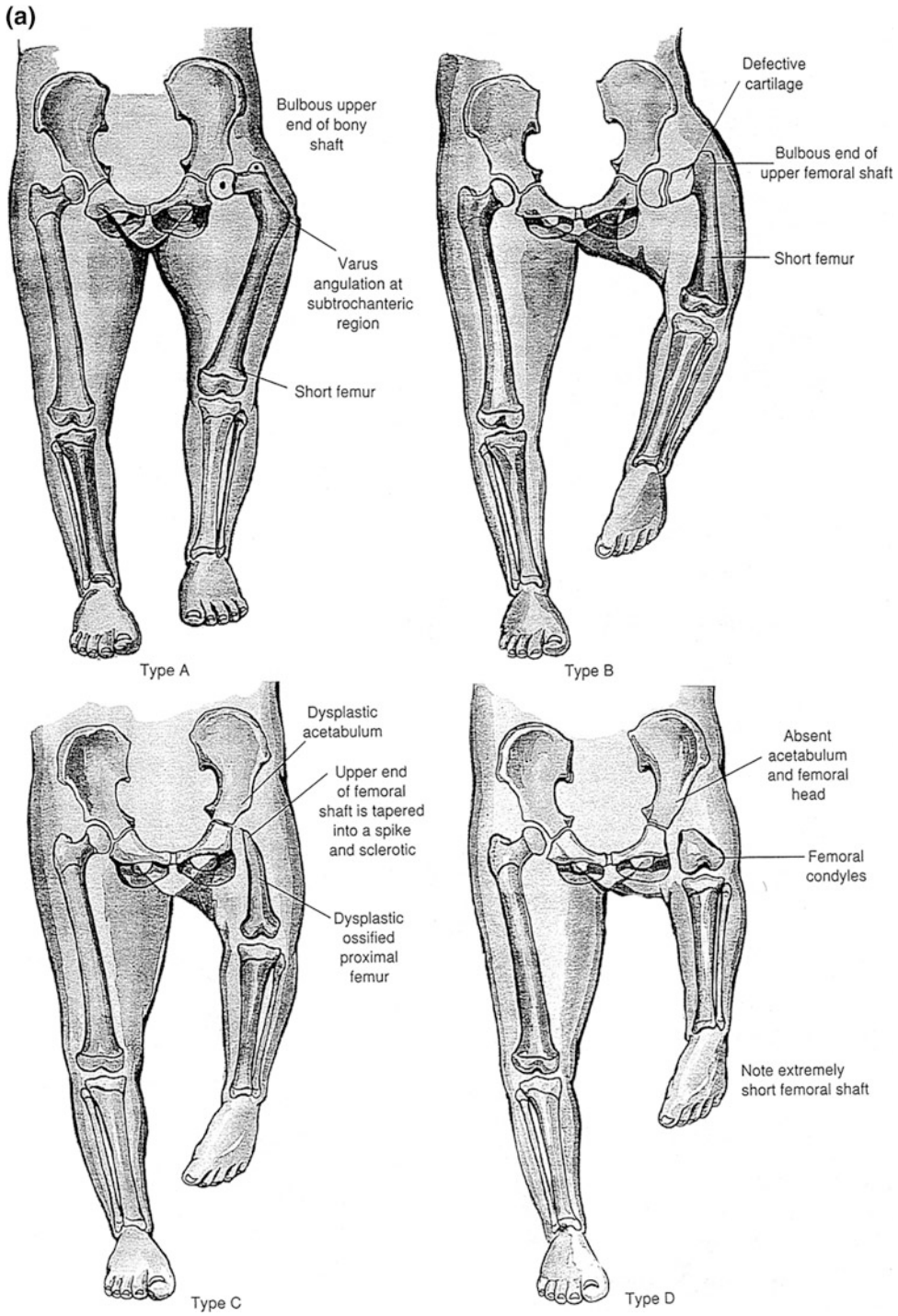


Fig. 6.5 (continued)

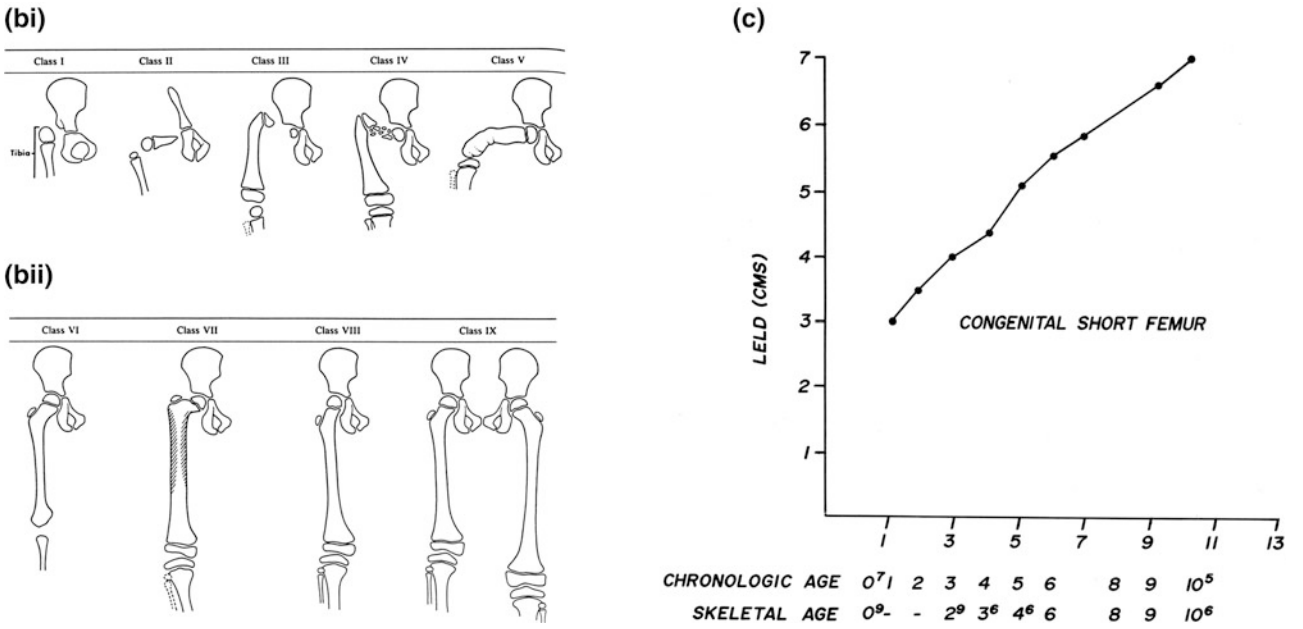


Fig. 6.5 **a** The classification of proximal femoral focal deficiency of Aitken is shown. **bi–ii** The classification of congenital abnormalities of the femur into 9 types as defined by Pappas (Reprinted with permission from Pappas A, Congenital abnormalities of the femur and related lower extremity malformations: classification and treatment. J Pediatr Orthop 1983;3:45–60. Copyright 1983 Wolters Kluwer Health). **c** A type I developmental discrepancy pattern in congenital short femur is shown

6.6.2.2 Congenital Short Femur Including Congenital Coxa Vara

This group included patients with congenital coxa vara, a congenitally short femur with coxa vara, and a congenitally short femur with lateral bowing and sclerosis but without coxa vara. Many of these patients also had associated mild or moderate anomalies of the pelvis, tibia, fibula, and foot. Excluded from this group were the patients with proximal femoral focal deficiency and those with a normally shaped and only mildly shortened femur who were categorized as having hemiatrophy (anisomelia). The average preoperative limb length discrepancy in this group was 5.92 cm (range 2.2–15.6 cm). Thirty-seven of these patients showed a type II or III developmental pattern. If a discrepancy reached 6 cm, it generally persisted with a type I pattern. Those patients, however, in whom the discrepancy was less great often had a type II or III pattern. Ring noted that patients with a congenital short femur alone—one with lateral bowing, cortical sclerosis, increased hip external rotation and minimal to absent internal rotation, but without coxa vara—will continue to have an increase in the discrepancy at a regular rate with time (type I pattern) [58]. The relatively marked length discrepancies in femoral developmental disorders are well documented [57, 59–62].

Two studies on length discrepancies in congenital femoral anomalies have been published in which both proximal femoral focal deficiency and congenital short femur with and without coxa vara have been assessed together. A separate detailed study also based primarily on patients followed longitudinally in the Growth Study unit of the Children's Hospital Boston was published by Pappas in which the large number of patients assessed allowed a more detailed subclassification into nine types of deformity [63]. Pappas defined the percent of femoral shortening in each of the nine classes; detailed the femoral and pelvic abnormalities; assessed the associated abnormalities of tibia, fibula, patella, and feet; and defined the treatment objectives (Fig. 6.5bi, ii). The large number of patients available for this study demonstrated a continuum of abnormalities. Class I refers to the situation where the femur is entirely absent and the acetabular region of the pelvis is markedly hypoplastic. In class II, the proximal 75 % of the femur is absent. In class III, there is no bony connection between the femoral shaft and head although the femoral head which has delayed ossification is present in the acetabulum. In class IV, the femur is present to approximately one-half its length but the proximal abnormalities show the femoral head in the acetabulum with the head and shaft joined by irregular calcification in a fibrocartilaginous matrix. It is these four disorders that are generally referred to as proximal femoral focal deficiency. In class V, the femur diaphysis and distal end are incompletely ossified and hypoplastic. In class VI, the proximal two-thirds of the femur are perfectly normal and the hypoplasia is in the distal third with an irregular distal femoral region and no evident distal epiphysis. Classes V and VI are essentially examples of distal femoral

focal deficiency. Class VII is congenital coxa vara with a hypoplastic femur which is shortened and somewhat bowed and also demonstrates lateral femoral condylar deficiency. Class VIII is infrequently seen but involves a proximal femur coxa valga, a hypoplastic femur, and an abnormality of the distal femoral condyles with the lateral condyle being somewhat flattened. Most would include congenital short femur in this category which perhaps most represents class VIII, although it characteristically has anterolateral bowing which Pappas does not demonstrate. The class IX femur is essentially normal and might be defined by others as having only shortness referred to as hemiatrophy or anisomelia. Pappas also demonstrates the frequently seen underdevelopment of the lateral femoral condyle predisposing to both a valgus deformity at the knee referable to the femoral deformity and a tendency toward lateral patellar subluxation. The ranges of femoral and tibial discrepancies found in each of the varying categories were listed. In class I, the femur was completely absent. In class II, the femur was shortened by 70–90 % of that on the opposite normal side. The tibia was also shortened. In Class III, femoral shortening was 45–80 % of the opposite side and tibial shortening ranged from none to 40 %. In class IV, femoral shortening was 40–67 % that of the opposite side and tibial shortening ranged from none to 20 %. In class V, femoral shortening was 48–85 % and tibial shortening was 4–27 %. In class VI, femoral shortening was 30–60 %; In class VII, femoral shortening was 10–50 % and tibial shortening was minimal to 24 %. In class VIII, femoral shortening was 10–41 % and tibial shortening was none to 36 %. In class IX, femoral shortening was 6–20 % and tibial shortening was none to 15 %.

Vlachos and Carlioz studied bone growth in 40 cases of congenital anomalies of the femur [64]. They categorized their patients into five groups with group I being congenital short femur without coxa vara but with shortening and curvature of the shaft; group II with congenital short femur and coxa vara; group III severe coxa vara with a dystrophic or pseudoarthrotic junction between the proximal femur which was in coxa vara and the diaphysis; group IV coxa vara, coxa vara with severe angular deformity proximally and discontinuity with the shaft of the femur; and group V where there was almost complete absence of the proximal femur and no hip joint articulation. Relatively few patients were followed to skeletal maturity with many being seen only to the ages of 3–10 years such that definitive pattern progression could not be determined. They felt, however, that all patients regardless of diagnostic category increased at a constant rate with time although this is somewhat distinct from our findings. Assessment of some of their charts would also indicate a type II pattern in some patients. They clearly documented both the percentage shortness and the absolute amount of shortness in cm in each group. In the mildest form, group I, the average shortening was 10 % of the normal side ranging between 88 and 97 % with the mean amount of shortening at 13 years of age being approximately 2.8 cm. In group II, shortening averaged 30 % of the normal side ranging between 64 and 80 % normal length and the mean amount of shortening around 10 years of age already 9 cm. In group III, shortening was in the range of 45 % of the normal side indicating 55 % length compared to the opposite side and associated with a mean discrepancy at age 12 of 19 cm. In group IV, the overall length was only 24–44 % of the normal side indicating in many cases a 75 % shortness which translated into a mean discrepancy of 11 cm although patients in this group had only been followed to a little >2 years of age. In the most severe category, proximal femoral focal deficiency, shortness was 90 % of the involved side translating into length of approximately 10 % normal only and leading to discrepancies at age 5 years which were already 25 cm.

A type I developmental discrepancy pattern in congenital short femur is illustrated in Fig. 6.5c.

6.6.3 Congenital Developmental Abnormalities of the Fibula; Fibular Hemimelia

Congenital abnormalities of the fibula are the most common lower extremity congenital deficiency syndrome. Coventry and Johnson noted the fibula to be the most common bone congenitally absent with the congenital absence of the tibia, ulna, radius, and femur following in that order of frequency [65]. Farmer and Laurin reviewed the congenital absence or severe maldevelopment of the long bones from 1931 to 1957 and noted 32 limbs with congenital absence of the fibula while complete or partial absence was also noted in femur 16, radius 13, tibia 5, and ulna 2 [66].

The fibular abnormalities are referred to as fibular hemimelia or lateral (external) hemimelia. They are always accompanied by tibial shortening and frequently accompanied by same side femoral shortening and it is this tibial and femoral shortening that length discrepancy treatment relates to. Since the primary bone undergoing treatment is the tibia, the disorder is sometimes referred to as congenital short tibia. In those with a hypoplastic fibula (fibular hemimelia), the major treatment considerations are the limb length discrepancies although on occasion measures are needed to stabilize the ankle usually by varus osteotomy of the distal tibia and fibula and occasionally by orthotic support [67]. Those with complete absence of the fibula present greater management problems because of the more significant length discrepancy and the equinovalgus foot deformity along with a subluxed or dislocated ankle [68]. There can

also be anterior bowing of the distal third of the tibia, absence of one or more rays of the foot on the lateral side, a tarsal coalition, and a ball-and-socket ankle joint [69].

Coventry and Johnson developed a classification into three types [65]. In type I, the patients have partial unilateral absence of the fibula with little or no bowing of the tibia. There is little or no deformity of the foot. The extremity is always shortened but the shortening can be quite minimal and is usually managed with an epiphyseal arrest. In type II, the fibula is completely or almost completely absent and involvement is unilateral. There is anterior bowing of the tibia, dimpling of the skin, equinovalgus of the foot, and absence or deformity of the lateral rays and tarsal bones. There is also marked shortening of the extremity and amputation was frequently needed in this group. They also defined a type III in which either the type I or type II deformity was associated with other congenital deformities which were usually either severe deformities of the ipsilateral femur or contralateral deformities of the other leg.

A slightly different three-part classification is favored by some. Type I is characterized by a slight to moderate shortening of the fibula, proportionately lesser shortening of the tibia, and minimal femoral shortening on some occasions. Catagni et al. report tibial shortening of 3–5 cm at the end of growth with little angular deformity [70]. On occasion, the associated outer fourth or fifth ray of the foot is also abnormal but rarely is this of clinical significance. Type II has major shortening of the fibula with particular underdevelopment or absent development of the distal one-half to one-third. The lateral malleolus is usually absent and the ankle is unstable with the foot moving into a position of valgus deformation. The tibia is shorter than in type I disorders and tends to a valgus deformation and slight distal recurvatum with posterior bowing and anterior concavity. Type III, the most severe form, is characterized by an absent fibula, showing in addition severe deformation and shortening of the tibia, a deformed foot held in a position of equinus and valgus and often associated with dislocation or severe subluxation of the ankle. Owing to the shortness of the extremity, the angulation of the distal tibia, and the deformed foot much extended orthopaedic treatment is needed, often including Syme or Boyd amputation for prosthetic fitting.

In a large series with 291 patients with congenital unilateral shortening of an extremity, presented by Pappas et al. 129 patients, i.e., 44 % showed greater than 10 % shortening of the fibula [71]. The extent of fibular shortening in 58 % was between 10 and 30 %, in 9 % between 31 and 50 %, and in 33 % more than 50 %. Although absolute length discrepancy numbers were not presented, the associated tibial shortening was often in the range of 10 % or more with fibular shortening >30 %. There was a clear correlation between the fibula shortening and foot deformities. Among the associated limb deformities, there was genu valgum and instability, absence of the fourth and fifth rays of the foot, anteromedial shortening and curvature of the tibia, tarsal coalitions involving the talonavicular or talocalcaneal joints, and a dome-shaped talus. Often, the fibula was absent in its proximal one-third.

Achterman and Kalamchi studied 97 limbs with congenital deficiency of the fibula [72]. They outlined a slightly modified classification defining type I deformities as those with hypoplasia of the fibula and type II deformities as those with complete absence of the fibula (Fig. 6.6). They noted that congenital anomalies of the femur were present in 76 % of patients with type I deficiency and in 59 % with type II. The femoral abnormalities were invariably underdevelopment of the femur leading to worsening of the limb length discrepancy. Congenital shortening of the femur was present in 46 of the 66 limbs where femoral abnormality was detected. Approximately, 20 % of the patients had some bilateral involvement. Measurements were difficult in patients with a proximal femoral focal defect and leg length inequality was assessed where data were available in 51 cases. In those where there was complete absence of the fibula (the type III categorization listed above), the amount of tibial shortening in the affected limb was 25 % of normal with femoral shortening 13 % of normal. In those cases where there was hypoplasia of the fibula, the type I deformity group showed fibular shortening 7 % of normal, tibial shortening 6 % of normal, and femoral shortening 12 % of normal and in the type II group where there was major shortening of the fibula, in particular with underdevelopment at the ankle, the fibular shortening was 38 % of normal, tibial shortening 17 % of normal, and femoral shortening (although on a small number of patients) 23 % of normal. Although detailed growth data were not presented, they felt that growth of the abnormal limb was proportional to that of the normal limb and that the degree of tibial shortening increased as the fibular deficiency became more marked. Treatment of length discrepancy was either by epiphyseal arrest or tibial lengthening depending on the clinical situation. If percentage shortening numbers are converted to length measurements for a male patient whose height is at

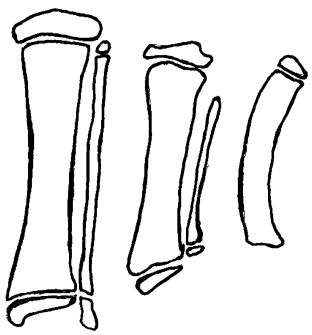


Fig. 6.6 Achterman and Kalamchi define a classification of fibular hemimelia type Ia (*left*) with fibular hypoplasia which is relatively mild, type Ib (*middle*) with fibular hypoplasia which is more with a length deficiency distally leading to a tilt of the distal tibia and its epiphysis, and a type II fibular deficiency (*right*) where the fibula is completely absent

the 50th percentile at skeletal maturity, a 6 % tibial shortening would represent 2.2 cm, 17 % shortening 6.3 cm, and a 25 % shortening 9.3 cm.

Lefort et al. reviewed 62 cases of fibular hemimelia concentrating in particular on the pathoanatomy of the leg and the associated femoral and tibial malformations [73]. They stressed in particular the anterior curvature of the tibia in those cases where the fibula was either completely absent or absent to a great extent. Absolute values for long bone shortening were not presented although percentage values were. Charts demonstrated a type I pattern of discrepancy development for both developmental abnormalities of the femur and of the tibia.

Hootnick et al. studied 43 patients with partial or complete absence of the fibula and a congenital short tibia [74]. They also determined that the relative difference in growth between the two limbs remained remarkably constant and thus adhered to the type I pattern of length discrepancy development. The patients studied had a strictly unilateral variant and all measurements were determined radiographically by scanograms or from films showing both tibias on the same X-ray plate in the youngest children. The serial radiographic measurements of leg length were available in 14 patients covering an average observation period of 9.3 years. Those with sequential radiographs were in the more severe end of the spectrum with the fibula absent in 11 patients and present but abnormal in 3. The amount of limb shortening was greater as the number of metatarsal bones diminished. There were 36 patients from whom assessments could be made in terms of the number of metatarsal bones and the amount of lower extremity shortening. In 12 patients with 5 metatarsal bones, the average shortening was 8.7 cm (range 3.6–12.7); in 11 patients with 4 metatarsals the average shortening was greater at 9.5 cm (range 3.8–13.5); in 11 patients with 3 metatarsals the average shortening was 11.8 cm (range 4.8–16.5); and in 2 patients with only 2 metatarsals the average shortening was 14.6 cm (range 11.9–17.3). The average age reached in the first three groups was 11 years and in the final group 9.5 years of age. The femur was only minimally affected in these patients. In the 14 followed radiographically, there is excellent documentation that the percent inhibition of growth in the affected limb compared to the normal remained unchanged from the earliest documentation to skeletal maturity. Femoral involvement at skeletal maturity was relatively small ranging from 86 to 96 % length compared to the normal side, while tibial involvement was somewhat greater ranging from 73 to 82 % length of the normal side. In patients followed for several years, although not quite to skeletal maturity, the same pattern persisted with femoral shortening in all patients except one being only 92–99 % of normal with associated tibial shortening 61 to 90 % of the normal side. They felt that if the predicted shortening was <8.7 cm efforts at limb equalization were warranted while if projected discrepancies were between 8.7 and 15.0 cm, amputation of the modified Syme's type was in order. In those discrepancies projected to be >15.0 cm, retention of the foot and its adaptation to a prosthesis was warranted.

The extent of growth discrepancy as well as management considerations were well assessed by Choi et al. [75]. They evaluated 48 extremities in 43 patients with the disorders skewed to the more severe types in their series. There were 7 fibulas of the type IA categorization, 2 type IB, and 39 type IIB (complete absence of the fibula or presence of only a distal vestigial fragment according to the classification of Achterman and Kalamchi). Treatment of groups varied between those having amputation and those having lengthening procedures. They subclassified their patients according to the amount of inequality projected for the lower limbs. In group I, the percentage of shortening was 15 % or less with the foot of the shorter extremity at the distal third of the contralateral normal limb; group II, between 16 and 25 % shortening with the foot of the shorter extremity at the level of the middle third of the contralateral normal limb; and group III, >26 % shortening with the foot of the shorter extremity at the level of the proximal third of the contralateral normal limb. They concluded that lengthening was best suited only for patients in group I who had stable hips, knees, and ankles, and a plantigrade foot while patients in groups II and III were best served by ablation of the foot and a prosthetic fitting. Either Syme or Boyd amputation was used with the latter increasingly favored. The data provided indicated the extensiveness of the shortening in these disorders. The group projected the limb length discrepancy at maturity which owing to the invariably type I pattern in these deformities is highly accurate. In 15 patients in the group I category, the mean discrepancy projected to skeletal maturity was 8.85 cm with a range from 5.0 to 12.07 cm. In group II, 20 involved limbs had a mean projected discrepancy of 16.29 cm with a range between 12.5 and 22.5 cm. Deformities were so great, both in terms of extent and bony deformity in group III, that numbers were not provided.

Farmer and Laurin recommended early Syme amputation when the length discrepancy was projected to be more than 7.6 cm (3 in.) at maturity, especially when severe foot deformity was present [66]. A similar recommendation was made by Westin et al. in their review of 32 patients with 37 fibular deficiencies [76]. Many of their patients underwent Syme amputation, the two indications of which were a foot deformity so severe that any surgery to make the foot plantigrade and functional was likely to fail and the second that a lower extremity length discrepancy of 7.5 cm or more would be present at skeletal maturity in the absence of any management. In their group amputation was performed in 29 of 37 cases. They considered the results of the Syme amputations to be uniformly good. They noted the growth

inhibition to be constant with time. The growth inhibition in those treated without amputation ranged from 7 to 12 % in the tibia and from 0 to 14 % in the femur. In the amputee group, the inhibition was 22–42 % in the tibia and 0–22 % in the femur. In a listing of 9 patients with unilateral Syme amputations who were followed to skeletal maturity and who had growth data to skeletal maturity, the final femoral and tibial discrepancy ranged between 7.8 and 24.1 cm with a mean of 14.4 cm with the tibial discrepancies themselves ranging from 6.7 to 14.8 cm with a mean of 11.0 cm.

6.6.4 Congenital Abnormalities of the Tibia

6.6.4.1 Congenital Developmental Abnormalities of the Tibia; Tibial Hemimelia

Partial or complete absence of the tibia is often referred to as tibial hemimelia. These disorders are rare and markedly less frequent than the fibular variant. There is marked shortening and bowing of the involved leg, a flexion contracture of the knee and a rigid varus foot. Four basic patterns have been defined [77]. In type 1A, the tibia is completely absent and there is a markedly hypoplastic lower femoral epiphysis. In type 1B, the tibia is also completely absent, but there is a normal lower femoral epiphysis. In both instances, the fibula rides high laterally in relation to its normal position had the proximal tibia been present. In type II, the upper proximal tibial epiphysis is present as is a small portion of the metaphysis but the rest of the tibia distally does not form. In type III, the proximal tibia is absent but the distal one-third is present. In type IV, there is a marked diastasis between the proximal tibia and the fibula and the distal one-third of the tibia is absent. The most distal tibial segment tends to be curved medially (Fig. 6.7).

In the type II deficiency, the knee is well preserved. In types I, II, and III, the foot is in an equinovarus position. In the type IV deformity, the knee tends to be well formed, but the talus has subluxated proximally between the now separated tibia and fibula. Treatment is directed toward early disarticulation of the knee and prosthetic fitting for type I lesions, tibiofibular fusions, and prostheses for types II–IV, fibulocalcaneal fusions for types III and IV, and frequent need for foot ablation for prosthetic fitting. Schoenecker et al. studied 57 patients with congenital tibial hemimelia [78]. There were 33 type IA patients, 6 type IB, 15 type II, 7 type III, and 10 type IV. In the 54 limbs with the type I or II deficiency, there were 22 who had knee disarticulation, 25 a Syme amputation, and 1 a Chopart amputation. The foot was retained only in 6 with these 2 variants. There were 17 extremities with a type III or IV deficiency and a Syme amputation was done in 9 and a Chopart in 4. In 4 the foot was retained. They report that 56 of 57 patients walked independently.

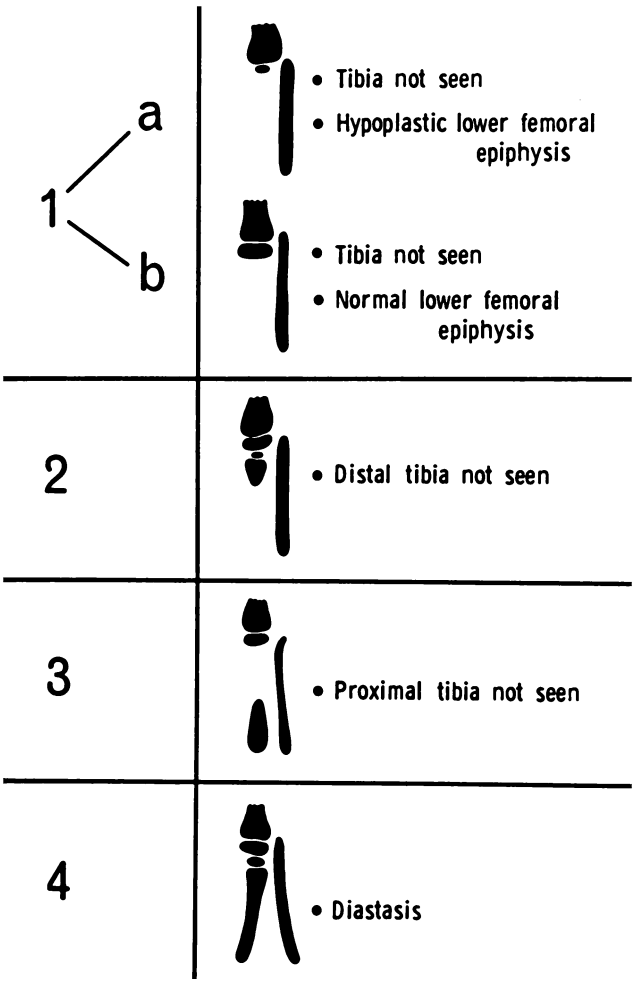


Fig. 6.7 Classification of tibial hemimelia (congenital absence of the tibia) by Jones et al. is shown. Several classifications are in use but this one shown defines the abnormalities clearly (Reprinted with permission from Jones et al. Congenital aplasia and dysplasia of the tibia with intact fibula: classification and management. J Bone Joint Surg Br 1978;60B:31–39)

Kalamchi and Dawe simplified the classification defining three types [79]. In type I, there was total absence of the tibia; type II, distal absence of the tibia; and type III, distal deficiency with tibiofibular diastasis. The fibula was always present but in type I was subluxed proximal and lateral to the distal femur, with a similar position sometimes being shown also in the type II variant. In type I, the disorder was also invariably associated with a marked flexion contracture of the knee, variable rotation of the leg, and marked inversion and adduction deformities of the foot. The distal femur was usually hypoplastic with marked retardation of the ossification center of the distal epiphysis. The functional status of the quadriceps muscle, the severity of the flexion contracture of the knee, and the position and function of the foot all had to be considered in planning surgical straightening or

ablation. Jones et al. stressed that in all three, the fibula is relatively normal in form and development although it often is situated in types I and II proximal to the normal relationship at the knee [77]. In some, the tibial segment is greater than it appears at birth since it is present in cartilage manifesting delayed ossification. Careful clinical exam and other forms of imaging are important to clearly define the anatomic structure in the newborn.

Courvoisier et al. reviewed 9 cases of type I or II (Jones) congenital longitudinal deficiency of the tibia managed by the Ilizarov technique [80]. Patients were assessed at a mean follow-up of 18 years (4–32 years). The mean maximum knee flexion was 35° (0–90°) in type I deficiencies and 118° (90–140°) in type II deficiencies. Only 1 patient underwent amputation and 1 had knee fusion. The Ilizarov technique provided satisfactory progressive corrections.

6.6.4.2 Posteromedial Tibial and Fibular Bowing

Posteromedial bowing of the tibia which is almost always associated with bowing of the fibula must be appreciated as an entity different from those described above. There is a considerable tendency for the posteromedial bow to correct during the first several years of growth, although considerable shortening often persists (Fig. 6.8a, b). The condition is unilateral. The deformity is exclusively in the distal one-third of the leg and is associated at birth with foot deformities of the calcaneovalgus type. The foot and leg deformity responds well to conservative treatment with repeated application of casts or splints. On occasion, osteotomy is resorted to but only after conservative management has reached a plateau. Shortening of the affected leg, however, is progressive, increasing with age, and must be followed until skeletal maturity. Sequential studies have demonstrated well the spontaneous correction of the bowing which in both anteroposterior and lateral projections becomes either perfectly straight or sufficiently straight that osteotomy is not needed by the time of skeletal maturity. The most rapid straightening occurs between 6 and 18 months of age. Pappas has indicated that the bowing was reduced by roughly 50 % in the first 2 years, but after the age of 3 years, the reduction in angulation continued at a much slower rate [81]. Little further correction should be expected after 10 years of age. The posterior bowing almost completely resolves with the medial bowing somewhat less likely to correct fully. The fibular bowing was equal to or slightly greater than the tibial bowing, corrected more slowly and some posterior bowing persisted in most even at maturity when tibial posterior bowing had fully corrected. The proportionate difference in lengths between the normal and bowed tibiae remain markedly stable throughout childhood showing a type I discrepancy pattern.

Fig. 6.8 Gradual correction of postero-medial bowing is shown in anteroposterior (**8a**) and lateral views (**8b**)

In the study of 33 patients by Pappas, the female/male incidence was 20/13 (1.5 to 1) and left/right involvement was 19/13 (1.5 to 1) [81]. In those patients whose limb lengths were determined radiographically within the first 2 months of life, the average initial discrepancy was 1.25 cm. Subsequent studies showed a constant increase with time. When all patients had discrepancies calculated to skeletal maturity, thus bypassing values obscured by epiphyseal arrest surgery, tibial shortening averaged 4.1 cm with a range from 3.3 to 6.9 cm. Femoral lengths were unaffected and foot lengths little affected. Owing to the extent of the length discrepancy, some form of limb equalization surgery was done or recommended for each patient but results were not reported. The abnormality is focused in the entire distal one-half of the tibia and fibula and soft tissues of the leg. The growth discrepancy was exclusively at the distal end of the tibia and fibula based on radiologic appearances of proximal and distal tibial and fibular epiphyses. In 4 of the 33 patients, osteotomies were performed at an early age to correct residual bowing; all healed uneventfully.

Hofmann and Wenger also noted a marked tendency to spontaneous correction of the posteromedial bowing with continuing progression of the discrepancy in limb length [82]. In 13 patients studied, there was a direct relationship between the degree of initial tibial bowing and the severity of the subsequent discrepancy which, stated slightly differently, indicates that slightly greater discrepancies in the earlier years of life would lead to greater discrepancies toward skeletal maturity. The mean posterior bowing at

diagnosis was 30° (range 4° to 60°) and the mean medial bowing was 27° (range 10° to 45°). They noted the relatively slow improvement of the posteromedial angulation over a few years compared with the rapid and complete correction of the calcaneovalgus deformity over a few months. The limb length discrepancy was progressive and present in each of the 13. The mean discrepancy was 3.1 cm (range 1.9–5.4 cm) but none had been followed to skeletal maturity and 10 patients were still only between 1 and 7 years of age. In the oldest 3 patients (10 years 4 months to 15 years 5 months of age), the mean discrepancy was 4.7 cm—a value similar to the 4.1 cm projection of Pappas. There were no femoral length discrepancies.

A similar picture of the effects of a posteromedial angulation was reported by Carlioz and Langlais [83]. They reported on 18 cases of congenital posteromedial bowing of the tibia and fibula, all of which were also associated with shortening. Both the valgus (medial bowing) and posterior bowing components corrected over the first few years of life. The valgus or medial bowing ranged between 10° and 56° initially and the posterior bowing or recurvatum between 10° and 65°. Although not all of the patients were followed to skeletal maturity, 5 had shown evidence of complete correction of both deformities during growth. The spontaneous correction occurred in 3–4 years. The posterior bowing or recurvatum tended to correct more completely than the medial or valgus deformation. Osteotomy was resorted to in three patients and in each instance healing was uneventful. Length differences were invariably seen and ranged between 10 and 20 % of the length of the normal tibia. In most, the discrepancy increased at a steady rate with time but on occasion with increased growth the rate of inhibition on the involved side lessened. Five tibial lengthening procedures were performed with the preoperative average discrepancy of 4.42 cm while 3 epiphyseal arrests were performed with a presurgery discrepancy of 3.7 cm. Other patients were still being followed such that additional surgery might well have been needed. The authors projected that discrepancies untreated would have reached between 1.5 and 7 cm at skeletal maturity with the majority being in the 3–5 cm range.

6.6.5 Skeletal Dysplasias with Asymmetric Involvement

In several of the skeletal dysplasias, asymmetric involvement is strongly associated with length discrepancies. The following variants are particularly likely to show such findings.

6.6.5.1 Hereditary Multiple Exostoses

Femoral–tibial limb length discrepancy measurements in 32 patients from the Children's Hospital, Boston indicated a range from 0.1 to 4.0 cm [84]. In 2 patients, femoral and tibial shortening were equal; in 20, femoral shortening was greater than tibial; and in 10, tibial shortening was greater than femoral shortening. On occasion, the shortening was limited to either the femur or the tibia. Of 22 patients who reached skeletal maturity, 11 (50 %) had limb length discrepancies in the range for which limb length equalization would normally be recommended. Of these, however, only 5 (23 %) actually had the procedure. The limb length discrepancies at the termination of growth in those who did not undergo growth–arrest procedures measured 2.1, 2.4, 2.3, 2.6, 3.1, and 3.5 cm. Reasons for not performing surgery were: subsequent planned correction of discrepancies with associated opening-wedge osteotomy for deformity on the short side or closing-wedge osteotomy on the long side; difficulty of performing epiphyseal arrests in regions where large exostoses are present; clinical impression of an acceptable situation despite the roentgenographic measurements; and reluctance of patients and their families to undergo more procedures.

Taking into consideration all 22 patients who had reached skeletal maturity and also the 7 who were close enough that it was possible to say whether they would or would not require an arrest, there were 29 patients, of whom 12 (41.2 %) had discrepancies within the recommended range for operative epiphyseal arrest.

All five patients who were operated on had distal femoral epiphyseal arrests, and 1 had a proximal tibiofibular epiphyseal arrest as well. The limb length discrepancies at the time that the arrest was performed and the eventual limb length discrepancy at the termination of growth were as follows: 2.9 cm, corrected to a 1.9 cm discrepancy; 2.8 cm, to 1.2; 2.4 cm, to 1.3; 2.3 cm, to 0.5, and 4.0 cm, to 4.0. There were no overcorrections, and although 4 of the 5 limbs were corrected into an acceptable range, all were short of equalization. The last patient was operated on too late by all criteria. In the other 4, however, the question arose as to whether growth anomalies in hereditary multiple exostoses might make prediction from the normal charts slightly unreliable. Femur-tibia length ratios were plotted along the appropriate percentile distribution in all the patients with hereditary multiple exostoses and compared them with the standard charts. The mean value for this length ratio in the patients with hereditary multiple exostoses was 1.27, which was exactly the same as the value from the charts for normal subjects with the same size distribution. Reference to the records of each patient who underwent epiphyseal arrest indicated that there had been considerable difficulty in assessing the skeletal age from the roentgenograms of the wrists.

The pattern of limb length discrepancy that can occur in this condition is variable. The discrepancy can remain unchanged for several years; it can increase at slow or moderate rates, which is the usual pattern; or it can, on

occasion, decrease spontaneously. The growth study data did not support the belief that there is an increase in longitudinal growth in an affected bone following removal of an exostosis. In addition, no correlation was seen between the degree of shortening in a particular bone and the number or size of the exostoses present.

Limb length discrepancies in hereditary multiple exostoses were frequent, and in approximately half of the patients they were great enough to warrant epiphyseal arrest. These discrepancies point to the asymmetrical growth pattern in patients with hereditary multiple exostoses. The discrepancies were mild to moderate and were readily managed by appropriately timed epiphyseal arrests. Extremely careful observation is required, however, as the discrepancies can remain stable, increase at varying rates, or even, on occasion, spontaneously decrease. Osteotomies can also alter limb length relationships. Some difficulties were encountered in determining skeletal age accurately due to the associated wrist and knee anomalies, but the Green-Anderson charts were appropriate for predicted corrections in this condition. The limbs were more affected than the spine, both the femur and the tibia were involved, and limb involvement was not invariably rhizomelic.

6.6.5.2 Ollier's Disease (Enchondromatosis)

The 17 patients with this intrinsic bone disease demonstrated a type I pattern of discrepancy development [50, 85]. As varus or valgus femoral and tibial deformities were often associated with the shortening, corrective osteotomy was done frequently and length discrepancy data unaltered by any bone surgery intervention throughout the growth period were rare. Relentless shortening was demonstrated, however. One patient with severe involvement who was followed to skeletal maturity, with no surgical intervention, had a type I profile, with a 35.7 cm discrepancy and no decline in the rate of increase. In all patients, the extent of shortening paralleled the extent of radiographic involvement. The average shortening prior to physeal arrest or diaphyseal lengthening was 9.79 cm. Enchondromatosis was the second most serious condition causing extensive discrepancies, being exceeded only by proximal femoral focal deficiency.

6.6.5.3 Maffucci Syndrome

The Maffucci syndrome is characterized by enchondromatosis, usually but not always unilateral, and vascular malformations. The enchondromas are present primarily in the hands and feet but may involve tubular long bones or any bone preformed in cartilage. The vascular malformations are either dermal or subcutaneous and adjacent to areas of enchondromatosis in most instances. They are usually venous but can be capillary or lymphatic. Thrombosis of the dilated blood vessels with phlebolith formation occurs in almost half of the cases. The vascular lesions are usually absent at birth but appear within the first 4 years of life with 25 % occurring during the 1st year. Intracranial tumors of cartilaginous origin are seen in approximately 15 % of patients. The incidence of chondrosarcomatous change is high, similar to the finding in Ollier's disease, with the reported incidence being 25–50 %. The matter is difficult to determine since some authors consider virtually all enchondromatosis tissue after skeletal maturity to be presarcomatous at least. The limb length discrepancy findings are similar to those with Ollier's disease, in particular where unilateral lesions predominate.

6.6.5.4 Dysplasia Epiphysealis Hemimelica

This disorder is often accompanied by a lower extremity length discrepancy in particular if the epiphyseal involvement is at the distal femur or proximal tibia. It is generally referred to as dysplasia epiphysealis hemimelica but other terms for the disorder are tarso-epiphyseal aclasis and epiphyseal osteochondroma. Many of the disorders occur at the ankle joint involving either the distal tibia or on occasion the talus. The discrepancies generally tend to be mild to moderate and more clinical difficulty is encountered with the asymmetric joint surface than with the discrepancy.

Trevor was the first to delineate the disorder formally, describing eight patients [86]. He noted that the initial description of such a disorder was a case described by Mouchet and Belot [87] in 1926 involving the talus. There was no true shortening in the eight patients assessed, although specific limb measurements were not taken. Sixteen patients with the disorder were reviewed by Connor et al. [88]. Each had only one leg involved but 12 multiple epiphyses affected. The commonest sites were the distal femur, distal tibia, and talus. Treatment of the lesion was by local excision and was generally effective around the knee although some at the ankle required arthrodesis. The disorder is characterized by asymmetrical overgrowth of one or more epiphyses in a limb or of a tarsal or carpal bone during childhood. In the 16 patients, most of whom were followed to skeletal maturity, inequalities of limb length were apparent in 5, 1 with lengthening, and 4 with shortening. Discrepancies were generally of a minor degree and caused few problems. In those with shortness on the involved side the amounts were 2, 1, 1, and 6 cm. In the one instance where there was overgrowth on the involved side it was only 1 cm and there was multifocal involvement of the distal femur, distal tibia, and talus. In the one patient with an extensive 6 cm of shortening, there was major involvement of the lateral half of the right distal femoral epiphysis. Approximately, 3/4 of the lesions are concentrated in 5 regions which, starting with the most common, involve the talus, distal femoral epiphysis, distal tibial epiphysis, proximal tibial epiphysis, and the tarsal navicular bone. When deformities are present, they tend to involve either genu

valgum or genu varum, valgus deformation of the ankle and equinus deformity of the ankle.

Kettelkamp et al. reported 15 new cases and also reviewed the literature; they noted that inequality of limb length was found occasionally and that the affected extremity could be either shorter or longer [89]. The distal fibular epiphysis and the medial cuneiform were also affected in some instances. When the seven most common sites of involvement were included, they accounted for 84 % of all lesions. Lower extremity length discrepancies were described in only three of their cases, although no specific comments about measurement were made otherwise. In those three instances, the involvement was marked with 1 patient having 3½ in. shortness and 2 with overgrowth having discrepancies of 1 and 2½ in.

Fairbank reported on 14 additional cases [90]. The length of the limb was usually unaffected but on occasion discrepancies did occur. He reported three instances of length discrepancy in 14 patients; 1/4 of an inch of shortening, 1 in. of lengthening, and ½ in. of lengthening.

If we summarize the length discrepancy descriptions from the papers of Connor et al. [88], Kettelkamp et al. [89], and Fairbank [90], the number of instances of clinically significant length discrepancy is relatively small with 11 out of 45 involved or about 1/4 (25 %) of the patients. Of those with involvement, 6 had shortness on the involved side and 5 were longer on the involved side. The range of discrepancy in those with shortening was from 0.6 cm to almost 9 cm (0.6, 1, 1, 2, 6, and approximately 9), while in those with overgrowth the values ranged from 1 to 5.7 cm (1, 1.2, 2.5, 2.5, and 5.7). In summary, therefore, while clinically significant lower extremity length discrepancy occurs in only approximately 25 % of patients and appears to be equally divided between shortening and overgrowth, on occasion it can be marked such that examination through the growing years is essential in regard to length discrepancy as well as angular deformity and range of motion.

6.6.5.5 Melorheostosis

The rare skeletal dysplasia melorheostosis is characterized by linear radiodensity or sclerosis primarily in the metaphyseal and diaphyseal regions and can be associated with length discrepancy owing to asymmetric involvement. Daoud et al. reported one case in which the predicted final discrepancy was 2.5 cm of shortness on the involved side [91]. Campbell et al. reported 14 patients with the disorder which was characterized by the radiographic long bone abnormalities with a primary clinical finding of contractures or limitation of joint motion [92]. The tendency of the disorder is to be either exclusively monomelic or at least concentrated in 1 or 2 of the major long bones. Any bone of the body can be involved, however. The clinical findings at birth or early in childhood involve contractures, fibrosis and abnormal skin with the bone changes occurring over a several year period afterward. They noted that the affected extremity was usually shorter although occasionally longer but that the affected limb usually appears larger in circumference and often has angular bone deformities. In the epiphyses and carpal and tarsal bones, there is often a spotty or patchy collection of increased radiodensity. An inequality in limb length ranging from ½ to 4½ in. was found in 9 patients; the involved or more severely involved extremity was almost always shorter except in one instance in which it was longer.

Younge et al. did a study of 14 children with the disorder [93]. The principal presenting clinical features were unilateral soft tissue contractures and inequality of limb length. The initial bony changes involved endosteal thickening or hyperostosis marked by streakiness of the long bones and spotting of the small. As in the Campbell et al. series [92], there was equal involvement of males and females. Eleven of the 14 were followed at least to 16 years of age. Soft tissue contractures causing severe and rigid joint deformities occurred in all and were the presenting complaint in 11. In eight patients, only one limb was involved, in three two limbs, in two three limbs, and one had all four limbs affected. Contractures were most commonly seen at hip, knee, ankle (club-foot), fingers, and iliotibial band. Each of the 14 patients had a lower extremity length discrepancy. In 13 the affected limb was shorter ranging from 1.2 to 10.0 cm with an average shortening of 4.1 cm. In the one patient whose limb was longer, the discrepancy was 2.5 cm. Firm thickening of the skin with tethering of the underlying fascia was seen in 5 patients. The problems of joint deformity, bone deformity, and contracture were marked and poorly responsive to nonoperative and even operative attempts at correction. Indeed amputation was required on 4 occasions, almost always after failed surgical procedures. Epiphyseal arrest was effective in treating the length discrepancies. More recently Marshall and Bradish reported successful tibial and fibular lengthening with the callotasis technique [94]. The discrepancy at maturity was 4 cm equally divided between femur and tibia. The regenerated bone in the distraction gap had the radiologic appearance of the original bone.

6.6.6 Destroyed Physes

If destruction and premature fusion of a physis occurs, a type I pattern of discrepancy development invariably follows except at the hip (as will be described), with no tendency to compensation by the other physes in the involved bone. Such destruction occurs most commonly today with certain physeal fracture-separations. Significant lower extremity length discrepancies are seen with distal femoral growth plate fracture-separations, especially if there are several

years of growth remaining since 70 % of femoral growth occurs distally. Successful focal transphyseal bone bridge resection will allow growth to resume in some instances. Other causative factors are physeal ablation during tumor resection and severe osteomyelitis, particularly in the pre-antibiotic era. Wilson and McKeever documented shortening in 18 (21.1 %) of 85 infected bones whose physes were damaged from an adjacent focus of osteomyelitis [95].

6.6.7 Abnormal Growth Following Use of Neonatal Umbilical or Femoral Catheters

On occasion prolonged use of neonatal umbilical or femoral catheters for newborn illness has been associated with mild growth stimulation on the involved side. More serious sequelae were reported by McCarthy et al. in four patients in whom significant lower limb length shortening occurred subsequent to neonatal catheter use [96]. This involved either umbilical or femoral arterial catheters or both. The projected length discrepancies were massive varying from 10 to 20 cm at maturity. Autopsies on other patients with indwelling catheters demonstrated varying degrees of thrombosis of the major associated vessels along with many embolic phenomena so the complication should be considered if length discrepancy problems surface after a prolonged or difficult neonatal hospitalization.

6.6.8 Poliomyelitis

In patients with poliomyelitis involving the lower extremity, the type I pattern was seen commonly. There was, however, a distinct tendency for the discrepancy to increase most rapidly in the first 4 or 5 years following infection, with the rate of increase diminishing after that (types II and III) (Fig. 6.9) [50]. This fact has been pointed out previously by Green and Anderson [97], Ratliff [98], and White [99]. Assessment of 115 patients who were followed for 10 years or more, either to skeletal maturity or to the time of surgical physeal arrest, indicated that almost one-third of the patients demonstrated a type II or type III pattern [50]. Improved function due to tendon transfers and bracing may be responsible for the lessening rate of discrepancy with time. Detailed studies during the poliomyelitis era described a good but variable correlation between the extent of shortening and the severity of involvement. No correlation between the age at onset and amount of shortening was found in one major study, although this finding was challenged (Fig. 6.9).

During an era when polio was common, it was noted by Ratliff that lower extremity shortening was seen in 219 of 225 affected patients [98]. Barr had stated that any child

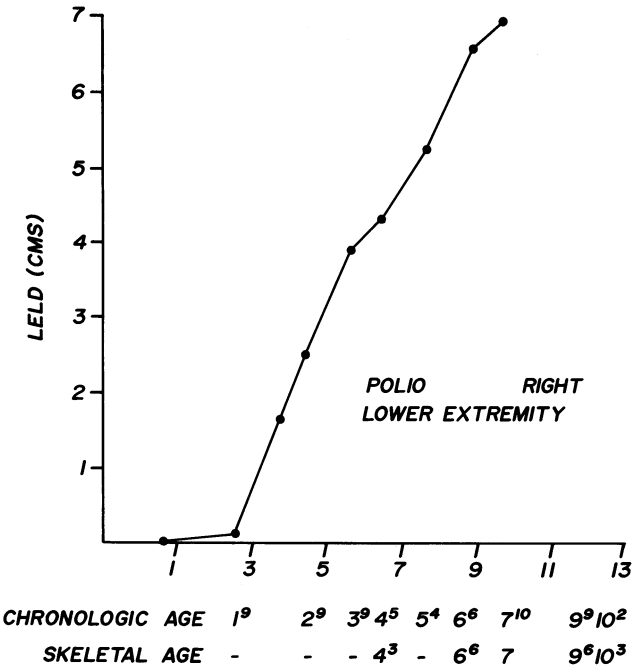


Fig. 6.9 Type I pattern of a developmental discrepancy in a patient with poliomyelitis is shown (Reprinted with permission from Shapiro F, Developmental patterns in lower extremity length discrepancies. J Bone Joint Surg Am 1982;64A:639–651)

developing poliomyelitis before the age of 10 with considerable difference in paralysis of the legs was almost certain to develop inequality of leg length [100]. Barr had indicated in an earlier study that the incidence of leg shortening in poliomyelitis was as high as 78 % of cases but more detailed studies revealed an even greater increase in the likelihood of shortening. To a certain extent, the shortening was related to the age of onset of the poliomyelitis and to the extent of the musculature weakened but these were not absolute correlations. Barr found that 35 % of patients developed a discrepancy of 1½ in. (3.8 cm) or more, and Green noted that 8 % developed a shortening >2 in. (5 cm) [100].

Ratliff analyzed several factors relating to limb shortening and poliomyelitis in 225 children in whom paralysis was confined to one leg [98]. Patients were assessed between 5 and 17 years after infection. The study assessed length discrepancy prior to any limb equalization procedures. Measurements were clinical from anterior superior iliac spine to medial malleolus. Shortening had occurred in 219 of 225 children (97 %) of whom 190 had some radiographic studies which led to effective measurement to within 1/16 of an inch. The greatest incidence of onset of poliomyelitis was within the first 3 years of life with relatively few developing the disease after the age of 8 years. The involved leg was always shorter. There were 65 patients followed into adult life, with no surgery having been performed, in which the shortening varied between 1/4 of an inch and 5 in. There was

only 1 patient with the 5 in. shortening such that the natural history would best be defined as leading to discrepancies between 1/4 of an inch and 3½ in. since each quarter inch gradation between those two numbers had patients involved. The discrepancy was 2 in. or greater in 25 of the 65 patients. The discrepancy was almost always greater in the tibia than in the femur. In 184 patients assessed in this regard, 12 had tibial shortening only, 94 had tibial shortening greater than femoral shortening, 47 had equal tibial and femoral shortening, 30 had tibial shortening less than femoral shortening, and only one had femoral shortening only. Ratliff felt, after careful analysis, that it was impossible to predict accurately the distribution of shortening from a study of the distribution of muscles paralyzed. In another subset of patients followed for at least 9 years after disease onset (130 patients), 3 patterns of progressive shortening were noted. One involved a rapidly progressive discrepancy pattern in which 2.5 in. or more discrepancy occurred within 9 years or less of the onset of the disease, slowly progressive in which the discrepancy increased at a constant rate amounting to 2–3 in. by adult life and a nonprogressive variant in which a discrepancy of up to 1.5 in. was present 5 years after onset of the disease and then remained constant until growth ceased (the type III pattern). There was no evidence that a decrease in the amount of shortening ever occurred (absence therefore of the type V pattern). Ratliff noted that almost 62 % of patients fell into the nonprogressive group III pattern. The classification of paralysis as mild, moderate, or severe could not reflect the pattern of length discrepancy progression. Although there was a considerable overlap between groups, in general those with mild paralysis had lesser amounts of shortening than those with severe paralysis, with moderate in between. For example, each of the five patients without any shortening had mild involvement. In 102 of the patients assessed 9 years after poliomyelitis, those with mild paralysis had shortening from 0 to 2 in., those with moderate paralysis from 0.5 to 2 1/4 in., and those with severe paralysis from 1 to 3.5 in. There was no significant difference in the range of shortening which occurred in patients suffering disease onset between 0 and 2 years of age and those between 3 and 7 years of age. The range of shortening was also similar whether the paralysis involved only one muscle or all of the muscles below the knee. No child with paralysis only below the knee, however, showed a discrepancy >1 3/4 in. On occasion, some transient lengthening of the involved paralyzed leg was noted during the first 2 years after the onset of the paralysis but this was always temporary and no patient was found in the series with lengthening of the paralyzed leg 5 years or more after onset. It is likely that inequality of leg length was present before the onset of the poliomyelitis which would of course not have been observed. Premature physeal fusion was not a feature of poliomyelitis.

Ring also studied limb shortening in relationship to paralysis in poliomyelitis [101]. His study did not provide absolute numbers of the amount of shortening but rather assumed (somewhat incorrectly) that it would occur at a constant rate with time. The degree of shortening was basically the same in limbs with muscle power graded as 2, 1, or 0. The amount of shortening progressively increased; however, as the grade of strength diminished from 5 to 4 to 3. Shortening was least in the strongest patients. The important feature was therefore not the degree of weakness but whether the muscles could function against gravity; within this group, the stronger the muscle the less the shortening. The cause of shortening in poliomyelitis was not felt to be weakness per se but rather the diminished vascularity which accompanied the decreased muscle mass. Absolute correlations, however, were never possible in relation to the age of onset of the disorder or the extent or type of muscle weakness.

Gullickson et al. determined that the average percentage shortening of unilaterally affected limbs with poliomyelitis did not appear different between the 0–5 year age group or the 6–10 year age group in terms of age of onset of the disorder [102]. They also noted no correlation between muscle strength of the leg and shortening of the tibia. There was, however, definite correlation between atrophy of the thigh or leg and shortening of femur or tibia. They provided percentages rather than measurements of limb shortening. In those with age of onset between 0 and 5 years of age, the percentage shortening of the tibia was 2.44 and of the femur 2.52 in 47 cases and in those from 6 to 10 years of age, the percent shortening of the tibia was 2.37 and that of the femur 1.96 in 29 cases.

Green in a discussion published in the *Journal of Bone and Joint Surgery* after an article published by Stinchfield et al. reviewed the fact that, in 257 cases of poliomyelitis studied in his unit in which one lower extremity was affected and the other was normal, the average maximum growth inhibition occurred from the second to the fifth year after the onset of the disease; there was less inhibition prior to the second year and less inhibition each year after the fifth year following onset [103]. It was thus recognized that not all patients with poliomyelitis increased their discrepancy at a constant rate with time. Green and Anderson showed that the final result of epiphyseal arrest treatment for poliomyelitis was within 1.2 cm (0.5 in.) of predicted amount in 88.5 % of 61 cases [97].

Barr provided an excellent review of inequality of leg length in poliomyelitis [100]. Based on assessment of 371 cases during an active era of poliomyelitis, with the onset before the age of 16 years, shortening was 0.5 in. (1.3 cm) or less in 41 %, over 0.5 in. but <1.5 in. (1.3–3.8 cm) in 24 % and 1.5 in. or more (3.8 cm+) in 35 %. Numbers from his clinic indicated that approximately 80 % of patients with

unilateral poliomyelitis developed shortening on the involved side. Subsequent studies showed the incidence to be higher with virtually all patients with unilateral poliomyelitis having some degree of shortening.

Stinchfield et al. attempted to project how much the growth discrepancy would be based on the muscle power in the affected extremity compared to the muscle power in the normal extremity [103]. A chart was constructed based on data from 64 cases which had reached adulthood such that the final discrepancy was known. The hope for clear correlation between muscle strength and limb length discrepancy was shortly disproven however.

6.6.9 Hemiparetic Cerebral Palsy

Most of these patients have a lower and upper extremity length discrepancy with the shortening on the more distal parts of the involved side. Type I and type III developmental patterns in the lower extremity predominated [50]. Lower extremity shortening in hemiplegic children occurred almost exclusively in the tibia, a correlation also noted by Staheli et al. [104]. Growth alterations in the hemiplegic child were studied in 50 children with spastic hemiplegia by Staheli et al. [104]. The hemiparetic side was always somewhat shorter than the contralateral normal side. Discrepancies in the affected upper extremities were actually larger than those in the lower extremities. The mean difference in the radius in terms of percentage growth inhibition in 25 cases was greatest representing 6 % while the inhibition in the humerus was approximately 4.2 % and in the tibia approximately 3 %. There was essentially no difference in the femoral lengths. The limb length inequality was far more significant in terms of functional disability in the lower than in the upper limb but lower limb discrepancies were not particularly great since femoral shortening was not a factor. A discrepancy of 2 cm or greater occurred in only 2 of 16 patients in the older age group and epiphyseal arrest was rarely resorted to. Of the 16 patients, 11 years of age or older the lower limb discrepancy was 1 cm or more in 10 children and >2 cm in only 2.

Lower extremity length discrepancy represents an important consideration in many hemiparetic patients. Of the 46 patients who were followed in the Growth Study Unit for 5 years or more, and who had a discrepancy of more than 1.5 cm, the average discrepancy just prior to physeal arrest or at maturity was 2.0 cm (range 1.5–3.2 cm). Physician referral strongly influenced study of this disease entity, unlike other diseases for which the condition itself was reason for referral. The majority of patients with cerebral palsy were not assessed for discrepancies. Femoral–tibial shortening alone does not give a true measurement of the functional discrepancy that may be present in the limb, as dynamic or static hip and knee flexion contractures and an expected, but rarely documented, shortness in the height of the foot may further decrease the functioning length of the hemiparetic limb. If a tendo Achilles lengthening is done and the lower extremity length discrepancy is not appreciated, there may be a tendency for equinus deformity to recur on a mechanical compensatory basis.

6.6.10 Septic Arthritis of the Hip

Damage to the femoral capital epiphysis in septic arthritis can produce serious growth discrepancies especially if it occurs in infancy [105, 106]. In one series such discrepancies tended to increase with time, but a type I pattern was seen only in 42 % of the patients, and most commonly when the infection had occurred relatively late, after the age of 7 or 8 years [50]. An assessment of pattern development in this group was obscured somewhat more often than in other groups because of the necessity for early and often frequent surgical intervention, although femoral osteotomy per se was done infrequently in growing children. The patterns in this assessment were based on femoral and tibial lengths. In following such patients, however, it is important to be aware that if dislocation occurs, the practical consideration in discrepancy relates to the distance between the iliac crest and the floor. This can be documented accurately by orthoradiographs, but a combination of measured blocks under the shortened extremity in association with a standing anteroposterior radiograph of the pelvis is also important.

Even with complete destruction of the epiphysis, however, femoral shortening did not invariably become worse with time, particularly in the younger patients and in those in whom femoral head dislocation did not occur. When the greater trochanter overtakes the involved femoral head in height, the femur resumes a somewhat more regular growth pattern as the greater trochanter and distal femoral physes are normal, thus accounting for the type II and III patterns that were seen. The relatively rare type IV pattern (Fig. 6.10a) was also seen with septic arthritis (Fig. 6.10bi–vi). There are instances where treatment effectively eradicates infection allowing physeal growth to continue for several years in seemingly normal fashion. On occasion, however, premature femoral head–neck growth plate closure occurs with no reactivation of infection leading to a worsening of the discrepancy several years after the infectious insult (Fig. 6.10bv, vi). The growth of the proximal end of the femur, in particular the relationship between the capital femoral and the greater trochanteric epiphyses, has been discussed in relation to normal, diseased, and experimental situations. The complexities of this particular growth area must be understood in order to plan the proper time for surgical intervention.

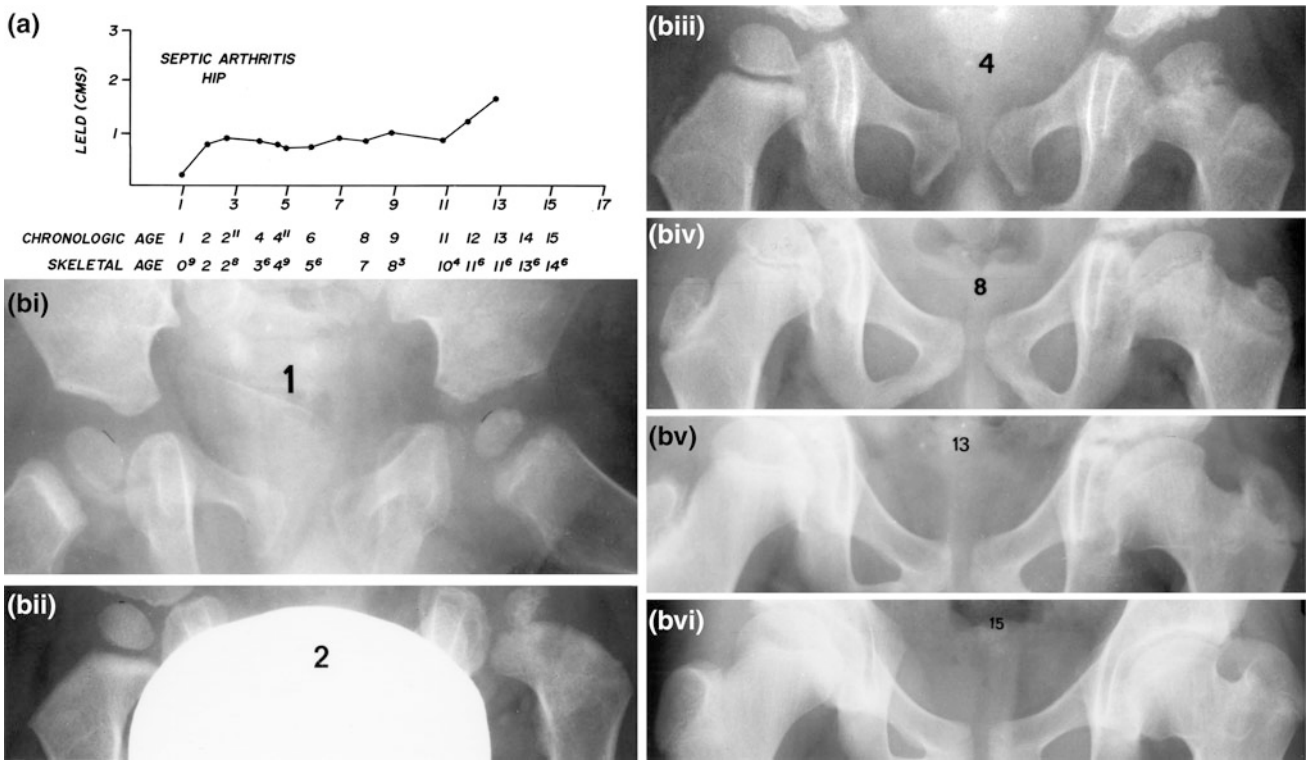


Fig. 6.10 **a** Type IV pattern in a patient with septic arthritis of the right hip in infancy is shown. The hip was treated early such that there was continuing growth of the physis for several years followed by premature cessation of growth which added an additional centimeter to the discrepancy at time of skeletal maturation (Reprinted with permission from Shapiro F, Developmental patterns in lower extremity length discrepancies. J Bone Joint Surg Am 1982;64A:639–651). **bi–iv** Radiographs (**i–iv**) at 1, 2, 4, 8, 13, and 15 years of age are shown. Note excellent structural recovery by 8 years of age, mild coxa vara at age 13 years with early evidence of premature physeal closure and clear trochanteric overgrowth with shortened femoral neck at age 15 years owing to premature physeal closure years after the initial infectious insult

Both Betz et al. [107] and Hallel and Salvati [108] found subsequent length discrepancies after neonatal septic arthritis of the hip to range between 3.0 and 3.5 cm if the femoral head remained located and 5.5–6.0 cm if dislocation occurred.

Hallel and Salvati reported on the end result of 24 cases of infantile septic arthritis of the hip in 21 patients, 3 of whom were involved bilaterally [108]. The disorders occurred in the first 7 months of life. A clear difference in length discrepancy was noted between those hips which had dislocated and those which remained located with the far more serious length discrepancies occurring in the former group. Fifteen of the 21 patients had reached skeletal maturity and each of these others ranged between 11 and 14 years of age. Shortening of more than 2.0 cm was noticed in 16 cases. In 8 instances, it was due to arrested or delayed growth of the physis of the femoral head and in 8 other cases the epiphyseal damage was worsened by a proximal migration of the head in either subluxated or dislocated hips. In those cases where the head remained located, the mean discrepancy was 3.4 cm (range 2.0–5.0 cm) and in the dislocated and subluxated cases the mean discrepancy was 6.0 cm (range 3.0–9.0 cm). The growth of the femoral shaft measured from the proximal tip of the greater trochanter to the lateral femoral condyle was not affected by the septic process and the growth rate of the trochanteric epiphysis remained equal to the opposite side even when the trochanter was placed into the acetabulum in the form of a trochanteric arthroplasty.

A long-term multicenter follow-up of the late sequelae of septic arthritis of the hip in infancy and childhood was published by Betz et al. [107]. They defined infantile cases as occurring from birth to 3 months of age and the childhood form in those whose onset occurred after age 3 months. All patients had reached skeletal maturity and the study involved 28 patients with 32 affected hips. The lower extremity lengths were assessed at skeletal maturity in those in whom no epiphyseal arrest had been performed or were determined as being the predicted length discrepancy had epiphyseal arrest or lengthening not been performed. In the infantile group, the projected lower extremity length discrepancy was a mean of 3.93 cm with a range from 0 to 7.0 cm. In the

childhood group, the mean discrepancy was 4.2 cm with a range from 0 to 8.0 cm. The discrepancy was 2.5 cm or greater in 7 of the 10.

Wopperer et al. studied 9 hips in 8 patients at a mean follow-up of 31.5 years after infantile hip sepsis, occurring between birth and 3 months of age [109]. Six of the hips had dislocated and three had remained located. The leg lengths were equal in the case with bilateral sepsis and dislocation leaving seven patients in whom length discrepancy owing to the disorder itself could be determined. In these seven, the discrepancy ranged from 0 (in 2 patients) to a maximum of 6.0 cm. The mean discrepancy was 2.86 cm.

Cottalorda et al. reported on the growth sequelae of 72 hips in 60 children with septic arthritis of the hip in early childhood [110]. Treatment was variable. In 28, there was no lower extremity length discrepancy; in 16 the discrepancy was 2.0 cm or less; but in 16 with poor results discrepancies >2.0 cm were present with an average of 3.5 cm and a range of 2.0–7.5 cm.

The type IV developmental growth pattern is limited almost exclusively to abnormalities of the proximal end of the femur that occur with septic arthritis of the hip, osteomyelitis of the femoral neck, Legg–Perthes disease, and avascular necrosis of the femoral head complicating treatment of congenital or developmental dislocation of the hip. In septic arthritis patients in whom damage was relatively mild, premature fusion of the proximal femoral capital physis was sometimes noted years after the infectious insult. The premature fusion can be detected 2 or 3 years prior to skeletal maturation by the progressive change in the relationship of the level of the greater trochanteric physis to that of the proximal femoral capital physis. It is, therefore, extremely important to continue periodic assessment of these children by monitoring carefully the relationship of the head and neck to the greater trochanter until skeletal maturity, even if the discrepancy has been in a plateau phase for several years. Although the average increase in the late phase was only approximately 1 cm, this amount could convert a clinically insignificant discrepancy to one of 2.4 cm or more, and thus warrants special consideration. Gage and Cary have shown the value of trochanteric epiphysiodesis in patients with severe growth damage to the femoral head–neck physis [111].

Manzotti et al. reported generally favorable results in 15 young adults, average 21 years, who had late sequelae of childhood septic arthritis of the hip [112]. The average limb length discrepancy was 6.5 cm. Patients underwent simultaneous hip reconstruction and femoral lengthening using a modified Ilizarov method. The hip procedure involved a proximal femoral support osteotomy with either acetabular, subacetabular, or pubic ramus support. Ten patients had good/excellent results, 3 fair, and 2 poor. At latest assessment, 13 were satisfied with the treatment.

6.6.11 Tuberculosis

Tuberculosis was frequently associated with lower extremity length discrepancy especially prior to the advent of antibiotics [113]. The hip was a common site of infection with the knee involved fairly often. The serious nature of the disease overall and the major sequelae of joint destruction limited the study of length discrepancy alone. There was early awareness, however, that tuberculous infection of the bones in childhood could affect growth. Langenbeck described decreases in growth with tuberculous involvement of the joints in the lower extremities [114]. Dollinger described 41 cases of tuberculosis of the knee joint and found that, in the active phase, the diseased leg grew either at the same rate or on occasion more quickly [115]. Since tuberculous infection was relatively indolent, there was a chronic synovitis associated with it and this stimulation of growth was similar to what one sees today in childhood rheumatoid arthritis. Dollinger also noted that retardation of growth occurred only when the disease became quiescent by which time in that era there had been sufficient damage to destroy the physis and also further decrease height by associated articular cartilage destruction. Increase in the length of the long bones after tuberculous infection was also noted by Reschke [116] and Pels-Leusden [117]. In spite of the fact that tuberculosis of the hip had been a common disorder, very little has been written of the extent of length discrepancies resulting, although one would expect values similar to those with septic arthritis.

Although the joint affected most commonly in tuberculosis was the hip and some of the femoral shortening was due to damage at the proximal end of the femur, it was frequently noted that there was premature distal femoral growth plate closure which led sometimes to marked length discrepancies. Gill demonstrated that, contrary to the previous feeling that it was disuse which led to the length discrepancy, there was often premature central closure of the epiphyseal cartilage plate of the distal femur and occasionally of the upper tibia which caused most of the discrepancy [118]. He described 15 cases of childhood tuberculosis of the hip in which the complication occurred. In each case, the limb had been immobilized for an extremely long period of time. In each instance, the age of the patient at the onset of the tuberculosis was <7 years. The distal femoral arrests were almost invariably central epiphyseal-metaphyseal bone bridges which, with continuing growth peripherally, caused

formation of an inverted V-shape to the distal femoral epiphysis with a deeper bicondylar notch than on the normal side. In the tibia, central fusion also tended to occur leading to a continuing peripheral overgrowth and a saucer shape to the proximal end. With any degree of eccentricity of the central fusion, angular deformity also occurred. In each instance, the premature closure of the distal femoral or proximal tibial growth plate occurred on the side of the diseased hip. There was no evidence of tuberculosis of the knee joint to serve as a direct cause of the physeal fusion. Gill noted marked osteopenia of the entire affected femur which he felt was due to a long period of immobilization leaving the cartilage plate more susceptible to traumatic damage even if slight.

Parke et al. also noted a relatively high frequency of premature epiphyseal fusion at both distal femur and proximal tibia in tuberculous disease of the hip [119]. They also felt it was due to the associated severe osteopenia of prolonged immobilization leading to rupture of the physis and transphyseal bone bridge formation. Much of the osteopenia was also due to the generalized suppression of new bone formation by the tuberculous disease. These severe sequelae were described in the preantibiotic era. The physeal fusion was primarily central initially. The occurrence was with prolonged disease which had to have been present for at least 2 years and frequently much longer. They assessed 91 diseased hips with a duration of disease varying from 4 months to 22 years. It was not trauma per se but rather severe osteoporosis which was the precursor to premature fusion. They noted 29 cases of premature fusion at the ipsilateral knee in the 91 tuberculous hips. The tibial epiphysis was involved in 26 patients and the femoral in 17. Both bones were affected in 14 cases, the tibia alone in 12, and the femur alone in 3. A central bulging defect was seen most commonly in the proximal tibia while in the femur a more fragmentary type of central physeal lesion was seen. Physeal growth of the normal limb was not unaffected. There was virtually no growth plate problem when the disease was <2 years of duration. The longer the disease had been present the greater the incidence of fusion such that in the 7 patients with a 10-year history of the disorder or longer each one showed premature fusion.

Sissons confirmed the histopathology of extreme osteoporosis in the knee joint region in eight cases of joint tuberculosis from amputation or postmortem specimens, three of which were studied in detail [120]. The osteoporosis appeared quite marked owing to removal of the transverse trabeculae making the longitudinal ones more prominent radiographically and involving also the subcortical bone adjacent to the articular surfaces and the bone in the neighborhood of the epiphyseal plates. He could not directly address the physeal cartilage since his studies were performed in young adults. The central tibial arrest led to a saucer-shaped conformation of the proximal tibial epiphysis and articular surface. Wilson and Thompson also commented on the negative effects on growth with tuberculosis of the hip [121]. They did note, however, that in relatively mild tuberculosis of the knee itself a growth stimulation sometimes occurred.

6.6.12 Premature Epiphyseal Fusion at the Knee Complicating Prolonged Lower Extremity Immobilization

Although premature epiphyseal arrest at the knee complicating prolonged immobilization of the hip for tuberculosis became a well-recognized clinical entity, in reality it was as much the prolonged immobilization as the tuberculosis itself which caused the disorder in the knee region. Subsequent studies showed that prolonged immobilization for many other hip disorders led to the same negative sequelae including such conditions as septic arthritis, chronic osteomyelitis, and slipped capital femoral epiphysis treated with casting. Negative sequelae have been described with prolonged immobilization for congenital dislocation of the hip by Kestler [122], and Botting and Scrase [123]. These negative sequelae occur with treatments in abduction splints in recumbency or with hip spicas for 12 months or longer. With prolonged immobilization, the disorder appears related to severe osteopenia such that even minor trauma can lead to transphyseal injury followed by linkage of the epiphyseal and metaphyseal circulations leading to bone bridge formation.

Ross also pointed out the occurrence of distal femoral and proximal tibial premature growth plate closure in association with prolonged disability of an extremity where the site of pathology was well away from the epiphyseal areas that subsequently fused [124]. He studied 13 patients, 9 of whom had tuberculosis of the hip with the others suffering from septic arthritis of the hip, slipped capital femoral epiphysis, polio, and osteomyelitis of the femoral shaft. Both epiphyses at the knee can be involved or there can be involvement of either distal femoral or proximal tibial regions alone. When the distal femur was involved, there was a high tendency for closure to occur centrally in almost all instances leading to the inverted V appearance of the physis and increased angulation of the intercondylar notch area. In the proximal tibia, peripheral fusions occurred more frequently than central fusions. The proximal fibula was not affected in any instance. Post-immobilization epiphyseal fusion occurred after extremely long periods of cast or splint protection of the limb, especially in comparison to current treatment protocols. In general, the immobilization was >1.5 years. Examples from the case reports indicate the following

periods of immobilization: 2 years and 10, 16 months (plaster cast), intermittent immobilization of the lower extremity for 3 years between 3.5 and 7.5 years of age, immobilization in plaster between the ages of 6 and 9.5, 4.5 years (plaster cast) immobilization during the period of rapid growth with weight bearing not allowed until the age of 13.5 years, a long leg brace between the ages of 6–8 years, 1 year, and 11 months (plaster cast), 7.5 months (plaster cast), and plaster immobilization between the age of 4–7 years.

In those patients where radiographs of the knee region were available during the course of the disorder, one of the early changes of developing growth disturbance was thinness of the physis and a transverse zone of dense bone on its metaphyseal aspect which would indicate a Harris arrest line. The growth retardation scars were numerous and osteoporosis of the regional bone was pronounced. The contour of the epiphyseal cartilage was irregular. Bony bridges were then noted to cross the physis. At the distal end of the femur, the point of arrest was commonly posterior to the central portion of the disk leading to a flexion deformity as well as shortening. At the proximal tibia, the arrest was often in the posteromedial quadrant leading to a tibia vara deformity. The tibial tubercle was sometimes the site of premature union leading to genu recurvatum. Histologic examples of transphyseal bone bridge formation were found. Cartilage from the physis showed fibrillation, disorganization, and shortening of the cartilage cell columns and diminution of endochondral growth. Histologic studies from the fibula showed normal physeal cartilage. The osteoporosis led to inappropriate support of the physis and with any weight-bearing transphyseal injury was prone to occur. The interpretation that weight bearing played a major role in causing further damage is supported by the fact that the proximal fibular physis almost invariably remained intact and continued to grow. This physis would clearly have been subject to the same immobilization osteopenia but as it is a nonweight bearing structure no negative sequelae occurred.

6.6.13 Osteomyelitis

Both overgrowth and growth retardation can occur in long bones that are the site of osteomyelitis. Growth changes in osteomyelitis vary depending on whether the infection is controlled in the acute phase or whether it persists as a subacute or chronic osteomyelitis [125, 126]. In addition, the precise site of the infection dictates the growth sequelae. If it traverses the physis, then premature growth retardation occurs leading to a shortening; whereas, if it remains in the diaphysis and metaphysis juxtaposed only to the physis, then the hyperemia leads to a growth stimulation with maintenance of physeal function. Pandey et al. have pointed out the change over several decades in growth phenomena related to osteomyelitis [127]. In the preantibiotic era, physeal damage with growth retardation was common; afterward, the disorder was better controlled although often not eradicated quickly, such that periphyseal hyperemia persisted and overgrowth predominated. Hentschel pointed out in as early as 1908 that osteomyelitis of the proximal tibia in the growing child could interfere with growth [128]. In a series of growing bones affected by osteomyelitis, Speed noted instances of both shortening and lengthening of the affected bone [129]. Another observer also was noted to have a case where osteomyelitis in a growing child led to 1.5 in. overgrowth. Speed pointed out that acute inflammation either arising directly in the epiphyseal area or spreading by continuity from the diaphysis could damage and destroy physeal cells leading to growth arrest problems. The associated thrombosis served to damage further the blood supply to the growth regions. Depending on the extent of the physeal damage there would be either complete stoppage of growth or uneven growth resulting from focal physeal destruction. If it became clear that the damaged epiphysis had ceased all growth and was no longer functional, Speed referred to the possibility of excising the contralateral epiphysis to stop its growth and thus limit any further worsening of the discrepancy.

In a subsequent work, Speed commented on specific instances of overgrowth of a long bone owing to stimulation of the epiphyseal cartilage by inflammatory processes [130]. He recognized that there was an actual stimulation of growth and that the increased length was not due to a delay in closure of the involved physis. He presented one case with chronic osteomyelitis which began at 6 years of age and persisted throughout the growing period. In adulthood, the involved side was 2 1/4 in. longer with 1 3/4 in. increased length in the infected tibia. One inch of overgrowth was noted in a chronic instance of osteomyelitis of the tibia in a 5 year old. Speed was one of the earliest to note that overgrowth of long bones could follow infections of those bones, in particular where the infection did not directly involve the epiphyseal region. He pointed out that patients should be warned that after infectious disorders of a long bone either shortening or overgrowth could occur.

Wilson and McKeever studied bone growth disturbances in 85 cases of osteomyelitis in the preantibiotic era [95]. They also noted that both lengthening and shortening could occur after such infections in a growing bone. The onset of infection in all their cases was prior to 12 years of age. Shortening of the bones was noted in 18 of 85 infections (21.2 %). The focus of osteomyelitis which caused interruption of growth was always located in the metaphyseal–diaphyseal region adjacent to the physeal cartilage. Serial radiographs showed the epiphyseal line to be interrupted, narrowed, and eventually prematurely closed in many. The amount of shortening ranged from 1.0 to 4.0 cm although

there was one case where 6.0 cm of shortening occurred in a distal femur although the infection there was complicated by a pathologic fracture. The amount of shortening would be dependent on the extensiveness of the growth arrest and the age of its occurrence. Fifteen of the 18 episodes of shortening occurred in the femur, tibia and humerus and the mean amount of shortening in these 3 bones was 2.6 cm. Lengthening of the involved bones, however, occurred to the same extent with 18 of 85 infected bones (21.2 %) showing an increase in length of the involved bone. Infection in all patients with bone lengthening was located in the metaphysis and diaphysis but not necessarily immediately adjacent to the physis. Lengthening occurred in the 18 instances in osteomyelitis of the femur, tibia, and humerus. The range of lengthening was between 1.0 and 3.0 cm except for one instance of a 5.0 cm lengthening which appeared somewhat usual. When that single case was eliminated, the 17 instances of overgrowth had a mean of 1.74 cm per bone.

Trueta and Morgan performed a long-term assessment of the late results in the treatment of 100 cases of acute hematogenous osteomyelitis shortly after the introduction of penicillin [131]. The earliest studies of the antibiotic era soon began to show that shortening was becoming much less common than previously. They noted seven instances in their series and in each it was due to primary epiphyseal damage usually in infants. Increased growth in length of the affected bones, however, was common and 32 cases demonstrated lengthening although in no case was the increase more than 2.0 cm. They felt that the increase was due to the increased vascularization of the periphyseal area following the damage of the nutrient vessels by the infectious process. Overgrowth following osteomyelitis lasted until medullary recanalization had occurred, a type III pattern in our classification, by which time the sequestra would have been resorbed and more normal vascular patterns would have been established [131, 132]. In chronic recurrent osteomyelitis of childhood, however, overgrowth will persist until the inflammatory focus is totally eradicated. With the increasingly widespread use of chemotherapy such as sulfathiazole after 1941 and penicillin after 1946, the mortality from osteomyelitis dramatically diminished as did many of the bone deforming complications in those who survived.

Patients with infantile osteomyelitis, within the first 3 months of life, continue to have serious bone sequelae. These were well illustrated by Roberts who documented the long-term disturbed epiphyseal growth at the knee after osteomyelitis of the distal femur or proximal tibia in infancy [133]. The distal left femur was involved in 13 and the proximal tibia in 2. In many instances in the distal femur, the physis and epiphysis were not affected equally across the diameter of the bone and severe varus or valgus malformation occurred. Multiple osteotomies may become needed along with attention to the length discrepancy. The lower extremity length discrepancies are of great magnitude owing to the early stage at damage and the fact that the majority of lower extremity growth occurs at the knee region. In the 15 patients followed either to skeletal maturity or into the second decade of life, the maximum discrepancy reached had a mean of 8.1 cm with a range from 1.0 to 14.0 cm.

6.6.14 Meningococcemia

Meningococcal septicemia associated with necrotic purpura, cardioshock, and neurologic signs is a relatively rare infectious disorder which usually requires intensive resuscitation. The patient can usually be stabilized medically but a serious complication of disseminated intravascular coagulopathy (DIC) can lead to ischemic lesions often with necrosis and on occasion full gangrene of the extremities. Once the initial and intermediate symptoms are stabilized, there is frequently evidence that a growth disturbance of the physes of several lower extremity bones has occurred secondary to emboli of the epiphyseal vessels directly linked to the DIC state.

Formal recognition of the late sequelae of meningococcemia on physeal growth came with two papers documenting the phenomenon. Fernandez et al. [134] reported on three patients developing epiphyseal–metaphyseal abnormalities limited to the lower extremities in multiple joints while Patriquin et al. [135] described growth-related physeal changes in four children where development of such lesions had been clinically unsuspected at the time of disease occurrence. Several years after the septicemic event, premature fusion of part of several physes with subsequent shortening and angular deformity were noted. Frequently, central physeal fusions resulted in a cone-shaped epiphysis. Robinow et al. also reported partial destruction of the right humeral and right femoral head and physeal regions in a 30-month-old girl 2 years after recovery from meningococcal septicemia and DIC [136]. There were also symmetrical epiphyseal–metaphyseal lesions of the lower femoral, and upper and lower tibial physes. The disorder was characterized radiographically by progressive narrowing of the physis which could be either uniform across the entire extent or focal, and many of the focal deformities tended to be centrally situated (Fig. 6.11).

A report from the University Hospital of Geneva, Switzerland assessed 46 patients with meningococcemia with an average age of occurrence at 4.5 years [137]. Twenty-six of the patients required immediate resuscitation in the intensive care unit and 15 of these subsequently died. Most of the survivors had serious complications involving cutaneous necrosis and four instances of gangrene of the upper and lower extremities. Two suffered serious bone growth disturbance due to partial or complete ischemic destruction of the physis with DIC. The negative growth sequelae usually did not

Fig. 6.11 Radiograph of bone bridge formation following meningococcemia of infancy. X-ray at 7 years of age shows the central bone bridge clearly

manifest for 1–2 years postinfection. They involve shortening of the affected limb and frequently angulation owing to asymmetric involvement. Radiographs will show generalized narrowing of the physis in the more severe instances although often a transphyseal bone bridge forms with the rest of the physis continuing its growth.

O'Sullivan and Fogarty reported two distal tibial physeal arrests as complications of meningococcal septicemia which occurred initially in a 2.6-year-old boy and in an 18-month-old boy [138]. The first patient returned at 8.5 years of age with a short leg and deformed ankle while a diagnosis of growth abnormality was made 1 year postinfection in the 18-month-old boy. The fibula was unaffected.

Monsell et al. reviewed 10 patients (14 ankles) with angular deformity of the ankle due to distal tibial physeal arrest as a late consequence of meningococcal septicemia. The distal fibular epiphysis was unaffected (in 13 of 14) and continued growth led to varus deformity [139].

Barre et al. documented epiphyseal and physeal abnormalities following meningococcal sepsis and disseminated intravascular coagulation [140]. They also reviewed three papers from the literature with the four works comprising nine patients. In each instance, there was no evidence of bone or joint sepsis during the period of hospitalization and the acute phase of the disorder. The changes became evident relatively late, anywhere from 4 months to 6 years after the septic episode. In these four studies, the patients were young averaging a mean age of 14 months with a range from 2 weeks to 48 months and had meningococcemia, with or without meningitis, complicated by septic shock and DIC. The skeletal abnormalities were of the epiphyses and physes and involved angular deformities and lower extremity length discrepancies. Involvement of the upper extremities was rare. The late radiographic changes appeared either as destructive of the secondary ossification centers reminiscent of avascular necrosis or involved epiphyseal–metaphyseal defects by which is meant narrowing of the physis usually in an asymmetric fashion or with premature central physeal closure that produced cupping or peaking of the metaphyseal regions and often transphyseal bone bridge formation. Involvement has been reported at the proximal capital femoral growth plate epiphysis leading to a coxa vara deformity, the distal femoral epiphysis where central involvement often leads to the inverted V appearance, the proximal tibial physis where central involvement was relatively common, and the distal tibial epiphyses where asymmetric involvement frequently led to varus or valgus deformation. In those instances where the lesions were bilateral, length discrepancy was either not present or was minor. Owing to the age of the patients at the time of infection major discrepancies have been reported in particular where involvement is at the knee and is associated with a bone bridge which often can extend to involve almost the entire physis.

Belthur et al. described 24 children (aged 1.3–11 years) seen in their facility in an 11-year period with orthopedic sequelae of meningococcal septicemia. The median time to presentation was 32 months (12–119) post-sepsis with angular deformity and limb length discrepancy due to partial growth plate arrest the main problems. Multiple growth plate involvement occurred in 14 children. The lower limbs were much more affected then the upper and angular deformity at the knee was common. Recurrence of deformity after osteotomy pointed out the need to assess and treat the physes (generally completing the arrest by epiphysiodesis) when correcting the angular deformities [141].

6.6.15 Physeal Damage Following Irradiation for Childhood Tumors

Limb length inequality remains a fairly frequent occurrence following radiation therapy in childhood for malignant tumors of the lower extremities and also for those of the kidney, abdomen and pelvis. Robertson et al. documented lower extremity length discrepancy in 12 of 67 patients

treated in childhood by radiation therapy in the above-mentioned regions [142]. The use of high dosage and early age of treatment correlate with the severity of the growth complications.

The more common tumors were Wilm's tumor, acute lymphocytic leukemia, non-Hodgkin's lymphoma, Ewing's sarcoma, Hodgkin's lymphoma, and rhabdomyosarcoma. No lower extremity length discrepancies were noted in any child who had symmetric radiation to the abdomen or pelvis. If the primary tumor was in tibia or femur, limb length inequality developed frequently. It also developed where there were asymmetric irradiation fields to the abdomen, kidneys, or pelvis. Limbs were equal where the radiation dose was <2400 cGys whereas length discrepancy was quite common in those where the mean level was between 4,000 and 5,000. The development of lower extremity length inequality was uniformly related to long bone physeal irradiation of 4,500 cGy or greater. Of the 12 children who developed lower extremity length discrepancies as assessed at skeletal maturity 5 had length discrepancies of 2 cm or less while 7 of the patients developed length discrepancies ranging from 2.5 to 9.0 cm.

Katzman et al. pointed to the many skeletal abnormalities in patients undergoing radiation therapy in the childhood years [143]. They assessed material from 19 survivors of 51 patients with Wilms' tumor and 13 survivors of 46 patients with neuroblastoma treated partially or completely with radiation. Epiphyseal damage was common. Although limb length discrepancy and long bone deformity were noted, no detailed analysis of these particular parameters was performed. Lewis et al. studied longer term morbidity in 55 patients with Ewing's sarcoma who survived 2 years or longer [144]. The dose level required to treat the tumor effectively with a minimal likelihood of recurrence is very close to the dose level that severely damages or destroys physeal cartilage. The length discrepancy is also dependent on the age of treatment and the region affected. In those patients who received <5,000 rads, 18 or 64 % had minimum or moderate morbidity. A dose of 5,000 rads was insufficient to ablate reliably a primary tumor with many at that level showing recurrence. The intermediate dosage level of 5,000–6,500 rads was most effective in terms of tumor ablation although at the higher levels the skeletal morbidity was proportionately increased. All patients had some degree of morbidity. Those defined as having minimal problems had <4 cm of shortening along with joint flexion deformities and muscle atrophy and fibrosis causing only minor limitation of activities. In the moderate group, shortening was defined as from 4 to 8 cm. In the severe group, gross shortening was present which could not be compensated for by epiphyseal arrest of the opposite extremity.

Dawson described the orthopedic problems with skeletal radiation for various lesions in 35 children. Anisomelia or lower extremity length shortening was present in 8 of 9 receiving abdominal, 1 of 2 receiving pelvic, and 6 of 7 receiving lower extremity irradiation [145]. There is an extremely long history of awareness of the negative effect of radiation therapy on epiphyseal function dating back to works of Perthes in 1903 [146]. The effects of radiation therapy on bone growth were well reviewed by Probert and Parker [147].

6.6.16 Fractured Femoral Diaphysis

6.6.16.1 Femoral Overgrowth in the Era of Conservative, Non-operative Treatment

The stimulation of femoral growth after a diaphyseal fracture in children who were 2–11 years old and were treated nonoperatively was well documented. It appeared to be an obligate phenomenon and occurred regardless of whether a fracture had healed with an overlap, end to end, or in a lengthened position, or whether it occurred in the proximal, middle, or distal third of the femur. The average femoral overgrowth from the time of fracture-healing in the series from Children's Hospital, Boston was 0.92 cm (range 0.4–1.8 cm) [148]. All patients were treated nonoperatively by a combination of skeletal traction and casting. Ipsilateral tibial overgrowth, averaging 0.3 cm, occurred in 82 % of the patients. Seventy-eight percent of the overgrowth had occurred by 18 months after injury. In 85 % of the patients, the overgrowth had terminated at an average of 3 years 6 months after fracture. The overgrowth phenomenon manifested itself as the type III slope–plateau pattern in 108 (93 %) of the patients, with the limb length discrepancy remaining unchanged throughout the remainder of growth (Fig. 6.12). If a fracture heals at length or with lengthening, the overgrowth produces an upward slope–plateau pattern. If a fracture heals with shortening, the overgrowth leads to a downward slope–plateau representation. A type II pattern occurred in eight patients whose fractures had healed with

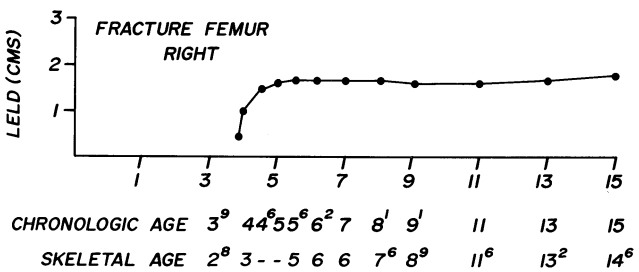


Fig. 6.12 Type III in the developmental pattern classification is shown in this example of length discrepancy following a fractured femur and healing associated with overgrowth (Reprinted with permission from Shapiro F, Developmental patterns in lower extremity length discrepancies. J Bone Joint Surg Am 1982;64A:639–651)

excessive angulation. In these, continuing overgrowth presumably occurred due to the prolonged remodeling process.

The Children's Hospital, Boston study assessed femoral and tibial growth after femoral diaphyseal fractures treated conservatively using orthoroentgenograms for documentation [148]. Methods of treatment for these fractures by traction and hip spice casting had been described by Griffin et al. [149]. A detailed review of the length discrepancy findings follows [148].

Level of overgrowth: In the entire group of 116 patients, 63 % of the fractures occurred in the middle third of the femur, 28 % in the proximal third, and 9 % in the distal third. In the 74 patients studied in greater detail, a similar distribution was seen with 66 % in the middle third, 27 % in the proximal third, and 7 % in the distal third. The site of fracture was similar regardless of age or sex.

Extent of femoral overgrowth: In the 74 patients with initial radiographs within 3 months of fracture, overgrowth of the fractured femur occurred universally. The average femoral overgrowth in all cases from the time of healing onward was 0.92 cm. The extent of overgrowth was not dependent on sex, age at the time of fracture, the position of healing, or the level of fracture. The 74 completely documented patients with fractured femurs were studied prospectively solely on the basis of having had a femoral shaft fracture.

Temporal aspects of the overgrowth phenomenon: Two patterns of overgrowth were seen. In the more common pattern, overgrowth continued after fracture healing for a limited time period, then ceased with no change in discrepancy throughout the remainder of skeletal growth. This is referred to as the plateau pattern or plateau phenomenon. Much less frequently, overgrowth continued until skeletal maturity although at a much slower rate after the first 18 months following fracture. In the group of 74 patients with early and continuing documentation of lengths, 92 % (67/74) showed temporally limited overgrowth (plateau pattern) while 9 % (7/74) continued overgrowth with time. In the entire group of 116 patients, 93 % (108/116) demonstrated the plateau phenomenon while 7 % (8/116) persisted in overgrowth. In the 74 completely studied patients, 64 % of the documented femoral overgrowth occurred within 9 months of healing (1 year postfracture). By 1.6 years, postfracture overgrowth was complete in only 12 %; by 2 years it was complete in 45 %; by 2.6 years it was complete in 45 %; by 3 years in 77 %; by 3.6 years in 85 % and by 5.9 years in 91 %. Premature epiphyseal closure on the fractured side with a late change in discrepancy did not occur.

Tibial overgrowth: The tibia on the side of the fractured femur increased in length from the time of femoral fracture healing such that at skeletal maturity 82 % of patients had slightly longer ipsilateral tibias. In 13 %, tibial length was equal and in only 5 % was the tibia on the contralateral, nonfractured side longer. The average tibial discrepancy was 0.29 cm longer on the ipsilateral side (range 0.1–0.5).

Epiphyseal arrest: In the group of 116 patients, 28 underwent epiphyseal arrest. The average preoperative discrepancy was 2.39 cm (range 1.7–3.4). The discrepancies occurred as a combined result of overgrowth and healing in anatomical or slightly distracted position. The average discrepancy postepiphyseal arrest at skeletal maturation was 0.66 cm (range 0–1.5) with 86 % of those operated showing a discrepancy of <1.0 cm. Five of the 28 patients requiring epiphyseal arrest had continued to increase their discrepancy with time due to continuing stimulation on the fractured side.

Martin-Ferrero and Sanchez-Martin studied femoral overgrowth in 71 patients under the age of 14 years [150]. All patients had been treated in various forms of traction except for a hip spica cast which was applied immediately after fracture in 7 %. Each had an isolated unilateral femoral shaft fracture. Femoral overgrowth averaged 0.86 cm (0.1–2.1 cm). They felt that the greatest amount of overgrowth occurred in those between 3 and 9 years of age who had had the most severely displaced fractures. Ipsilateral tibial overgrowth occurred in 60 % and averaged 0.1 cm. Most of the overgrowth occurred during the first year after fracture but continued to a lesser extent during the second year and for as long as the fifth year postinjury in 27 %. After this time, the growth rate of both femurs was equal in all. These values were remarkably similar to those from the Children's Hospital, Boston study.

Reynolds studied growth rate changes after fractures of the shaft of the femur and tibia in children using serial radiographic measurements of length accurate to the nearest millimeter [151]. The fractures were all treated by conservative nonoperative methods with no attempt made to achieve anatomical reduction. The increased growth rate postinjury was greatest within 3 months of injury and was 38 % in excess of normal with both femoral and tibial fractures. The rate then decreased but remained significantly raised for 2 years returning to normal in the tibia approximately 40 months after injury, and in the femur between 50 and 60 months after injury. In unilateral femoral fractures, the uninjured tibia in the same limb also underwent an acceleration of growth but to a much lesser degree. An uninjured femur was not particularly affected by fracture of the ipsilateral tibia. Reynolds concluded that the acceleration in growth of the fractured bones reached a maximum between 3 and 6 months after injury with subsequent acceleration decreasing and the growth rate returning to normal between 3 and 5 years after injury. He felt that significant measurable overgrowth ceased within 2 years after fracture of the femur and within 1.5 years after fracture of the tibia. The observations of greatest value were on 55 children with tibial fractures and 32 with femoral fractures

followed for between 2 and 5 years. The average increase in femoral length was 0.7–0.8 cm (range 0.1–1.7 cm) and every femur exhibited some increase in the growth rate. The average increase in the tibia was 0.3–0.4 cm (this for actual tibial fractures) with a maximum of 1.1 cm. Overgrowth occurred in all except three.

Stephens et al. studied leg length discrepancy after femoral shaft fractures in children and assessed 30 skeletally mature patients [152]. All patients were treated conservatively in skeletal traction. Only isolated closed femoral shaft fractures without other injury to the limbs were assessed. When the fracture had occurred between the ages of 7 and 13 years, the limb overgrew about 1 cm regardless of sex, age, fracture site, or configuration. They recommended that treatment aim for 1 cm of overlap at union to compensate for the post fracture overgrowth phenomenon. Treatment was either by skeletal or skin traction for an average of 6 weeks followed by a spica plaster or cast brace. The average tibia overgrowth was 0.18 cm. After fracture at 7–13 years of age, limb overgrowth averaged 1.1 cm (range 0–2.4 cm). Since tibial overgrowth accounted for only 20 % of the total, the average femoral overgrowth was 0.92 cm.

Hougaard performed a prospective study of the overgrowth phenomenon after femoral shaft fractures in 67 children using radiographic measurements of both lower limbs at 6 weeks and 6, 12, and 24 months postinjury [153]. Mean femoral overgrowth was 10.6 mm with largest 26 mm. There was no relationship between shortening at the time of healing and sex, age, type of fracture, level of fracture, and the magnitude of overgrowth 2 years later. Angulation itself caused some shortening.

The overgrowth phenomenon and its extent with conservative, nonoperative treatment of femoral diaphyseal fractures in childhood has been well documented. In large numbers of patients studied by radiologic measurements, Hedberg [154] demonstrated overgrowth in 86 % (38/44); Aitken [155] documented overgrowth in all fractured femur patients but one (64/65), and Viljanto et al. [156] documented overgrowth in 50 out of 51 patients over 2 years of age. The average documented femoral overgrowth in the Children's Hospital, Boston series was 0.92 cm which compares well with Viljanto et al. [156], 1.07 cm; Aitken [155] 1 cm from position on discharge; Hedberg [154], 0.9 cm; Martin-Ferrero and Sanchez-Martin [150], 0.86 cm; Reynolds [151] 0.7–0.8 cm; and Stephens et al. [152] 0.92 cm. The same average amount of overgrowth occurred regardless of the age at fracture when the patient group was divided into the age brackets 2–4 years, 5–7 years, and 8–12 years. Hedberg [154] and Staheli [157] noted slightly greater overgrowth in those 4–8 years of age and 2–8 years of age, respectively, but Viljanto et al. [156] found no statistically significant difference in average overgrowth in those <3 years old, 3–9 years old, and more than 9 years old. Overgrowth also occurred regardless of whether the fracture had been allowed to heal in a shortened position, at length, or in a lengthened, distracted position. This is an important finding as regards the cause of overgrowth and is in agreement with Staheli [157] and Viljanto et al. [156]. Overgrowth did not appear to be influenced by whether the fracture was in the proximal, middle, or distal third. Because of the large size of this series and the accurate method of assessment using frequent orthoroentgenograms, these data appeared to reflect the actual situation more closely than studies which rely on clinical measurements or less accurate radiologic measurements. Truesdell, in one of the earliest documentations of the overgrowth phenomenon, noted that overgrowth occurred whether the fracture was in the upper, middle, or lower third of the femur [158]. Similar overgrowth regardless of level disagrees somewhat with the opinion of Staheli [157] who felt that proximal fractures demonstrated more overgrowth but is consistent with the work of Viljanto et al. [156].

6.6.16.2 Physiological Consideration Underlying the Overgrowth Phenomenon

The overgrowth phenomenon was recognized as early as 1867 by Ollier [159] and received ample documentation in the early 1900s [160–162]. Increased blood supply to the healing bone was felt by Ollier [159], Levander [163], and Bisgard [164] to be the primary cause of the overgrowth. Although there was early disagreement as to the cause of the phenomenon with some attributing it either to "young bone yielding to pull" as the shortening corrected itself [161] or to a law of compensatory overgrowth [162], most investigators eventually considered the overgrowth to be a physiologic process [165] associated with the increased vascularity of the involved bone owing to healing and remodeling. The increased vascularity extends to the epiphyseal plate regions where the overgrowth stimulus occurs. This now appears amply confirmed especially with the demonstration that overgrowth occurs regardless of the position of fracture healing and that it occurs in all patients treated nonoperatively thus indicating that it is an obligatory phenomenon rather than one called into play only to compensate for shortening. In addition it has been demonstrated to occur with humeral [166] and tibial [167] fractures. Kellernova et al. demonstrated increased vascularity to the entire limb following experimental tibial fracture using venous occlusion plethysmography [168]. The tibial overgrowth documented postfemoral fracture also provides evidence for a total limb response. Increased length of the ipsilateral tibia averaging 3 mm in 82 % of the patients with only 5 % showing a longer contralateral tibia is taken as presumptive evidence of overgrowth in association with femoral fracture.

Such tibial overgrowth was also documented by Stephens et al. [152] 0.18 cm, and Martin-Ferrero and Sanchez-Martin [150] 0.1 cm.

The frequent length assessments and the accuracy of the orthoroentgenographic method in the Children's Hospital, Boston series have allowed for detailed study of the temporal aspect of overgrowth. The impression that most of the overgrowth occurs within the first year of fracture and that it is virtually complete by 18 months is valid but it is demonstrated that the overgrowth phenomenon can persist for 3 or 4 years and, more importantly, in 7–9 % of patients it continues for the remaining period of skeletal growth [160, 162, 165]. Prolongation of overgrowth beyond 18 months or 2 years has been alluded to by Hedstrom [166] and Viljanto et al. [156] on the basis of remodeling which can continue for that period of time. These two findings are important in following children with femoral fractures especially if they have been allowed to heal at length or with some distraction.

In the eight patients whose overgrowth continued, assessment following fracture demonstrated overgrowth averaging 1.98 cm in contrast to the entire group which averaged 0.92 cm. The overgrowth 18 months following fracture was only 39 % in comparison to the overall group where 78 % of overgrowth had occurred by that time. Overgrowth was continuing 8 years postfracture in these patients. Five of the 8 had a discrepancy sufficiently large to require epiphyseal arrest. In four of the eight patients, no unusual factor could be identified which might have contributed to the continuing overgrowth but in four of the patients hyperemic stimuli may well have persisted owing to excessive angulation prolonged the remodeling phase and one had myositis ossificans which also is associated with an increased blood supply.

During the early weeks of fracture healing there is slight motion at the fracture site and it was neither feasible or necessary to perform accurate orthoroentgenographic length measurements. There is no accurate radiographic documentation of the lengths prior to fracture: Barford and Christensen in a clinical study of 431 normal children found 8 % with unequal length of the lower limbs although only 0.7 % had a 1 cm or more difference [169]. These limitations in all clinical studies have been discussed in detail [166]. Both Hedstrom [166] and Bisgard [164] attempted to assess overgrowth from the time of fracture in experimental animals. It is unknown, however, whether the vascular response begins simultaneously throughout the whole extent of the femur or whether it spreads from the fracture site toward the epiphyses. If the former mechanism occurs, then overgrowth would probably be somewhat greater as it would begin earlier; if the latter, overgrowth may well represent primarily a postconsolidation repair and remodeling phenomenon.

Wessel and Seyfriedt reviewed 221 patients regarding leg length discrepancy whose treatments were divided closely between nonoperative (123) and operative (98) methods [170]. Those in the nonoperative group were treated by skin traction (96), skeletal traction (11), and immediate cast bracing (16). Most of the operative patients were treated by intramedullary nailing (59) or plate fixation (34). A total of 127 patients were followed to skeletal maturity allowing for accurate length discrepancy determination. Of the 127, a leg length discrepancy of 10 mm or more was documented in 45 (35 %). Shortening was seen in 7 (mean 14.3 mm, range 10–30) and lengthening in 38 (mean 14.1 m, range 10–25). Overgrowth was most extensive with fracture in the 4–9 year old group. Plate fixation was most commonly associated with increased length. Several cases (7) continued to increase the length discrepancy more than 2 years posttraumatically.

Over the past two decades widely adopted treatment methods for femoral diaphyseal fractures include a Pavlik harness for infants up to 6 (or 18) months of age, immediate hip spica casts, or operative intervention (especially after 6 years of age) using such methods as external fixation, intramedullary nailing with either a rigid interlocking rod or two flexible intramedullary nails, or plate fixation using either a traditional compression plate or a submuscular locking or nonlocking plate. The implications of these treatment methods for eventual femoral length are reviewed.

6.6.16.3 Nonoperative Treatment: Newborn to 6 Years of Age

At present, skeletal or skin traction is infrequently used in patients with femoral diaphyseal fractures from birth to 6 years of age. Femoral length and position of healing must still be carefully considered regarding long-term length discrepancies.

(i) *Pavlik harness*: Femoral shaft fractures for infants up to 6 months of age are increasingly treated with a Pavlik harness. Some report such treatment up to 18 months of age. No clinically significant problems were reported in the initial use of this method by Stannard et al. in 16 fractures sustained between birth and 18 months [171]. In a subset of 11 fractures followed for 12–30 months (mean 20 months), all fractures healed in good alignment with leg length discrepancies <1 cm by clinical measurements. This approach is now most common from birth to 6 months of age where shortening at the start of treatment and during the early stages of consolidation is <2 cm.

(ii) *Immediate hip spica cast*: This is generally used from 1 to 6 years of age. Some use the Pavlik harness up to 18 months and some use the cast until older ages but a consensus seems to indicate more problems in those

over 80 pounds weight treated by this approach. With the child under general anesthesia longitudinal traction is applied to the fractured limb as a well padded, snug fitting cast is applied. Most seek to achieve restoration of length at time of cast application. Early spica casting is indicated for fractures with <20 mm of shortening desired by most. A single leg or 1½ spica can be used. Early spica casting is indicated for fractures with <20 mm initial shortening or for fractures that are held in cast after manual reduction with <10–20 mm shortening. Martinez et al. recognized that excessive shortening of the fragments could be a problem with early spica cast immobilization [172]. They reported that shortening >20 mm occurred in 43 % of 55 children 3–11 years of age. If detected early enough treatment in 10 was changed to skeletal 90–90 traction for a few weeks before resuming spica management and all healed with <20 mm shortening. Eleven patients did not have the shortening detected early enough and went on to healing with >20 mm shortening (range 24–35 mm, mean 28 mm). Analysis showed that excessive shortening in cast was considered to be >10 mm, and especially in older patients.

Buehler et al. also recognized that shortening of the femur was the most frequently reported complication of early or immediate spica casting treatment [173]. They felt that much of this problem related to the extent of soft tissue (muscle) injury and periosteal stripping at the fracture site. To assess this clinically they devised the "telescope test". With the patient anesthetized, gentle manual compression was applied to the distal femur along the longitudinal axis to document the amount of fracture overlap using standardized radiographs. The level of overlap was determined when a distinct endpoint of movement was reached. Acceptable shortening on the test was considered to be 5–15 mm. A 1.5 hip spica was applied if the overlap criteria were met; if not a period of skeletal traction was used to diminish the shortening and allow early callus to stabilize the position. Weekly standardized radiographs were done with overlap <25 mm during early callus formation considered desirable re subsequent length. Fifty patients underwent detailed study; 41/50 (82 %) had successful outcomes at healing (<25 mm shortening) and 9/50 (18 %) failed with >25 mm overlap at 4 weeks. The telescope test for those who failed spica casting was 37.2 mm. The authors determined that the most predictive level was above or below 30 mm. A negative telescope test led to a 95 % chance of successful early spica casting. A positive telescope test led to approximately 20 times the risk of failing with early spica. Expansion of the series to 100 patients found the earlier results accurate and reproduceable.

Thompson et al. extended this study a few additional years until it included 100 patients [174]. They determined that 81 % had an acceptable outcome and 19 % an unacceptable outcome by the definition of more than 25 mm of fracture fragment overlap after clinical healing. The telescope test had a sensitivity of 80 % and a specificity of 85 % for predicting outcome. The relative risk of failure of spica cast treatment with a positive telescope test was 20.4.

A large review of early spica casting by Illgen et al. further clarified the shortening phenomenon in 115 fractures [175]. The telescoping test was not used. Closed reduction under general anesthesia with application of a 1.5 hip spica was done. Average age was 3.2 years. A subset of 62 patients was seen at 18 + months (average 21 months). At presentation, shortening averaged 1.36 cm with 32 > 2 cm. Postreduction shortening averaged 0.55 cm with none >2 cm. At the time of union, the average shortening was 0.92 cm with 2 ≥ 2 cm. The degree of initial shortening was the most significant predictor or loss of reduction in cast. With the initial shortening of 0.5 cm, there was a 10 % probability of loss of reduction and progressively 1 cm about 14 %, 1.5 cm about 18 %, 2 cm at 26 %, 2.5 cm at 36 %, 3 cm at 48 %, and 3.5 cm at 60 %. They concluded that the early hip spica casting was warranted in children aged 6 years or less regardless of initial deformity, with the knee flexed in cast >50°, and preferably use of 90–90 "sitting" spica. An initial shortening of >2 cm was closely observed to make certain further length was not lost in the spica.

Ferguson and Nicol studied 101 femoral shaft fractures treated by early spicas in patients from 1 to 10 years of age [176]. The crucial time period for assessing shortening was 7–10 days. They accepted <2 cm of shortening, measured radiographically, to allow for continuation of spica management. If shortening was greater than this or other variables were beyond acceptable criteria, the patient was switched to other treatment methods. Initial shortening of <2 cm occurred in 71 fractures, 2–4 cm in 21, and >4 cm in 9 on initial radiographs. Four patients had casts removed at 7–10 days for shortness >2 cm and they were switched to traction. Excluding these, 90 patients at review had shortening <2 cm by scanogram. Of 17 patients 8 years and older, 5 had excess shortening while only 3 of the 81 up to 8 years had excess shortening. The authors demonstrated that in 98 of 99 fractures, the position accepted at 7–10 days after spica application was the position found 3–6 months postinjury. Since overgrowth was rarely as great as 2 cm, they subsequently accepted only 1.5 cm of shortening. Corry and Nicol reported a mean of 6.9 mm overgrowth (range 0.2–8.6 mm) in 50 femoral fractures as measured by scanograms at a mean of 3.9 years after fracture in children <10 years of age (at time of fracture) [177].

Infante et al. studied 175 patients (between 10 and 100 pounds) treated with immediate closed reduction and application of a well-molded hip spica cast under conscious sedation or general anesthesia [178]. With a minimum of 2 years postfracture follow-up, none of the children required external shoe lifts, epiphysiodesis, or limb lengthening for length discrepancy. They eventually recommended the immediate spica cast treatment from birth to 10 years of age for children who weigh <80 pounds. The ages of patients in Group 1 (10–49 pounds) was 1–6 years; Group 2 (50–80 pounds) was 7–11 years; and Group 3 (81–100 pounds) was 12–13 years. The average shortening at the time of fracture and after reduction and casting was 1.7 cm (range 0–3 cm) decreasing to 0.7 cm (0–2 cm); 1.5 cm (0–4 cm) decreasing to 1 cm (1–3 cm); and 2.1 cm (1–4 cm) decreasing to 0.9 cm (0–2 cm), respectively. Those with >2 cm shortening postcasting were re-reduced. Overgrowth corrected all slightly excessive (but <2 cm) discrepancies into a clinically acceptable range. Epps et al. noted shortening >2.5 cm in 5 of 45 patients during the course of casting but were able to correct the problem by altering the treatment in 4, although one proceeded to healing with a 2.6 cm leg length discrepancy by scanogram [179].

Shortening is therefore the main length discrepancy concern with immediate/early hip spica or Pavlik harness management. The use of 90–0 casts with the hip flexed 90° has minimized shortening. If early (1–2 week) shortening is measured radiographically with early cast treatment, most recommend to switch to skeletal traction to decrease the shortening to <2 cm for a few weeks until stabilizing callus is seen, after which casting is resumed. As long as shortening <1.5–2 cm is present at time of healing this method should give no long-term problem since overgrowth will further diminish the discrepancy.

6.6.16.4 Femoral Overgrowth in Relation to Operative Treatment for Diaphyseal Fractures

Even when virtually all femoral fractures in childhood were treated by nonoperative means, some centers used operative stabilization for certain subsets of patients. Efforts were made to document postfracture overgrowth in these patients. Viljanto et al. reported on growth responses following operative treatment of femoral shaft fractures in children [180]. During a 10-year period from 1957 to 1966 they treated 35 femoral shaft fractures (18 % of their patient population) by operative means and assessed 19 of these patients at skeletal maturity. The average age of the group at time of fracture was 9.8 years compared with 7.2 years in the group treated conservatively. The age range at fracture in the 19 patients undergoing assessment was from 2.6 to 16 years. Sixteen of the 19 patients demonstrated femoral overgrowth. One patient with a comminuted fracture lost 7 mm of length. The overgrowth phenomenon was demonstrated, however, even in those having surgical correction. The mean longitudinal overgrowth of the fractured femur treated by operation was 9.8 mm with a wide range from 0 to 30 mm. The corresponding group of 52 patients treated by traction and casting had an overgrowth of 10.7 mm. Slightly less overgrowth was seen in those treated with intramedullary nailing with the overgrowth value registering 7.2 mm while those treated with other means of osteosynthesis had a 13.5 mm overgrowth. In the 19 patients assessed intramedullary nailing with the Kuntscher nail was done in 7, intramedullary Rush rods in 4, cerclage wires in 3, screw fixation in 2, plate fixation in 2, and open reduction in 1. Walsh also found that the greatest growth stimulus was seen in cases treated by open reduction and internal fixation with an average stimulus of 9 mm [181].

Since the early 1990s there has been markedly increased use of operative treatment for childhood and early adolescent femoral diaphyseal and metaphyseal fractures. Currently, skeletal traction for several weeks followed by hip spica or long leg cast immobilization is infrequently used for these injuries. The matter of the overgrowth phenomenon remains important. In the previous era of traction/nonoperative treatment, bones were allowed to heal with 1 cm of shortening or overlap (bayonet apposition) in the expectation that remodeling and overgrowth would allow for normal length in the long-term. However, with operative intervention the fragments are positioned to heal at anatomic length (external fixation or open reduction and internal fixation). It was suggested that overgrowth would be markedly diminished in those with childhood femoral shaft fractures treated with external fixation or internal stabilization. The matter is of some importance since it will define the desired position of the bone fragments during healing. If the increased stability leads to more rapid healing and anatomic reduction favors less need for remodeling then stabilization at full length with anatomic reduction minimizes the need for long-term follow-up. If overgrowth occurs because of fracture itself, then anatomic reduction and either internal or external fixation would still lead to overgrowth.

(i) *External fixation*: The tendency is to report few problems with length discrepancy although many other problems related to the use of external fixators have limited its use for uncomplicated fractures. Hedin et al. studied 98 fractures treated with external fixation at a mean age of 8.1 years (range 3–15 years) [182]. Only 1 length discrepancy was >2 cm. A second paper from this group specifically assessed overgrowth after anatomical reduction and external fixation [183]. All 97 patients were followed by standardized orthograms for 1 year and a subset of 45 for 2 years postfracture. The

mean overgrowth was only 0.3 cm at 1 year and 0.5 cm at 2 years. They recommended fixing the fractures without shortening.

Blasier et al. wrote an excellent review of their experience (favorable) with use of external fixation for 139 femur fractures, mean age 9 years [184]. A small subset of patients followed radiographically for more than 2 years had lengths ranging from −7.7 to +8.7 mm. These indicated no discrepancy problems but did not comment on the overgrowth phenomenon in detail. Miner and Carroll noted variable length discrepancy from −2.1 to +1.8 cm but a high rate (21.6 %) of refracture in 37 cases [185].

(ii) *Intramedullary Fixation*:

(a) *Rigid rod*: Proximal to distal insertion of a rigid interlocking intramedullary rod in the growing child is limited to those older than approximately 11 years due to size considerations. Even in the older group, however, the main problem limiting use of this approach is the risk of avascular necrosis of the femoral head due to damage of the medial circumflex artery when placing the rod though the piriformis fossa [186]. This event has been minimized by an insertion approach through the tip of the greater trochanter but this can cause some damage to trochanteric growth. Raney et al. demonstrated five cases of growth damage to the greater trochanteric epiphyseal growth plate due to passage of a rigid single intramedullary rod in children 9–13 years of age [187]. This often resulted in a valgus femoral head and neck but without subluxation. Since the single rigid rod method tends to be used in older adolescent patients, often very close to skeletal maturity, overgrowth appears not to be a concern. Momberger et al. using a greater trochanteric starting approach at a mean age of 13.2 years (range 10–16) in 50 cases noted average leg length discrepancy of only 1 mm (range −10 to +11 mm) [188].

(b) *Flexible intramedullary rods*: Intramedullary fixation using two flexible rods became widely used for stabilization of childhood and adolescent femoral diaphyseal fractures in the mid 1980s. The approach referred to (in English) as elastic stable intramedullary pinning (ESIP) (or ESIN-nailing) was developed by Metaizeau and colleagues in Nancy, France using two flexible steel or titanium rods introduced in closed fashion via the distal metaphyseal region [189–191]. Treatment in the United States by Mann et al. [192] and Heinrich et al. [187] favored the use of the Ender nails. Excellent results overall, including reports of minimal to no problems with length discrepancy, led to wide adoption of the technique which continues to the present time. The method is sufficiently stable to allow the child to be mobilized early but without casting but still allows for relatively abundant external callus. The approach requires end to end reduction/apposition at full femoral length for stabilization. The method is now commonly used for children 6 years old or older with fractures in the middle 2/3rds of the femoral diaphysis. Some use it for younger children, incorporating only one rod if the canal is too small for two. Care must be taken to prevent distraction at the fracture site (lengthening) or excess shortening with badly comminuted fractures.

Ligier et al. documented 123 femoral fractures treated at a mean age of 10 years 2 months (range 5–16 years) by the ESIN method using rods of 3.0, 3.5 or 4.0 mm diameter and made of steel or titanium [190]. Length assessments using radiologic documentation were done in 62 cases followed for at least one year (mean 1 year 10 months). A mean femoral lengthening of 1.2 mm was noted. In 29 simple transverse fractures, the mean lengthening was 2.06 mm, but there were four cases of lengthening of more than 10 mm (11, 15, 17, and 23) and three of shortening >10 mm (15, 15, and 13). The range in spiral fractures was −12 to +17 mm. The study did not assess overgrowth as a phenomenon but included final length in effect which combined healing in a shortened or lengthened position as well as any overgrowth. Regardless, only 2 of the 62 cases (3.2 %) required eventual epiphysiodesis for discrepancies of 23 and 20 mm. Stabilization was provided by the two elastic nails themselves (internal elastic support) but also by the bone (cortical end-to-end reduction) and surrounding muscles [189–191]. The elasticity, compared to rigid plate or single wide IM rod fixation, allows for some movement at the fracture site ensuring optimal development of the external callus by reducing shear and converting it into compression and traction forces. The fracture hematoma and the endosteal circulation remain intact.

Mann et al. used two Ender flexible nails in 16 femoral fractures in children 9–15 years of age [192]. Their impression of results was highly favorable. Regarding lengthening, “legs were clinically equal in all patients at a mean follow-up of 3 years 9 months (range 1½–7 years)”. A larger series by Heinrich et al. of 78 fractures treated by Ender nails at a mean age of 9 years (range 2½–18 years) also produced favorable results [193]. In a subset of patients followed for 12 months or longer 20 % had 8.5 mm average “overgrowth” (range 6–26 mm) and 14 % an average of 9 mm shortening.

Virtually, all studies of operative treatment of femoral fractures by intramedullary fixation mention length

discrepancies but there is variability in the findings which, to a great extent, represents extensiveness of efforts to document this component of childhood femoral fractures. Postfracture limb length discrepancy is fairly complex to study. Not all papers distinguish shortening from lengthening. Some use the term overgrowth when they appear to mean longer length. Increased length of femur postfracture can occur because of (i) healing in a lengthened position and (ii) overgrowth of the fractured femur mediated by increased blood supply to the entire bone stimulating proximal and distal physeal growth. Increased limb length also occurs with a few (2–4) mm overgrowth of the ipsilateral nonfractured tibia, a fact documented in studies of other treatment modalities. Also an unknown factor is slight prefracture length discrepancies in many normal individuals.

To accurately assess overgrowth postfemoral fracture treated by operative stabilization (external fixation, intramedullary rodding or diaphyseal plating), a study should mention length of follow-up postfracture, the extent of angular deformity, the quality of the reduction (anatomic, shortening, lengthening, translation), and the method of documenting length of the lower extremities (radiographic or clinical assessments). The length of follow-up is particularly important since overgrowth can continue as long as 2–3 years postinjury and even longer if angular deformity needs to be remodeled. Vierhout et al. specifically reviewed the long-term outcome of elastic stable intramedullary fixation (ESIF) of femoral fractures in children [194]. They assessed 71 of their own patients operated at 3–16 years of age in a prospective study for the purpose of evaluating leg length discrepancies. Two and half years postinjury, six showed a persistent LLD of more than 10 mm (range 10–25 mm) (with the fractured limb longer in all) and at 10 years the LLD persisted in five. They also reviewed 10 published papers regarding LLD in ESIF approaches. The findings were variable with six studies noting no cases of LLD > 1 cm but other studies reported excess lengths (>1 cm) in 4 % of 122 cases (Ligier et al.) [190], 10 % in 100 patients (Flynn et al.) [195], 14 % (Luhmann et al.) [196] and as high as >1 cm in 8 of 17 patients —47 % (Maier et al.) [197]. They stressed not only awareness of the length discrepancy following intramedullary fixation but also the need for long-term follow-up preferably until overgrowth stops.

Wright systemically and critically reviewed the treatment of childhood femoral shaft fractures in 2000 including assessing reports (15 studies) that compared the results of two or more forms of treatment [198]. While all of the common clinical parameters were assessed, leg length discrepancies >2 cm were seen in 3 % of early hip spica cases, 10 % of traction (with or without spica) cases, and 25 % of internal fixation cases (due to excess length).

Several series published since 2000 are reviewed below regarding LLD with intramedullary stabilization.

Cramer et al. in a subset of patients treated with Ender rods seen at least 1 year postsurgery (mean 20 months) and assessed by scanogram showed no clinically significant length discrepancy >2 cm [199]. The 22 patients had a mean of 7 mm lengthening (range 1–19 mm). All patients were between 5 and 14 years of age at surgery.

Ozdemir et al. found only an average lengthening of 1.8 mm (range 1–3) measured by scanogram 24 months after surgery using two Ender-like nails in children 6–14 years of age [200].

Houshian et al. reviewed 30 fractures treated with ESIN (2 rails) at a median age of 6 years (4–11 years) [201]. At 1–3 years follow-up, leg length discrepancy up to 1 cm was found in six legs.

Song et al. showed no discrepancy in 27 flexible retrograde nailings [202].

Oh et al. treated 31 femoral shaft fractures with retrograde flexible intramedullary nailing at a mean age of 6.7 years (5–10) years [203]. At a mean follow-up of 27 months, there was no limb length discrepancy exceeding 1 cm.

Ho et al. studied 94 flexible titanium intramedullary nails at a mean 8.6 years of age (range 3.2–15.1) with a mean follow-up of 13.7 months (0–56) [204]. The length discrepancy section of the study was limited by the relatively short follow-up and lack of clarity between shortening and lengthening. They did indicate that lengthening of the fractured side was more common. Subjects assessed were not clearly defined. Eleven patients (12 %) had total limb discrepancy >1 cm at 12 months.

Salem et al. assessed 68 femoral and 5 tibial fractures treated by ESIN at a mean age of 5.7 years (range 1.9–11.5) [205]. There were nine patients with length discrepancy >10 mm. Some were shorter and some longer but follow-up time (not mentioned) appears to have been limited. The study did show, however, that transverse fractures tended to heal with increased length on the involved side while spiral fractures showed a tendency for shortening.

Bopst et al. studied use of the flexible intramedullary nail in 72 younger children at a mean age of 4.1 years (range 1.5–5.9) [206]. Leg length discrepancy was carefully checked in every child with follow-up available in 62 at a mean age of 36.7 months (4–124). Femur overgrowth occurred in 27. More than 1 cm of femur overgrowth (always lengthening) was seen in 6 children (8.2 % of the entire group; 9.7 % of the detailed 62

studied) all but one of whom had transverse fractures. Follow-up in these 6 ranged from 39 to 124 months with discrepancies of 12, 13, 20, 21, and 25 mm. They stressed the need to follow children postfracture at least 24 months or until the lengthening stabilized.

(iii) *Femoral Plating*:

(a) *Compression Plates*: Treatment of diaphyseal femoral fractures prior to growth plate closure was reserved initially for patients with head injury, major vessel injury, or polytrauma where rigid stabilization was essential in the context of the associated injuries. Anatomic reduction was achieved prior to plate application. The value of the technique was shown in the 1990s. Ward et al. used an AO femoral compression plate in 25 children ranging in age from 6 to 16 years of age. Leg length discrepancy was described as "not a problem" [207]. Hansen reported on 13 femoral shaft fractures treated with an AO compression plate [208]. The mean age at operation was 11 years (6–14 years) and all patients were followed until closure of the epiphyseal plates. Patients were reviewed at an average 8 years postsurgery. Orthoroentgenography was used for postoperative documentation. In the surgical cases where the operated femur was longer than the contralateral femur (one femur was shorter), the mean overgrowth was 8 mm (range 3–25). Only one patient had a severe overgrowth problem of 25 mm. Kregor et al. reported on 12 patients who had compression plating [209]. Scanograms in 7 patients with uninjured contralateral femur showed 9 mm femoral overgrowth (range 3–14 mm).
Compression plating came to be used more commonly and was used in some centers as the primary treatment of choice for many otherwise healthy patients. Some subsequent papers tended to show no leg length problems where follow-up was relatively short and only clinical assessment was done. Fyodorov et al. used compression plating (DCP) in 23 fractures between 8 and 12 years of age with follow-up averaging 16 months [210]. They indicated that none of the patients developed a leg length discrepancy. Caird et al. used AO compression plates in 60 patients with a mean age of 8 years (range 3–15) and a mean follow-up of 21 months (range 7–98) [211]. They did not refer to leg length discrepancy other than mentioning that clinical assessment of leg lengths was recorded and symptomatic limb length discrepancy occurred in two children. Eren et al. however, used dynamic compression plates for 46 femoral fractures between 4 and 10 years of age [212]. Leg length discrepancy averaged 12 mm (range 0.4–18 mm) with lengthening on the operated side in 15 patients with an average of 12 mm.

(b) *Bridge Plates*: In order to minimize soft tissue dissection to the fractured femur some use bridge plating or submuscular plating (with or without locking plates). These plates were initially used for problematic cases such as severely comminuted fractures. The plates were placed under fluoroscopic imaging in the submuscular plane against the shaft following indirect/closed reduction. Each plate was held with a 2–3 screws at top and bottom. The average age in three studies was 11.3 years [213], 9 years [214], and 11 years [215]. Leg length problems have not been a major concern; they are either absent or clinically insignificant or, if present, attributable mainly to the difficult fractures, many with significant shortening.

6.6.16.5 Summary

The overgrowth phenomenon following femoral diaphyseal fractures in childhood and early adolescence occurs regardless of the method of treating the fracture. When the Pavlik harness or immediate hip spice casting are used the main concern is with femoral shortening that the overgrowth cannot compensate for. If the fracture ends early in the healing process are overlapped by more than 2 or 2.5 cm., consideration should be given to switching treatment to traction to decrease the overlap (shortening). When operative intervention with external or internal fixation is used, the tendency is for excess femoral length to occur since the fragments are usually reduced anatomically for optimal fixation. Patient should be followed until the overgrowth has reached a plateau (no further change) even if this is several years postinjury.

Excellent reviews of the treatment options in pediatric femoral shaft fractures have been written by Flynn and Schwend [216] and Anglen and Choi [217]. Lascombes et al. have provided an excellent review of flexible intramedullary nailing in children and adolescents [218].

6.6.17 Fractured Tibial Diaphysis

Tibial overgrowth following tibial fracture has been reported as being most marked in patients who are <9 years old. In an isolated tibial fracture, overgrowth rarely is severe enough to require continuing long-term length assessment, but it can be troublesome when there is an ipsilateral femoral fracture.

Srivastava et al. [219] and Lascombes et al. [218] have used elastic stable intramedullary nailing for difficult tibial fractures without significant growth sequelae.

6.6.18 Overgrowth Syndromes and Lower Extremity Length Discrepancies

Overgrowth syndromes are relatively rare but are frequently accompanied by asymmetric involvement including overgrowth of digits, localized parts of limbs, or entire limbs and often present for orthopaedic management of length discrepancies. Overgrowth (macrosomia) of the infant is considered to exist when birth weight is >4500 g, which occurs in 0.4–0.9 % of newborns. There are many causes but assessment for syndromal types and lower (and upper) extremity length discrepancies is needed. As well as length and weight abnormalities, many have associated malformations (especially of the head and neck), vascular lesions, and neoplasia. Vascular lesions can be composed primarily of capillary, arterial, venous, lymphatic, arteriovenous, or mixed vessels. Neoplastic involvement is common in kidneys (Wilms tumor), liver (hepatoblastoma), and adrenals (adrenocortical carcinoma) but many other organ tumors are seen such as neuroblastoma, glioblastoma, rhabdomyosarcoma, pheochromocytoma, and pancreatic tumors. Benign tumors are also common. It has been estimated that neoplasms are present in 7.5 % of those with the Beckwith–Wiedemann syndrome, 5.9 % with hemihypertrophy, and 2.2 % in Sotos syndrome.

6.6.18.1 Hemihypertrophy and Hemiatrophy (Anisomelia)

This diagnostic category has been frequently used in the orthopedic literature to refer to two different diagnoses, hemihypertrophy and hemiatrophy. A more accurate term is hemihyperplasia since the disorder is due to an increase in cell number rather than an increase in cell size. One study reviewed patients who had been assessed over a 40-year period and it was frequently not clear what criteria were used to include a patient under each particular designation, but the diagnosis of hemihypertrophy did not include patients who were noted to have hemangiomas, lymphangiomas, lipomatosis, or neurofibromatosis (who were assessed separately) [50]. At present, the diagnosis of hemiatrophy is applied to patients in whom both limbs individually appear to be structurally and neurologically normal, with the short limb diagnosed as being hemiatrophic. The developmental patterns in both groups were similar, however, and for the purposes of classification the entity was referred to as anisomelia. The term anisomelia, which means a condition of inequality between two paired limbs, is nonspecific and is infrequently used today. Most of these patients (57 %) demonstrated a type I pattern, with the remainder equally divided between type II and type III. The average maximum discrepancy in these 113 patients was 3.16 cm (range 1.5–6.90 cm). Beals mentions two patients with hemihypertrophy who experienced spontaneous correction of limb length inequality in early childhood with the maximum discrepancies radiographically documented at 1.4 and 1.0 cm prior to 4 years of age with no discrepancy at 6 years of age [220]. We did not note this pattern in our patient group where inclusion required at least a 1.5 cm discrepancy at some time. Pappas and Nehme also reported on lower extremity length discrepancies associated with hypertrophy in a separate study of patients from the Children's Hospital, Boston, Growth Study Unit [221]. Many of these patients would have been included in the developmental pattern study so it is not surprising that the results were similar. They divided their assessments into patients with idiopathic hypertrophy and those with vascular disease, neurofibroma, and lymphangioma. Graphs in their work showing the progression of length discrepancies with age showed a distribution with type I, type II, and type III patterns. In 35 patients with idiopathic hypertrophy, the lower extremity length discrepancy immediately prior to epiphyseal arrest averaged 3.6 cm. In those with vascular disease, mean discrepancy in 18 patients preoperatively was 3.3 cm. The mean discrepancies in this group were somewhat larger reaching a mean of 5.3 cm preoperatively. Many patients with neurofibromatosis, however, had either no hypertrophy or clinically insignificant hypertrophy. In 90 patients followed until the time of epiphyseal arrest, the average preoperative discrepancy was 3.4 cm. In each of the four groups, mean values indicated that there was almost always both femoral and tibial lengthening but that tibial lengthening was greater than femoral in each of the subgroups and usually by a 2 to 1 margin.

Hemihypertrophy is rarely a simple increase in length of the femur and tibia on the involved side. There are almost always mesodermal abnormalities associated, many in particular with vascular anomalies and also a high incidence of neuroectodermal abnormalities. Bryan et al. studied 27 cases of congenital hemihypertrophy in which the entire side of the body was affected or there was segmental hypertrophy in which only one particular extremity was markedly affected compared to the contralateral side [222]. The maximal lower extremity length discrepancies were measured. The ranges of length discrepancy involvement seemed to be comparable in the hemihypertrophy and segmental hypertrophy cases. In 22 patients in whom discrepancy data were listed, the range varied from 0.9 to 6.4 cm. Although the large majority of the patients had reached skeletal maturity, a few still had several years of growth remaining. The mean discrepancy in 13 patients 12 years of age or older as measured prior to surgical correction was 3.92 cm.

MacEwen and Case reviewed 32 cases of hemihypertrophy noting a limb length discrepancy in 26 [223]. Of these they felt that 65 % had, or would develop, a discrepancy great enough to require epiphyseal arrest. In six patients who had already been treated with epiphyseal arrest, the mean discrepancy was 3.3 cm.

There is a very large subset of patients with hemihypertrophy, primarily associated with a wide range of vascular and other connective tissue abnormalities. These are outlined in the next few sections.

6.6.18.2 Initial Delineation of the Hemihypertrophy Syndrome—Trelat and Monod

Initial delineation of the hemihypertrophy syndrome occurred in an 1869 monograph by Trelat and Monod "On Unilateral Partial or Total Hypertrophy of the Body" [224]. They reviewed the clinical findings, considered previous case reports including one of their own and used the term hemihypertrophy to describe the entity. They indicated that Isidore Geoffroy Saint-Hilaire [225] in his book on developmental anomalies in man had commented on asymmetric development which often involved only a region or small part of one side in relation to the other. They reviewed reports from 1836 onward to present "a general history of this defect of conformation." They defined it specifically as a hypertrophy of one side and not an atrophy of the other since atrophic conditions appeared almost always to be associated with neuromuscular abnormalities and a weakened state. The initial clinical reports were accompanied by extremely detailed measurements and they were able to indicate that the average discrepancy in hemihypertrophy was between 3 and 5 cm at maturation but that the range was great going from 1.5 to 19.0 cm. The disorder not only involved increased length but also a proportionate increase in soft tissue size in those areas affected. They pointed out the large number of vascular abnormalities present on the hypertrophic side. In virtually all instances, the limb itself was the site of abnormality which in the standing position caused an elevation of the pelvis most obvious as an elevation of the iliac crest on the hypertrophic side; it was not the pelvis or trunk that were abnormal but rather the changes of position were due to the increase in lower extremity length. The truncal abnormalities and pelvic obliquity were not fixed deformations but were due to positional effects based on limb length discrepancy in the upright and walking position. In 11 of the 12 cases, the skeleton of the trunk was normal. There were almost invariable skin changes on the involved side involving discoloration and changes in thickness. In many instances, the skin was thickened and elevated by numerous swollen venules. In one of the cases with the largest discrepancy, there was enormous hypertrophy of the lower extremity (19 cm), congenital lipomas, and elephantiasis. By review of many case studies, they defined hemihypertrophy as a true congenital malformation. They noted that "vascular dilatations were frequent and encountered in varying degrees in the large majority of instances." There were two types involving skin capillaries in some and presenting in others with birthmarks (naevi) involving lesions of the subcutaneous veins which were often true varices. The cutaneous and vascular abnormalities were unilateral, always present on the hypertrophic side, and exactly limited to the hypertrophic regions. The cutaneous naevi were present from birth. These lesions rarely, if ever, crossed the midline and the spots, veritable naevi of reddish discoloration, had a variable series of configurations but were always limited to the particular region of the hypertrophy. Varicose veins were often present although somewhat less frequently than the cutaneous vascular changes. These too were limited to the regions of hypertrophy and it was felt that they were specifically connected with the general hypertrophy. Many observers also noted superficial arteries to be more dilated on the hypertrophic side. The large number of observations did not note any particular changes of the deep arterial circulation but rather frequent modifications of the veins and capillaries of the involved side of a general character of "angiectasies." They felt that the condition was not hereditary although they considered that the unilateral hypertrophy or hemihypertrophy was congenital. It progressed after birth and during the entire period of development leading to the increasing limb length discrepancies. The disorder produced hypertrophy of several tissues but some of the findings such as the varices were variable.

Studies over a century later continue to point out associated developmental abnormalities such as the variable skin lesions, central nervous system abnormalities (hemimegalencephaly, macrocephaly, seizures), liver cysts and hyperplasia, renal unilateral disorders (nephromegaly, polycystic kidney, abnormal collecting system), a high incidence of unilateral dental and oral maldevelopment, and tongue and facial hemihypertrophy.

6.6.18.3 Association of Hemihypertrophy with Neoplasia

There is a well-documented incidence of childhood neoplasia in overgrowth syndromes [226–228]. In a prospective study of 168 patients with idiopathic hemihyperplasia (hemihypertrophy), a total of 10 tumors in 9 patients were found, an incidence of 5.9 % [226]. The most common tumor was the Wilms tumor (nephroblastoma) of the kidney (6) with 2 adrenal cell carcinomas and 1 each of hepatoblastoma and small bowel leiomyosarcoma. Another study in idiopathic hemihypertrophy found that 3 of 250 children (1.2 %) developed an abdominal neoplasm. There were two cases of Wilms tumor and one with adrenal carcinoma [227].

These studies assessed patients with IHH only, excluding those with other malformation syndromes such as Beckwith–Wiedemann or Klippel–Trenaunay. Tumors occurred contralateral and ipsilateral to the hyperplastic side of the body.

Tumor risk in Beckwith–Wiedemann syndrome has been determined to be 10.6 % of a total of 520 patients (or 13.7 % of 402 who had molecular data available [228]. More accurate diagnosis of tumor risk is becoming possible with molecular subtyping. In this meta-analysis, the commonest lesions were Wilms tumors (nephroblastoma) 67 %, hepatoblastoma 11 %, rhabdomyosarcoma 5 %, neuroblastoma 4 %, other embryonic tumors 3 %, and a series of other single tumors. The occurrence of embryonic tumors in patients with the Beckwith–Wiedemann syndrome varies between 4 and 21 % in many studies from 1976 on [228]. Most occur before the age of 4 years and only rarely do the tumors develop after the first decade of life. Since most are intraabdominal, the primary screening-diagnostic study is an abdominal ultrasound.

Merks et al. studied 1073 children with cancer to determine the frequency of malformation syndromes [229]. They diagnosed a syndrome in 42 patients (3.9 %) and suspected the presence of a syndrome in another 35 patients (3.3 %) for a total incidence of 7.2 %. Many syndromes other than those with asymmetric overgrowth were identified but of the 42 with recognizable syndromes, 14 had hemihypertrophy (hemihyperplasia) with nephroblastoma 10, rhabdomyosarcoma 2, neuroblastoma 1, and Hodgkin lymphoma 1. The two patients with Beckwith–Wiederman syndrome had nephroblastoma and hepatoblastoma.

While neoplasia can occur in both syndromal hemihypertrophy and non-syndromal (isolated or idiopathic) hemihypertrophy, it appears to be more common in the better defined syndromal types, and especially with the Beckwith–Wiedemann syndrome. Wiedemann reported a 7.6 % incidence (5/66) of embryonal tumors [230]. Beckwith detailed the screening approach of renal sonography, concentrated in those under 10 years of age and done as often as every 6 months to allow for earlier diagnosis [231]. Ballock et al. reviewed the issue of neoplasia with hemihypertrophy from the pediatric orthopedic viewpoint [232]. The occurrence rate of 5–10 % appears to be at that level where professional opinion varies as to whether close clinical assessment might be sufficient compared to exposing the large majority of children (and their families) who will not get the disorder to the expense and stress of multiple assessments. The gene assessments outlined by Rump et al. should be helpful in categorizing the likelihood of occurrence [228]. Along those lines, Niemitz et al. showed that the frequency of hypermethylation of *H*19 in children with idiopathic hemihypertrophy and Wilms tumor at 20 % (3/15) was significantly lower than the frequency in children with Beckwith–Wiedemann syndrome at 79 % (11/14) indicating differing epigenotypes [233].

Other tumors include pheochromocytoma, retroperitoneal sarcoma, testicular carcinoma, and cerebellar hemangioblastoma. Any patient being followed with hemihypertrophy must be assessed periodically for visceral neoplasms. No specific standard of evaluation has evolved but renal and abdominal ultrasound is an easy and relatively effective way of screening for renal Wilms' tumor and other abdominal and retroperitoneal lesions.

6.6.18.4 Association of Hemihypertrophy with Silver-Russell Syndrome

Silver [234, 235] and Russell [236] described a syndrome which subsequently became well defined and is referred to as the Silver–Russell syndrome. It was described by Silver as congenital hemihypertrophy, shortness of stature, and elevated urinary gonadotropins. Russell commented on the syndrome as involving intrauterine dwarfism recognizable at birth with craniofacial dysostosis, disproportionately short arms, and other abnormalities. With further study, manifestations of the syndrome came to involve the significant asymmetry, shortness of stature present at birth even though the child was born at term, variations in the patterns of sexual development which involved elevated urinary gonadotropins or early sexual development or markedly retarded skeletal age in relation to sexual development, unusually short fifth fingers often with increased curvature, a triangular shape to the face, and occasional cafe au lait areas of the skin. A detailed natural history study of the Silver–Russell syndrome by Tanner et al. showed height at referral (4.6 years mean) averaging 3.6 standard deviations (SD) below the mean with that level persisting throughout growth [237]. The height at a mean age of 13 years was 3.4 SD below the mean. The predicted adult height in males was 153.5 cm and in girls 147.0 cm. The limb asymmetry was a hemihypertrophy of the longer side rather than an atrophy of the shorter. The asymmetry was relatively mild being <1.0 cm, which they felt was a normal variation, in 31 of 36 patients. Where hemihypertrophy was present the discrepancies, in cm, in children with some growth remaining were 1.0, 1.17, 1.25, 3.33, and 6.12.

Specht and Hazelrig reviewed the lower extremity length discrepancies in the Silver syndrome including 4 of their own cases and 47 from the literature [238]. The 51 cases gave a good overview of the length discrepancy involvement. The asymmetry was noted either at birth or during the first year of

life in 29 of 40 instances where data were available. The length difference increased in proportion to the child's skeletal growth. The length discrepancy varied from 0.5 to 6 cm although the length data included relatively few who had reached the age of skeletal maturity. There was no sex preference for the disorder. In 4 patients who had reached skeletal maturity, each had a significant discrepancy from 4 to 6 cm. There were 7 instances in younger children in whom the discrepancy was already in excess of 3 cm. There were 40 patients in whom the length discrepancy was referred to. There appeared to be a continuing increase in the discrepancy with time. If the numbers provided are studied by age groupings, there were 13 values of lower extremity length discrepancy listed from birth to 5 years of age, 15 measurements from 5+ to 10 years of age, and 12 measurements from 10+ years of age to skeletal maturity. In the youngest group of 13, the mean discrepancy was 1.75 cm with a range from 0 to 5.0 cm; in the next age group, the 15 measurements indicated a mean discrepancy of 2.44 cm with a range from 0 to 4.0 cm; and in the oldest age group the 12 values listed had a mean discrepancy of 3.44 cm with a range from 1.0 to 6.0 cm. The impression is of a type I pattern with perhaps some showing a type II in the later years of growth. Beals describes a patient with the Silver–Russell syndrome with a leg length discrepancy of 3.0 cm at 11 years of age [220].

6.6.18.5 Association of Hemihypertrophy with Abnormalities of the Cerebral Vasculature

Fischer et al. described two patients with congenital hemihypertrophy and associated vascular abnormalities of the brain on the side of the hypertrophy and in the posterior fossa [239]. The abnormalities included giant aneurysm, capillary hemangioma, and arteriovenous malformation. Literature review indicated only one previous similar patient, a girl who died at the age of 6.5 years with a vascular malformation of the thalamus. The hemihypertrophy in one patient reached 5.0 cm at 11 years of age at which time an epiphyseal arrest was performed while in the other patient the maximum length discrepancy reached was 1.6 cm at 2.5 years of age after which the discrepancy diminished by a few millimeters over the next 15 years and surgical correction was not required. The vascular abnormalities were assessed by CT scans, arteriograms, and examination at open neurosurgical intervention in one case. The extent of the hemihypertrophy did not correlate with the presence or extent of associated of cerebrovascular malformations. Other neurological abnormalities reported with hemihypertrophy include ipsilateral loss of sweating, ipsilateral indifference to pain, neurofibromatosis, metachromatic leukodystrophy, ipsilateral ventricular enlargement, and bilateral and ipsilateral enlargement of the cerebral hemispheres.

6.6.19 Congenital Vascular Malformations Associated with Lower Extremity Length Discrepancies

Many lower extremity length discrepancies are associated with vascular anomalies of the affected limb. This correlation has been known for some time but there is a vast array of involved vascular disorders with many patterns of irregularity noted at histopathologic examination. Most patients with these disorders do not undergo surgical exploration and clinical and imaging criteria alone are used for diagnosis. Many of these disorders are grouped under the term "hemangiomas" in the older orthopaedic literature even though, in a histopathologic sense, the lesions associated with major length discrepancies are not true hemangiomas. Orthopedic surgeons and geneticists have used syndromal name-based eponyms based on the clinical appearance of the limbs and the presence of overgrowth (hemihypertrophy) or less frequently diminished growth (hemiatrophy). A more specific biologically based terminology has been utilized by pathologists, vascular surgeons, and plastic surgeons in their dealings with these disorders. Previously, some used the general term "angiodysplastic disorders" to refer to this broad array of conditions. A two part article by Malan and Puglionisis provided correlations of clinical symptoms, anatomic findings and histopathologic descriptions of the wide array of congenital angiodysplasias [240, 241]. It has been recommended that the term should no longer be used and replaced with the term "congenital vascular malformation". Current terminology, therefore, outlines two distinct types of vascular anomaly. These are vascular tumors represented by neonatal/infantile hemangioma which resolve and are not associated with limb length discrepancies and congenital vascular malformations (CVM) which do not resolve spontaneously and are often associated with limb length discrepancies [242].

Mulliken and Glowacki introduced a biological classification of cutaneous vascular anomalies incorporating cellular features, physical findings, and the natural history of the various disorders [242]. The two major categories of cutaneous vascular anomalies were defined as **hemangioma**, a lesion demonstrating endothelial hyperplasia, and **malformation**, a lesion with normal endothelial turnover. The use of the term hemangioma should be restricted to a lesion of vascular origin that grows by cellular proliferation. It is the most common tumor of infancy and demonstrates spontaneous regression. Malformations result from embryonic errors of vascular morphogenesis and are subdivided into slow-flow and fast-flow lesions. The slow-flow lesions encompass capillary malformations, lymphatic malformations, and venous malformations while fast-flow lesions involve arterial malformations, arteriovenous fistulae, and

arteriovenous malformations. Combined vascular malformations are seen frequently involving capillary-lymphatic, capillary-venous, lymphatic-venous, and arteriovenous lesions. Once this distinction was made, it became apparent that the vast majority of skeletal changes were associated with vascular malformations. The term hemangioma is now restricted to common childhood tumors distinguished by rapid postnatal growth but followed by slow involution.

Skeletal malformations are rarely seen with hemangiomas but are commonly associated with vascular malformations. Hemangiomas passed through a proliferating and an involuting phase. Histologic study during the phase of rapid growth showed endothelial cell proliferation and hypercellularity while during involution the tissue showed diminished cellularity with onset of fibrosis. Malformations showed a normal endothelial cell cycle and persisted, growing commensurately with the child. Tissue was not hypercellular but rather composed of vascular channels lined by flat mature endothelium. Most of the lesions were predominantly venous but the full range of capillary, venous, arterial, and lymphatic vascular elements often combined were seen.

When skeletal abnormalities were assessed in relation to the hemangioma/malformation categorization, it was noted that of 356 hemangiomas only 3 (1 %) had bone changes, while 224 vascular malformations demonstrated bone changes in 77 (34 %) [243]. Of the 77 patients with vascular malformations, 27 were in the head and neck region and 50 in the extremities. In the extremity group, lymphatic malformations were frequently associated with hypertrophy and on occasion with distortion of the shape of the bone. The extremity venous malformations, however, were frequently associated with hypoplasia and demineralization. When the vessel malformations were of the combined type, both shape distortion and hypertrophy and hypoplasia and demineralization were found. High-flow malformations tended to produce hypertrophy and shape distortion of the bones in the terminology used by Mulliken and Glowacki.

6.6.19.1 Hemangiomas as Used in the Older "Orthopaedic" Terminology

As used for a diagnostic category in the older orthopaedic literature, including our paper on developmental patterns, "hemangioma" encompassed a wide histopathological variety of vascular anomalies, including capillary hemangioma (port-wine stain), cavernous hemangioma, arteriovenous aneurysms and fistulae, congenital varicosities, and mixed lymphangioma-hemangioma lesions. The term "hemangioma" had been used by orthopaedic surgeons over a period of several decades in a generic sense to refer to any type of vascular anomaly. Ipsilateral overgrowth occurred in 29 (83 %) of 35 patients, while in the remainder the limb was shorter on the ipsilateral side [50]. Nine (31 %) of the 29 patients who showed overgrowth had the type I pattern, the remainder being type II or III. Involution is a well-known occurrence in some types of hemangiomas and may account for slowing of growth stimulation. Although there were some well-documented instances where partial resection of the soft tissue lesions also diminished the growth stimulation, most patients demonstrated a type II or type I II pattern in the absence of any surgery. The average discrepancy prior to bone surgery in this group of patients was 3.09 cm (range 1.8–5.60 cm). The developmental pattern in this group must be observed carefully in the middle years of the first decade of life, as considerable discrepancy may develop and projections that are based on the expectation of the same rate of growth stimulation can be misleading.

In a study of hemangioma of the extremities in 35 cases in which a broad array of histopathologic diagnoses were included, McNeill and Ray noted 16 limbs with equal lengths, 8 with overgrowth on the involved side, and 11 with shortening or atrophy on the involved side. It appears that overgrowth when present was far more extensive than shortening since no indication of the amount of shortening, other than its presence, was made. Overgrowth, where amounts were listed, ranged from 1 to 8.75 cm [244]. A generalized overview of growth with limb hypertrophy was provided by Maroteaux [245].

Hemangiomas, as currently defined: Owing to the fact that the vast majority of hemangiomas as defined by Mulliken and Glowacki undergo spontaneous regression, axial skeletal overgrowth is almost never seen in conjunction with these lesions [242]. Most hemangiomas first appear in the early neonatal period and 80 % of them grow as a single lesion with the rest multiple. Infantile hemangiomas are the most common type of vascular anomaly but are completely benign. They are typically noticed in the first 2 weeks of life. They are far more common in females with a 3–5 to 1 female–male ratio. Once established there is rapid neonatal growth during the first 6–8 months of life with a plateau in size being reached at 1 year following which the lesions grow proportionately with the child with regression beginning around 5 years and continuing until approximately 10 years of age. As the tumor proliferates in the superficial dermis, the skin becomes raised and develops a vivid crimson color. If it is deeper in the dermis and into the subcutaneous layer, the overlying skin lends a bluish color to it. Contained blood cannot be evacuated completely by manual pressure. Hemangiomas can be divided into a proliferating phase during which they enlarge and the subsequent involuting phase. Histologically, they originate from endothelial cells and there is endothelial cell proliferation. Active pericytes are often seen as well. As the tumor regresses endothelial cell activity also diminishes. Mast cells make their appearance during the involuting phase. The term capillary or cavernous hemangioma should not be used.

6.6.19.2 Vascular Malformations

Vascular malformations are all present at birth but may not always be obvious. Unlike hemangiomas, they do not have a growth cycle and then regress but persist and grow slowly throughout life. They are benign. Venous malformations, in particular, may manifest later during childhood. Males and females are equally affected. Vascular malformations tend to grow proportionately with the child. The malformations are classified as arterial, venous, arteriovenous (AV) shunting, lymphatic, capillary, or combined vascular malformation. Each structural category of vascular malformation has a typical cutaneous appearance. The types of vascular malformations are: (i) capillary (CM) (port wine stains), present at birth as pink or purple skin lesions); (ii) venous (VM) (soft color disappears when compressed, common on jaw, cheek, tongue and lips); iii) lymphatic (LM) (excess fluid accumulates within lymphatic vessels); (iv) arterial; (v) arteriovenous (AVM) (abnormal connections between arteries and veins leading to pulsating collections of blood vessels); and (vi) mixed (a combination of any of the other 4 types). Each of the major categories of vascular malformation has its particular histopathological appearance but combined forms (CVM, CLM, LVM) can be difficult to distinguish even histologically. The characteristic histopathologic finding is a lining of endothelial cells without high activity similar to what is seen in normal vessels. Vessel walls, in particular with venous and lymphatic anomalies, are of variable thickness and mast cell distribution in vascular malformations is normal.

Hamburg Classification

The Hamburg classification of congenital vascular malformations (with modifications) has five groups: predominantly arterial defects, predominantly venous defects, predominantly arteriovenous shunting defects, predominantly lymphatic defects, and combined vascular defects (mostly hemolymphatic) [246, 247]. Each group of defects is then subdivided into two anatomical forms, extratruncular and truncular forms depending on the stage of embryonic life when the developmental arrest occurred [247, 248].

The extratruncular (ET) form is an embryonic tissue remnant following development arrest at the earlier stage of embryonic life, while the vascular system is in the reticular stage. The tissue remnants retain the characteristics of mesodermal cell origin (mesenchymal cells) and can grow rapidly with stimulation from trauma, surgery, hormone therapy, or pregnancy. The lesions carry a considerable risk of recurrence after therapy. The ET lesions can be either infiltrating or limited causing mechanical pressure as well as their hemodynamic impact.

The truncular (T) form develops in the later stages of embryonic life and lacks alterability after losing mesenchymal cell characteristics. They have minimal risk of recurrence but more serious hemodynamic implications since they often present as a persistent fetal remnant (truncal) vessel that does not involute normally. They are obstructive (aplasia, stenosis, membranous) or dilated (aneurysm [local] or ectasia [diffuse]).

Mulliken-Glowacki Approach, Now Expanded to ISSVA Classification (International Society for the Study of Vascular Anomalies)

Once congenital vascular malformations were distinguished from hemangiomas, the Mulliken-Glowacki concept stressed the hemodynamic differences in the various types of lesions in implicating clinic profiles [242]. These were broadly categorized as slow-flow or fast-flow lesions. These terms depend on the amount of blood supplying the malformation. The size of the shunt is determined by the volume of blood that enters the feeding vessels. High shunt lesions correspond to macrofistulous AV malformations.

In the ISSVA classification, there are the two broad groupings of vascular tumors (hemangiomas) and vascular malformations [249]. There are several variants of hemangiomas including: infantile, congenital, rapidly involuting congenital, noninvoluting congenital, hemangioendothelioma (± Kasabach–Merritt syndrome). In the vascular malformation group, the slow-flow variants are capillary malformations (CM): port-wine stain, telangiectasia; venous malformation (VM): several variants including Maffucci syndrome); and lymphatic malformation (LM) and the fast-flow variants are: arterial malformation (AM), arteriovenous fistula (AVF), and arteriovenous malformation (AVM). Many combined vascular malformations are intermediate in hemodynamic effects including: CVM, CLM, LVM, CLVM, AVM-LM, and CM-AVM.

Upton et al. studied upper limb vascular malformations in 270 patients seen over a 28 year period [250]. The female: male ratio was 1.5 to 1. The malformations were categorized as either slow flow (venous = 125, lymphatic = 47, capillary = 32, combined = 33) or fast flow (arterial = 33). MRI with and without contrast was the best modality to identify site, size, flow characteristics, and involvement of contiguous structures. CM, LM, and VM are generally "slow-flow" anomalies and AVM and arterial malformations are "fast-flow" anomalies. The lesions can be present in skin and subcutaneous regions but can also occur in most organs including muscles and bones. Combined forms tend to affect the extremities where they are associated with growth irregularity.

Vascular surgeons seeing the disorders use increasingly sophisticated studies to provide hemodynamic and anatomic–physiologic information. Noninvasive tests are used primarily including duplex sonography (color Doppler image and spectral waveform analysis), whole-body blood pool scintigraphy (WBBPS) using radioisotope-tagged

erythrocytes, T1 and T2 magnetic resonance imaging, transarterial lung perfusion scintigraphy (TLPS) using radioisotope albumin, and lymphoscintigraphy (TLPS) using radioisotope albumin, and lymphoscintigraphy. Invasive studies are rarely needed but can include percutaneous phlebography and selective arteriography [248].

There are two characteristic hematologic findings associated with these disorders: (1) platelet trapping, referred to as the Kasabach–Merritt phenomenon, is a rare complication and usually occurs in the neonate with thrombocytopenia, <10,000/mm^3. (2) In vascular malformations, an intravascular chronic consumptive coagulopathy can occur with minimally depressed platelets from 50,000 to 150,000/mm^3. It is associated not with hemangioma of infancy but with two vascular tumors Kaposiform hemangioendothelioma and tufted angioma. Patients with KTS can develop the milder intravascular coagulopathy. The vascular malformations are associated with the various syndromes leading usually to hemihypertrophy and appendicular skeletal overgrowth.

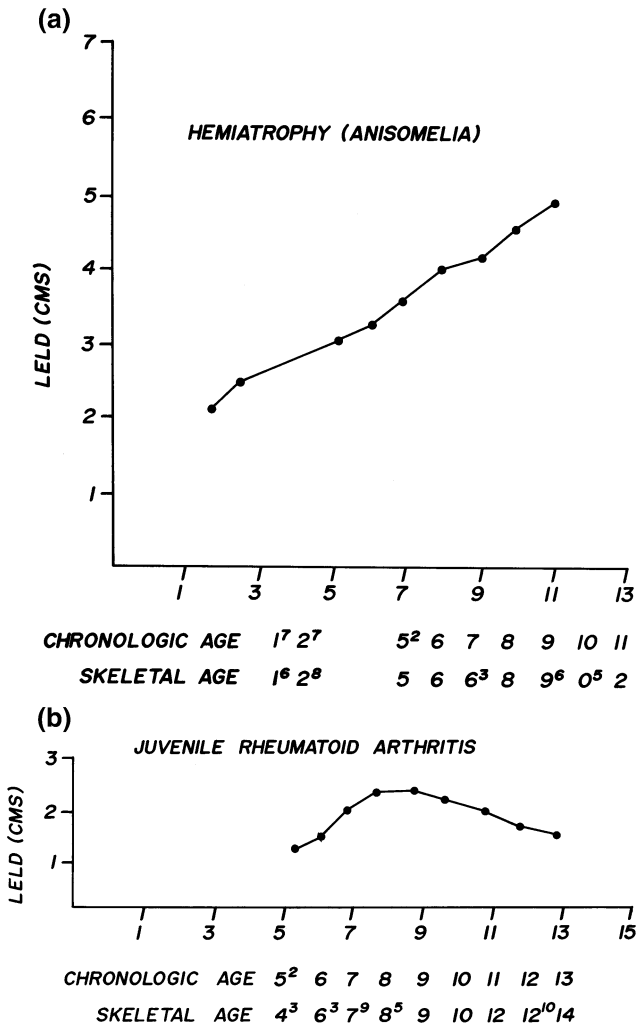


Fig. 6.13 **a** A patient with hemihypertrophy owing to unilateral overgrowth with the Klippel–Trenaunay syndrome (Reprinted with permission from Shapiro F, Developmental patterns in lower extremity length discrepancies. J Bone Joint Surg Am 1982;64A:639–651). **b** Type V discrepancy pattern in juvenile rheumatoid arthritis. The initial stimulation led to a discrepancy with ipsilateral overgrowth which then reached a plateau and eventually self-correction with premature fusion owing to the continuation of the synovitis

In most studies the predominantly lymphatic defects are most common, followed by the predominantly venous variants and much more common than the arteriovenous shunting malformations. The reasonably well-defined syndromes associated with hemihypertrophy, or infrequently hemiatrophy, are described below. Terminology can vary significantly in different papers and in particular in papers written several decades apart. Name-based eponyms have been used for decades to describe these disorders but they lack precision. The lesions are increasingly described using the Hamburg Classification or the ISSVA classification for more precise clinical, anatomic, histopathologic, embryologic, and hemodynamic definition. An excellent overview of vascular malformations has been written by Gloviczki et al. [251]. Syndromes seen frequently with lower extremity length discrepancies include the Klippel–Trenaunay syndrome (KTS), Parkes Weber syndrome, the Proteus syndrome, Beckwith–Wiedemann syndrome, congenital arteriovenous fistula, cutis marmorata telangiectatica congenita, and Maffucci disease. The Parkes Weber syndrome is an extremity arterial malformation with arteriovenous fistulas along with capillary, venous, and lymphatic malformations and skeletal hypertrophy. The Klippel–Trenaunay syndrome is a combined lymphatic-venous malformation with cutaneous port wine stain (capillary malformations) with or without associated bone hypertrophy or hypoplasia. Hypoplasia, for example, was characteristic of venous or combined extremity malformations and demineralization was another common finding in venous malformations while intraosseous and lytic changes were characteristically seen with high flow lesions. Many of the complex vascular abnormalities are associated with a spectrum of disordered neuroectodermal and mesodermal elements often with skeletal overgrowth.

6.6.19.3 General Classification of Angiomatous Lesions Based on Their Size and Position. Goidanich and Campanacci

Goidanich and Campanacci derived a classification of the congenital and developmental vascular disorders based on their position and size in the extremities [252]. Their approach was based on dissatisfaction with confusing and variable descriptive terms for this group of disorders. They felt that the clinical management could best be guided by consideration of the size and position of the vascular

anomalies. Their six groups included: (1) localized cutaneous and subcutaneous vascular hamartomata; (2) localized deep vascular hamartomata; (3) extensive deep vascular hamartomata; (4) multiple deep vascular hamartomata; (5) diffuse deep vascular hamartomata; and (6) infantile angioectatic osteohyperplasia. They felt that each group had distinctive clinical and pathologic characteristics although some cases showed transitional features. For each group they documented whether there was hemihypertrophy or hemiatrophy, radiographic bone changes, varicose veins, skin temperature, skin angiomata, pain, functional impairment, and swelling. The classification was derived from a study of 94 cases with the largest group, deep localized vascular hamartoma, comprising 45 cases and the smallest, infantile angioectatic osteohyperplasia, 7 cases. They considered all the angiomata of the soft tissues of the extremities to be hamartomatous with the lesion being present from birth and cessation of growth after skeletal maturity. In terms of extremity length, examples of both overgrowth and retardation were noted. In patients with cutaneous and subcutaneous vascular hamartoma, limb length was essentially equal in each of 11 cases. In all 7 cases with infantile angioectatic osteohyperplasia, there was overgrowth on the involved side. In the other four groups, however, there were examples both of overgrowth and retardation in association with the vascular lesions. In the four groups, there were 16 patients with overgrowth and 17 with decreased growth. In terms of length discrepancy, therefore, even site and extent of the lesion with the two exceptions noted above offer little prognosis as to the extent of any discrepancy and whether or not there will be overgrowth or retardation.

6.6.19.4 Klippel–Trenaunay Syndrome

This syndrome described in 1900 by Klippel and Trenaunay, refers to a congenital abnormality consisting of a cutaneous nevus (port-wine hemangioma), varicose veins, and bone and soft tissue hypertrophy (Fig. 6.13a) [253]. It is usually unilateral and affecting the lower limb but occasionally more than one limb is involved. Klippel and Trenaunay stressed that the bones on the hypertrophic side while larger maintained a normal anatomic shape and proportion. They called the syndrome "le noevus variqueaux osteo-hypertrophique." Klippel and Trenaunay noted that there was considerable awareness of the existence of hemihypertrophy often including skull and facial asymmetry, asymmetric soft tissue development of the extremities and in particular asymmetric vascular anomalies of the skin and subcutaneous tissues. They commented on the unique triad of abnormalities involving the nevus, varices, and osteophypertrophic changes. They pointed out that Trelat and Monod as early as 1869 had described a syndrome in which the characteristics were unilateral bony hypertrophy generally involving the lower extremities and frequently accompanied by a vascular dilation which could be of two types—capillary involving the nevae and subcutaneous venous involving the varices [224]. In the words of Klippel and Trenaunay, however, "they did not observe the remarkably frequent coexistence of the nevus, the hypertrophy of the skeleton and the venous dilations," feeling that they were secondary occurrences to the primary symptom which was the hemihypertrophy. Klippel and Trenaunay on the other hand insisted "on the simultaneous presence of these three principal signs." They pointed out several examples from the literature of the soft tissue abnormalities associated with hemihypertrophy and referred to previous cases to support their contention that the triad of abnormalities was a unique congenital lesion apparent since birth. The nevus and the hypertrophy existed since birth and the varices became evident around 8–10 years of age. The length discrepancies were extensive; they listed discrepancies in the lower extremities of 4.5, 4, 2, 4, and 9 cm. The triad of disorders present in the same subject were not lesions grouped by coincidence but resulted from a single disorder. The hemihypertrophy often involved an entire whole side including the face and skull but was often segmental and occasionally just involved either the hand or the foot and often individual digits. The bone was uniformly increased in size in terms of length, width, and thickness but anatomic shape was normal without angular or other deformations. The limb hypertrophy was present at birth but progressed with growth, occasionally increasing to 10 cm. Owing to the limb length discrepancy, secondary deformations of the pelvis and lower spine occurred. The disorder was not particularly rare.

The affected tissues do not contain hemodynamically significant arteriovenous communications but there are often other soft tissue, lymphatic, and bony abnormalities. It is similar to the Parkes Weber syndrome but it is better to consider them separately although some studies link the two describing the Klippel–Trenaunay–Weber syndrome. Baskerville et al. note that the presence of arteriovenous fistulae excludes the diagnosis of Klippel–Trenaunay syndrome and is characteristic of the Parkes Weber syndrome [254]. In their detailed study of 49 KTS patients with 56 abnormal limbs (53 lower extremity and 3 upper extremity), the male–female ratio was 1.3 to 1. All 49 had visible varicosities, 47 had a naevus, and 47 had limb hypertrophy. In 43 of the patients, the abnormality was noted at birth. There was no clinical evidence of an arteriovenous fistula in any of the 49 patients including 22 who had arteriography. In 36 patients, the affected limb was longer (>2 cm) and in only two was it shorter. The feet were also usually hypertrophic. Varicose veins were visible in all 49 patients. 68 % had a large incompetent vein on the lateral aspect of the limb which arose on the dorsum of the foot or ankle and extended a variable distance up the leg. Phlebography showed that approximately 50 % of the abnormal lateral veins drained

into the main stem leg veins with 33 % extending to the buttocks and draining via the gluteal veins into the internal iliac vein. More than one quarter of the patients had intrapelvic venous abnormalities as well. Other abnormalities included 15 % with lymphedema and 22 % with cutaneous lymphatic vesicles. Five patients demonstrated gigantism of the toes.

A convincing argument is made to separate the Klippel–Trenaunay syndrome in which arteriovenous fistulae are absent and the Parkes Weber syndrome which is characterized by arteriovenous fistulae [255]. Appreciable overgrowth of the limb may occur in the absence of arteriovenous fistulae. The difference in lower extremity length discrepancies rarely increased after the age of 12 years which would imply a type II or type III discrepancy pattern. Absolute numbers for the extent of the discrepancy were not provided but epiphyseal stapling was performed in only four patients (4.5 %) although problems with vascularity make surgical length discrepancy management potentially dangerous.

Servelle provided much useful information on KTS with his review of 768 operated cases [256]. It was his contention that surgical release of compressive fibrous bands of the deep veins in the lower limb improved the clinical symptoms. Elongation of the involved limb was invariably found although he did not comment on the extent. He indicated that he had operated (on the venous system) in 48 children between 6 and 12 years of age with "a pronounced difference in the length of the 2 limbs". Of deep vein malformation, the popliteal vein was involved in 51 %, superficial femoral vein 16 %, both popliteal and superficial femoral veins 29 %, iliac veins 3 %, and lower vena cava 1 %. He felt that overgrowth was due to venous hypertension with blockage of the deep venous channels. In 614 of his operated cases, involvement of the lower limb occurred in 80 %, upper limb 13 %, upper and lower limbs 3.2 % with occasional involvement of all four limbs or both lower limbs. Varicose veins served as substitute channels for obstructed deep veins. Venous obstructive lesions involved fibrous compressions (especially in the popliteal and superficial femoral sites), perivenous sheaths, hypoplasia (especially in the iliac and superficial femoral veins), and agenesis (iliac veins). In the upper extremity brachial and axillary veins, compression lesions were most common. Collateral venous drainage often led to symptomatic varicosities at bladder, rectum, and vagina. The venous stasis and often associated lymphatic malformations led to soft tissue swelling and edema in 84 % of involved limbs.

Jacob et al. reviewed 252 patients from the Mayo Clinic seen in 1956–1995 [257]. They presented a far more conservative management profile with surgery limited to far more specific indications. Sex distribution was relatively the same (136 female, 116 male) and 91 % had evidence of the syndrome at birth. Capillary malformations (port-wine stain) were seen in 246 (98 %), varicosities/venous malformations in 182 (72 %) and limb hypertrophy in 170 (67 %). All three features were present in 63 % and two of 3 in 37 %. Atypical veins including lateral foot/leg veins and persistent sciatic vein occurred in 72 %. Operations were done in 58 % including epiphyseal arrest, stripping of varicose veins/venous malformations, excision of vascular malformations, debulking procedures and amputations. Similar to Servelle, lower extremity involvement only was 70 %, upper extremity only 11 %, and upper and lower extremities 18 %, with additional involvement of thorax, pelvis, abdomen, or head and neck. The mean limb length discrepancy in the 42 % who had scanograms was a mean of 1.75 cm (range 0.1–9.6 cm). The involved limb was usually longer, being shorter only in 7 %. Jacob et al. provided detailed listings of the numerous other congenital anomalies and symptoms in these patients.

Baskerville et al. suggested that KTS was caused by a mesodermal abnormality during fetal development [255]. There appears to be no true atresia of the deep veins with abnormalities concentrated in the superficial system. Histologic studies, similar in all patients, showed an increase in the number and diameter of the venules in a cross section of the deeper layers of the dermis and subdermal fat. There was also widespread hypertrophy of the smooth muscle in the walls of the subcutaneous veins owing to response to chronically increased flow. There were normal deep veins and normal calf pump function in 60 and 84 % of patients, respectively. Both Bourde [258] and Baskerville et al. [254, 255] suggest that KTS is due to the persistence of part of the embryological vascular system and that a mesodermal defect acting primarily on angiogenesis could explain the condition. The findings were felt to be consistent with a later than normal regression of the embryonic vascular reticular network in the developing limb bud. This would lead to increased capillary and venular blood flow during intrauterine development and to the superficial varicosities. A mesodermal abnormality would also explain the other venous abnormalities with the syndrome involving developmental abnormalities such as absence of valves in the deep veins or reduplication of axial veins and a large often valveless lateral venous channel.

Management. At present, the general management approach is observation and conservative medical management with elastic stockings and shoe lifts for mild discrepancies [257]. Operation should not be done to improve cosmesis at the expense of function. The outcomes of surgery are limited and recurrent varicosities are common. In a review of their experience, ligation and stripping of varicose veins was done in 49 patients with better outcome in only 40 %, excision of angioma in 44 with better outcome in

60 %, epiphyseal arrest in 41 with a better outcome in 90 %, and debulking procedures in 11 with a better outcome in 65 %.

A more aggressive approach in younger children, (mean age 10.3 years at surgery) has been reported by Baraldini et al. in 29 children involving stripping of persistent marginal vein, 16; multiple ligation of bulking varicosities, 10; sclerotherapy, 14; laser photocoagulation, 13; and excision of lymphatic malformations, 5 [259].

Management considerations involved correction of bony overgrowth, excision of soft tissue hypertrophy, and removal of varicose veins but only in those veins causing pain or discomfort [254, 257, 258, 260]. The widespread removal of varicose veins had not proven to be particularly successful. Cohen has summarized the Klippel–Trenaunay syndrome defining its three features as: (i) combined vascular malformations of the capillary, venous, and lymphatic types; (b) varicosities of unusual distribution in particular the lateral venous anomaly observed during infancy and childhood; and (c) limb enlargement [261]. The lower limb is involved in 95 % of patients, the upper alone in only 5 % with a few having both upper and lower involvement. The capillary malformations of the skin are bluish to purplish in color, unilateral or bilateral, without facial involvement, and often intermixed with lymphatic and venous components. The classic varicosity is the lateral venous anomaly found in about 80 % of patients. The malformation begins as a plexus of veins on the dorsum and lateral side of the foot and then extends superiorly for variable distances. Lymphatic abnormalities are found in 70 % of KTS patients.

6.6.19.5 Parkes Weber Syndrome

Parkes Weber pointed out the combination of vascularization abnormalities with hemihypertrophy of the limbs. A particular syndrome has come to be associated with his name; it involves the KTS triad of cutaneous naevus (port-wine hemangioma), varicose veins, and soft tissue and bone hypertrophy with arteriovenous malformations. In his initial presentation in 1907, he drew attention "to a group of cases in which hypertrophy of one limb, or else hemihypertrophy, is found to be associated with tumor-like overgrowth in the corresponding portion of the vascular system" [262]. He felt that the disorder was congenital in most instances. In differentiating a particular syndrome from previously known developmental abnormalities of the vascular and lymphatic systems, he pointed out that the condition under consideration was distinguished by the associated vascular abnormalities and the actual increase in length of the bones of the affected limb. He pointed out that even in the late 1800s, there were many cases reported of hemihypertrophy with some form or other of angiomatous formation. In his second communication in 1918, he linked the congenital limb hypertrophy to dilatation of arterial and venous trunks with a specific arteriovenous communication [263]. He indicated that "the communication between the arterial channels and the venous channels may be so free that in it a definite kind of thrill or pulsation, rhythmical with the heart's contractions, is transmitted to the veins as in cases of arteriovenous anastomosis of traumatic origin." All cases are sporadic. The involved limb is warm, the skin color is pink and diffuse, and 77 % involve the lower limbs. He referred to the condition as "congenital or developmental phlebarteriectasis" or hemangiectatic hypertrophy of limbs. Both his papers were accompanied by abundant descriptions of vascular anomalies and limb overgrowth from the late eighteenth and early nineteenth centuries from English, French, and German reports.

(a) *Sturge–Weber Syndrome*: In this syndrome, there is capillary malformation of the leptomeninges overlying the cerebral cortex with or without choroid and facial involvement (port-wine stain on the ipsilateral side). Only capillary malformations are found in the Sturge–Weber syndrome and limb changes similar to those in KTS do not occur. Seizures occur in about 83 % of cases. Overgrowth of the maxilla is common. Involvement can be unilateral or bilateral. Capillary malformations can appear anywhere on the body. These can be hemiparesis and mild associated hypotrophic limb development.

6.6.19.6 Proteus Syndrome

The Proteus syndrome is characterized by patchy or segmental hamartomatous overgrowth and hyperplasia of multiple tissues and organs along with susceptibility to the development of tumors. Associated abnormalities include macrodactyly (overgrowth of the hands and/or feet), hemihypertrophy, asymmetry of the limbs, connective tissue nevi, epidermal nevi, lipomas or a regional absence of fat, vascular (capillary, venous) and lymphatic malformations, and cranial hyperostoses. There is concern about neoplastic disorders and a large number of developmental abnormalities of many types with this syndrome [264, 265]. There is generalized thickening and soft connective tissue swellings of the skin and subcutaneous tissue. The connective tissue nevi are particularly common on the soles of the feet but may involve hands, abdomen, and nose. Histologically, they are composed of dense collagenous accumulations. The overgrowth may involve the whole body or it may be unilateral involving one limb or occasionally it is localized even to a digit. The skin and subcutaneous thickening is associated with lipomata, lymphangiomata, or hemangiomata. There is a relatively high proportion of skeletal abnormalities other than the hemihypertrophy including contractures, bony prominences

over the skull, angular deformities of the knees, scoliosis or kyphosis along with the dysplastic vertebrae, hip dislocation, and hallux valgus. There is disproportionate involvement of the hands and feet with macrodactyly and often soft tissue hypertrophy, in particular over the plantar surfaces of the feet. The craniofacial skeleton is large and misshapen due to some or all of hyperostosis, unilateral condylar hypertrophy, craniosynostosis, and underlying hemimegalencephaly. Cohen and Hayden differentiated the various symptoms from other overgrowth syndromes, in particular neurofibromatosis and the Klippel–Trenaunay syndrome [266]. The name Proteus was suggested by Wiedemann et al. who described four patients documenting partial gigantism of the hands or feet, nevi, hemihypertrophy, subcutaneous tumors, macrocephaly, or other skull anomalies, accelerated growth and visceral affections [267]. Developmental abnormalities were described later including progressive kyphoscoliosis, subcutaneous abdominal lipomas, dilated veins and/or hemangiomas, facial anomalies, mental retardation (20 %), and occasional seizures (13 %) [268]. One of the characteristics of this disorder is the changing phenotype with time. The patients are normal at birth to clinical assessment and develop the characteristic findings over the first year of life. This is a primary differentiating feature from other overgrowth syndromes (such as Klippel–Trenaunay) which have hyperplastic overgrowth of the limbs at birth. With Proteus, patients are normal at birth or show mild alterations (hyperplasias, hamartoses). Progressive asymmetric overgrowth evolves postnatally. Once established, the abnormalities tend to be progressive throughout childhood with growth of the hamartomata and generalized hypertrophy increasing during the first few years of life. The bone and soft tissue overgrowth is stable after puberty. Morbidity is considerably greater than with the KT or PW syndromes. Of 11 patients evaluated by Clark et al. 2 required amputation of the leg, 6 had fingers or toes removed, and 2 women had breast implants and reconstruction [269]. Spinal stenosis and neurologic sequelae can develop due to vertebral anomalies or tumor infiltration. A recent multidisciplinary workshop addressed earlier orthopedic interventions since if surgery is delayed too long the condition may become inoperable. They suggested soft tissue releases to counteract contractures and aggressive and early use of epiphysiodesis to limit limb length discrepancies [270].

The Proteus syndrome is caused by a somatic activating mutation in AKT1, proving the hypothesis of somatic mosaicism and implicating activation of the PI3 K-AKT pathway in the clinical findings of overgrowth and tumor susceptibility [265]. Of 29 patients with the Proteus syndrome, 26 had a somatic activating mutation in the oncogene AKT1 encoding the AKT1 kinase, an enzyme mediating processes such as cell proliferation and apoptosis. AKT1 in murine chondrocytes controls cartilage calcification and can activate ectodermal defects and impair bone morphologenetic signaling. Previously, grups had reported Proteus to be due to PTEN mutations. It now appears that patients with PTEN mutations were clinically distinct from those with Proteus and that Proteus patents do not have the PTEN mutations. PTEN mutations underly a similar but different syndrome referred to as SOLAMEN syndrome characterized by segmental overgrowth, lipomatosis, arteriovenous malformation, and epidermal nevus.

6.6.19.7 Beckwith–Wiedemann Syndrome

The Beckwith–Wiedemann syndrome is associated with hemihypertrophy leading to lower extremity length discrepancy in about 25 % of cases [271, 272]. The hemihypertrophy may not be apparent at birth. This clinical entity is characterized by macroglossia, omphalocele or other umbilical anomalies such as umbilical hernias, macrosomia with large muscle mass and thick subcutaneous tissues, hemihypertrophy, linear creases in the lobule of the external ear, and abdominal visceromegaly especially including large kidneys. Whole body overgrowth onset can occur from the prenatal period to as late as 1 year of age, is rapid throughout the first few years of life but then shows a decreased growth rate from mid-childhood to puberty leaving mature height in the high normal range.

Other developmental anomalies can be seen. Hypoglycemia is present in early infancy in approximately ½ of the cases and there is an increased incidence of embryonal tumors such as Wilms tumor and hepatoblastoma. None of the three cardinal features [macroglossia, macrosomia (height and weight equal to or greater 97th percentile), and omphalocoele] is a diagnostic requisite but at least 2 of the 3 are usually present. Geneticists recommend two major and one minor criteria to make the diagnosis but milder phenotypes should be considered for tumor surveillance.

6.6.19.8 Congenital Arteriovenous Fistula

Horton drew attention to the overgrowth phenomena with congenital arteriovenous fistula involving the extremities [273]. He detailed findings in 23 upper and lower extremity disorders in which documentation of the length discrepancy was made. In 23 patients, the limb circumference was from 2 to 8 cm greater than the corresponding normal side and in 18 of the cases there was an increase from 0.5 to 7.0 cm in the length of the bones on the abnormal side. The involved extremity was hypertrophied and showed marked evidence of engorgement, swelling of superficial veins and skin ulcers in most. There was marked increase in the pulsations of the arteries and a definite increase in the surface temperature of

the extremity involved. He used the term arteriovenous fistula to designate any abnormal communication or communications between arteries and veins by means of which arterial blood passes from an artery to a vein without passing through a capillary bed. There were 15 patients with lower extremity length discrepancies described, 12 of whom had reached skeletal maturity. Two of the patients had no increase in the involved side length but the others all showed increase in length. The discrepancies varied from 0.5 to 7.0 cm. In the 13 patients with a lower extremity length overgrowth, the mean discrepancy was 3.2 cm with 9 of the 13 showing a discrepancy of 2.5 cm or more. McKibbin and Ray implicated abnormalities of venous return in experimental arteriovenous fistulae with bone overgrowth [274]. The direction of blood flow in the vein distal to the fistula was reversed for a considerable difference. As the venous collateral channels, including those in the bone, developed the periphyseal blood supply was also altered.

6.6.19.9 Cutis Marmorata Telangiectatica Congenita

Cutis marmorata telangiectatica congenita is characterized by a persistent vascular mottling of the skin usually involving the limbs and usually in an asymmetric pattern. The disorder was described initially by Van Lohuyzen [275] and a detailed review by Gelmetti et al. listed approximately 150 cases described in the literature. Spontaneous regression has been observed in the majority of patients in the first few years of life but many lesions persist to adulthood. The disorder is also referred to as congenital phlebectasia. Lower extremity length discrepancies occur on occasion in the disorder. As with many congenital vascular abnormalities, there is a high frequency of multiple associated congenital abnormalities including neuroectodermal and mesodermal defects. Gelmetti et al. pointed out that abnormalities of the central nervous system, musculoskeletal system, and vascular system were involved. Several instances of hemiatrophy or hemihypertrophy on the involved side have been described [276]. In the review referred to above, there were 11 cases of shortness or hemiatrophy of the involved side and 7 cases of hemihypertrophy of the involved side as well as other categorizations involving retardation of growth and asymmetric growth where specific limb length determinations were not clear. Dutkowsky et al. described a 15-year-old male with 2.9 cm of shortness on the involved side and two other patients 2–3 years old with 1–1.6 cms shortness on the involved side [277]. These studies indicate that some discrepancies in limb length could be present in as high as 25 % of cases, that both hemiatrophy and hemihypertrophy on the involved side could be seen, and that evidences of growth retardation are perhaps somewhat greater than those of growth stimulation.

6.6.19.10 Lower Extremity Length Discrepancies in Vascular Malformation Syndromes

Klippel and Trenaunay in their original article listed discrepancies of 2.4, 4, 4.5, and 9 cm in some of their patients [253]. Peixinho et al. described eight patients with the KTW syndrome treated for lower extremity length discrepancy [278]. There were seven patients who had growth remaining at time of treatment, ranging between 10 and 15 years of age, and one patient treated at skeletal maturity at 19 years of age. This report concentrates on the more severe variants but shows the extensiveness of the length discrepanices that can develop. The range of disorders treated was between 1.5 and 10.0 cm with those undergoing epiphyseal arrest between 2.9 and 10.0 cm. In these six patients, the average discrepancy was 6.35 cm. In the five patients with epiphyseal arrest followed to skeletal maturity, the mean discrepancy initially was 6.82 cm and at skeletal maturity it had decreased to a mean of 2.1 cm. An additional patient had shortening of the femur at skeletal maturity diminishing the discrepancy from 4.8 to 0.8 cm. A better overview of the expected extent of length discrepancies in a large group of patients was provided by Jacob et al. who did scanograms on 105 patients finding a mean value of 1.75 cm (range 0.1–9.6 cm) [257].

A review of 40 patients with the KTS syndrome from the Mayo Clinic documented equal male-female distribution [279]. Thirty patients had findings noted immediately at birth with three being diagnosed before the age of 1 year and four between 1 and 6 years of age. A strict distinction was made between the Parkes Weber syndrome and KTS with patients with arteriovenous fistulae not included in the KTS grouping. The lower extremity was involved in 38 patients (95 %) and the upper extremity in 6 patients (15 %) with 4 patients (10 %) bilateral. The disorder was unilateral in 34 patients (85 %), bilateral in 5 (12.5 %), and crossed bilateral in 1 (2.5 %). The affected extremity was longer in every case. In 29 patients documented by scanogram, the average difference in documented length was 2.39 cm with the largest 12 cm. Hemangioma was present in 39 cases (97.5) while lymphangioma was the histologic diagnosis in 1 case (2.5 %). The 2 together were found in 5 additional cases. The typical port wine flat cutaneous hemangioma was present in 30 cases (75 %). Varicosities were marked and significant with incompetent perforators in 25 cases (62.5 %). Seven of the 25 had persistent large embryonic veins on the lateral aspect of the thigh. Arteriography was performed in nine cases with no arteriovenous fistulae diagnosed. All except two of the patients were still under 10 years of age in terms of their assessment for length discrepancy.

Guidera et al. described 28 patients with limb overgrowth and the diagnosis either of KTW (18 patients) or Proteus (10 patients) syndromes [280]. The results were pooled. Most

patients had a large array of mesodermal abnormalities. All patients but one had extremity involvement. Twenty-seven of 28 had lower extremity involvement consisting of overall limb hemihypertrophy in 15, localized gigantism in 6, and macrodactyly in 10. Nine patients had lower extremity length discrepancy varying from 1 to 12.8 cm. No specific analysis of the discrepancies was made. The authors warned of the need to be extremely cautious concerning surgical intervention. Soft tissue debulking operations and vascular operations in particular often appeared of dubious benefit especially with the danger of heavy bleeding. They felt that the timing of epiphyseal arrests was not predictable in equalizing limb length discrepancies, although that does not appear to be the experience of others.

Rogalski et al. utilized the term angiodysplastic lesions of the extremities to review 41 patients [281]. They used this terminology rather than the more common syndromal terms referred to above indicating that "identification of a specific syndrome appeared to depend on the speciality and training of the treating physician and was not predictive of initial symptoms or outcome." They felt they could not categorize the vascular malformations according to either histologic or angiographic descriptions and preferred to describe the malformations based on the system of Goidanich and Campanacci [252] based on size and location of the malformations. Eleven patients had limb length discrepancies with hemihypertrophy and four of these had epiphyseal arrest. No specific details concerning the extent of the discrepancies were given. The shape and size of the extremities, and the associated vascular problems as well as the large number of additional malformations throughout the body made the length discrepancy itself relatively less important than in other individuals. Anatomic location and overall size were predictive of symptomatology and were the more important factors. They determined that the majority of the lesions (59 %) were subcutaneous, while 20 % were specifically identified as intramuscular. No bony lesions were identified. All limb length discrepancies were associated with overgrowth of the involved limb. The authors also commented on the limitations of surgical interventions in particular where cosmetic improvement was being sought.

Paley and Evans also felt that it was the depth and extent of the lesions that were the most significant prognostic characteristics [282]. Kim et al. provided an excellent review assessing risk factors for leg length discrepancy in patients with congenital vascular malformations [283]. They studied 361 patients from 1994 to 2005 as part of assessments for congenital vascular malformations affecting the lower extremities. Scanograms were used in 229 where discrepancies were detected clinically. Risk factor analysis was performed for clinically significant discrepancy > 2 cm in relation to age, gender, features of CVM (type, extent, depth), and deep vein status (agenesis, hypoplasia, phlebectasia). Overgrowth (lengthening) and undergrowth (shortening) were assessed. The male: female ratio was 153 (42 %): 208 (57 %); CVMs were venous 215 (60 %), arteriovenous 43 (12 %), lymphatic 46 (13 %), and combined venolymphatic 57 (16 %). On the scanograms, only 26 patients (7.2 %) had a length discrepancy >2 cm with 20 due to overgrowth and 6 due to undergrowth of the affected side. Statistical analysis showed that a whole leg CVM was the single most important risk factor for length discrepancy and for overgrowth in particular. Overgrowth was significantly more common in females. Venolymphatic lesions were also significant for developing length discrepancy. Neither the depth of the CVM lesion nor joint involvement were a significant factor for length discrepancy development.

6.6.19.11 Hemangiomas of Bone

Hemangiomas of bone occur but are extremely rare. When present they almost invariably affect either the vertebral bodies or the skull. In those infrequent instances when they affect the long bones, they tend to be innocuous in terms of clinical significance. Cohen and Cashman reported one instance where hemihypertrophy of a lower extremity was associated with multifocal intra osseus hemangioma [284]. In the one patient described involvement of both the right femur and right tibia led to overgrowth on the right side at 12 years of age but this was due to a combination of the right tibia being 2.9 cm longer while the femur was 1.1 cm shorter. The hemangioma was present in both epiphyseal and metaphyseal bone but the intervening growth plate was normal. The authors noted that in the few previous cases of long bone hemangioma described no growth changes were reported.

6.6.20 Neurofibromatosis

Neurofibromatosis is associated with length discrepancies in two types of clinical situations [285–288].

6.6.20.1 Bones Appear Structurally Normal

The bones may be structurally intact but the soft tissues of the affected limb are characterized by cafe au lait spots of the skin and/or subcutaneous neurofibromas. Growth stimulation was documented on the involved side in 17 patients who did not have a tibial pseudarthrosis [50]. Prior to physeal arrest, the average discrepancy was 4.40 cm (range 2.0–8.8 cm). Shortening was also associated with neurofibromatosis in the six patients in whom a pseudarthrosis occurred. The type I pattern was commonest, although type II, type III, and type V patterns were seen also.

6.6.20.2 Congenital Pseudarthrosis of the Tibia

There may be a congenital pseudarthrosis of the tibia, which is often seen with neurofibromatosis although cutaneous

abnormalities or neurofibromas of the involved segment may not be present. As surgical intervention in an attempt to establish union was so frequent in the patients with pseudarthrosis, the natural length discrepancy patterns in our series were infrequently available for assessment. Some information is available however on the maximum lower extremity length discrepancies reached from large series of pseudarthrosis of the tibia described previously. Virtually all of these patients will have had surgical interventions, often multiple times, on the affected tibia in efforts to obtain straightening and union. The discrepancies were at times worsened by angular deformity, the need to resect scarred-sclerotic diaphyseal tissue and by intramedullary rod passage through the tibial epiphyses in efforts to enhance stabilization. Van Nes pointed out, that a considerable amount of the shortening in congenital pseudarthrosis of the tibia was due to associated developmental abnormalities of the distal tibial epiphysis which often led not only to diminished growth but also to premature fusion [288]. The distal tibial secondary ossification center was often delayed in appearance. Throughout the growing years, the physis can often be noted to be misshapen and thin. Van Nes stated that the retardation of growth in the distal tibial epiphysis indicated involvement with the same segmental dysplasia as the distal part of the diaphysis that caused the pseudarthrosis originally. Both the pseudarthrosis and the retardation of growth were to be considered symptoms of the same developmental defect of the distal tibia. The closer the pseudoarthrosis was to the epiphyseal region, the greater the epiphyseal involvement and the less the associated growth. Van Nes clearly pointed out that spontaneous physeal fusion could occur as early as 10–12 years of age. He presented case reports on 22 individuals. Length discrepancy measurements were listed in 18 patients, virtually all after 10 years of age and prior to any epiphyseal arrest for the length discrepancy. One patient had no discrepancy and the others ranged from 1.25 to 11.0 cm. Mean discrepancy in the 18 patients was 5.4 cm. The discrepancies were due to a combination of factors including angular deformity, multiple surgical procedures some involving resection of bone in efforts to obtain union, diminished function of the distal tibial epiphysis due to its involvement in the dysplastic process and premature fusion of the distal tibial epiphysis. On occasion, the physis was damaged by intramedullary nails passed through it although many instances of continued growth following this procedure were also noted.

In a long-term study from the Mayo Clinic, Masserman et al. reviewed 52 cases [286]. Of these, 20 (38 %) had a known diagnosis or the clinical manifestations of neurofibromatosis. Lower extremity length discrepancies were documented in 32 of the 52 patients. Of these, five had no specific number mentioned but appeared to be insignificant. In all instances except one, the involved leg was shorter. There were two patients whose limbs where equal, eight where the difference was between 0 and 1 in.; five between 1 and 2 in.; three between 2 and 3 in.; 4 between 3 and 4 in.; one between 4 and 5 in.; and 3, 6 in. of discrepancy. The one patient with tibial overgrowth was 2.0 cm longer.

Morrissy et al. analyzed 40 cases of congenital pseudarthrosis of the tibia. Half the patients in the series had neurofibromatosis [287]. As in the study by Masserman et al. the diagnosis of associated neurofibromatosis does not affect the overall result in comparison with the group without that diagnosis. The amount of shortening in congenital pseudarthrosis of the tibia correlated extremely well with the eventual result achieved. This serves as a biologic reflection of the extensiveness of the bone abnormality which affects not only the diaphyseal regions but also the entire bone. In those with good results, the average amount of shortening was 1.4 cm (range 0–4.0 cm); with fair results, the average amount of shortening was 3.4 cm with one patient having a 6.0 cm shortening and another a deficit at one time of 8.1 cm; and with poor results the average shortening was 5.5 cm (range 2–8 cm) with all but one patient having at least 4.0 cm of shortness. Amputation was done eventually in 14 patients. There was a significantly greater amount of shortening in patients with tenuous union or with nonunion. Much of the growth discrepancy was secondary to failure of growth in the distal physis while relatively normal growth proximally continued.

6.6.21 Juvenile Rheumatoid Arthritis

Lower extremity length discrepancies occur commonly in patients with juvenile rheumatoid arthritis where joint inflammation is prolonged and asymmetric. Asymmetric bone growth occurs in many instances of moderate to severe juvenile rheumatoid arthritis, characterized by overgrowth on the involved side early in childhood, and a tendency to premature physeal closure leading to shortening in those affected toward the end of skeletal growth [289–296]. Griffin et al. noted overgrowth as great as 2.6 cm in one patient with knee involvement and shortening as great as 3.8 cm and 5.1 cm in others [297].

A retrospective study at the Children's Hospital, Boston, determined the course of limb length discrepancies occurring in patients with monoarticular and pauciarticular juvenile rheumatoid arthritis [298]. Data were assessed on 36 patients followed to skeletal maturity, (group I); on 15 patients who had not reached skeletal maturity but who had been followed for 4 years or more, (group II); and on 49 patients followed for 3 years or less (group III). In 72 of the 100 patients, the onset of the disease occurred before they were 5 years old, and 90 patients had involvement of the knee. Of the 51 patients included in Groups I and II, while all had some length discrepancy, in 35 (70 %) a length discrepancy of

1.5 cm or more developed during the study period. Twenty-one patients had a discrepancy of between 2.0 and 2.9 cm and in three it was 3.0 cm or more.

All patients in whom the disease developed before the age of 9 years had overgrowth of the involved extremity, but that overgrowth never exceeded 3.0 cm. The major discrepancy developed within the first 3–4 years and either increased very slowly and thereafter, remained level, or decreased. Of the 36 patients who were followed to skeletal maturity, in 29 a discrepancy of 1.5 cm or more developed at some time during the period of assessment. Twelve of the 36 patients had diminution of the discrepancy to the extent that epiphyseal arrest was not required. Fifteen eventually had an epiphyseal arrest. Rapid premature closure of the epiphyseal growth plate occurred only in those patients in whom the disease developed after the age of 9 years. This led to immediate shortening of the involved side and on occasion to marked limb length discrepancies as much as 5.1 and 5.9 cm.

In the patients with unilateral disease who had the onset of their disease before the age of 9 years, the involved side was almost invariably the longer one (39 of 40 cases). Those who had the onset of disease within the first 3 years of life tended to have a discrepancy >1.5 cm (24 of 34 patients) relatively more often than children 3–8 years old, but overgrowth in the younger children never amounted to more than 3.0 cm. When the disease occurred initially after the patient was 9 years old (5 patients), the involved side usually became shorter (with one exception).

Regardless of age at onset, the major discrepancy that developed did so within the first 4 years after onset of the disease. Thereafter, in the Group I patients, the discrepancy either increased very slowly (6 patients), remained unchanged (14 patients), or decreased spontaneously (12 patients). The other 4 patients, whose discrepancies continued to increase, were patients with late onset of the disease whose epiphyses fused prematurely on the involved side. Continuing involvement of the knee for several years in one patient resulted in a continuing increase with time until a pre-arrest discrepancy of 2.4 cm was reached, but such an occurrence was unusual.

In the 12 patients whose discrepancies decreased, there was a gradual inhibition of growth in the involved limb over several years. In 7 of the 12, the discrepancy became clinically insignificant. The changes in discrepancy with time were: 2.8–0.3, 2.5–1.2, 2.3–1.3, 2.2–0.4, 2.0–0.2, 1.8–1.4, and 1.5–0.9 cm. Evidence for rapid premature epiphyseal growth plate closure was noted only in four patients who had discrepancies because of shortness on the involved side.

In patients with the monoarticular or pauciarticular form of juvenile rheumatoid arthritis who have predominant involvement of the major joints of one lower extremity, the length discrepancy occurs as a result of two factors: (1) a stimulation of the epiphyseal growth plates, predominantly about the knee joint, during the time the disease is active and for some time afterward; and (2) inhibition of the growth potential of the involved extremity.

The epiphyseal growth plates at the knee account for 70 % of the growth potential of the lower extremity. They are sufficiently close to the synovial capsule to be affected by the hyperemia that occurs during the inflammatory process, while not being adversely affected by the concomitant destructive process. Since the knee is commonly involved in the type of arthritis under discussion and so often is involved unilaterally early in the course of the disease, a great potential exists for growth stimulation of the involved lower limb.

However, the severity of the disease often causes a decrease in the use of the involved extremity, either because of the patient's symptoms or because of the treatment. Such decreased use can explain the gradual reduction in epiphyseal stimulation and inhibition of growth. When the patient has activity of the disease in early adolescence, consequent hyperemia about the knee could cause rapid and premature fusion of one or both of the growth plates, with sudden decrease in growth of the involved lower limb.

The most common and well-defined pattern of development of length discrepancy was ipsilateral lengthening in patients who had the onset of the disease before the age of 5 years. The major part of the discrepancy occurred within the first few years of the onset of disease. Thirty-nine of the 40 patients with unilateral involvement whose disease began before the age of 9 showed this pattern. Early in the course of the disease, the predominant factor is stimulation of the epiphyses about the involved knee joint. The pattern of development of a limb length discrepancy just described most often is followed by lack of a significant continuing increase in the discrepancy. Although occasionally (in two patients in this series), the discrepancy will increase over the ensuing years; in most patients, it will decrease or remain unchanged with time.

It is important to note the rapid premature closure of the epiphyseal growth plates about the involved joint that occurred at the end of growth in four children in this series. All of them had onset of the disease after the age of 9 years, and all showed shortening of the involved side. Their length discrepancies ranged from 1.9 to 5.9 cm, with the two patients who were 9–10 years old at onset of the disease showing larger discrepancies at skeletal maturity than the other 2, who were 11–12 years old at onset. Early epiphyseal growth-plate fusion has been recognized as a complication of juvenile rheumatoid arthritis for many years.

In patients with monoarticular or pauciarticular juvenile rheumatoid arthritis, variable developmental patterns

occurred. Types I, II, III, and V were all seen (Fig. 6.13b). The knee is the commonest area of involvement in juvenile rheumatoid arthritis and its involvement is most likely to result in clinically significant discrepancy. The type I pattern was seen most frequently in patients whose initial attack of rheumatoid arthritis occurred after the age of 9 years. In these patients, a type I pattern with shortening on the involved side developed due to the relatively rapid, premature physeal fusion of the bones comprising the involved joint. The type II and type III patterns were seen most often in patients whose initial synovitis occurred in the first few years of life and resulted in physeal stimulation and overgrowth. Once the synovitis had resolved, physeal growth altered toward a more normal rate and the discrepancy either persisted unchanged or increased at a much slower rate. The type V pattern resulted from a slowing of physeal stimulation over a few years prior to plate closure (Fig. 6.14). Whether the type V pattern was due to decreased use or to an alteration in the timing mechanism for closure due to disease, or to both, is uncertain, but the phenomenon itself was well documented. It was not possible to predict which patients would have a type II, III, or V pattern. Similar overgrowth can occur following other inflammatory conditions about the knee in childhood such as tuberculosis, septic arthritis, and hemophilia. In what appears to represent a description of a type V pattern, Phemister quoted Bergmann as observing "equalization of length years after overgrowth produced by tuberculosis of the knee beginning in early childhood." [299].

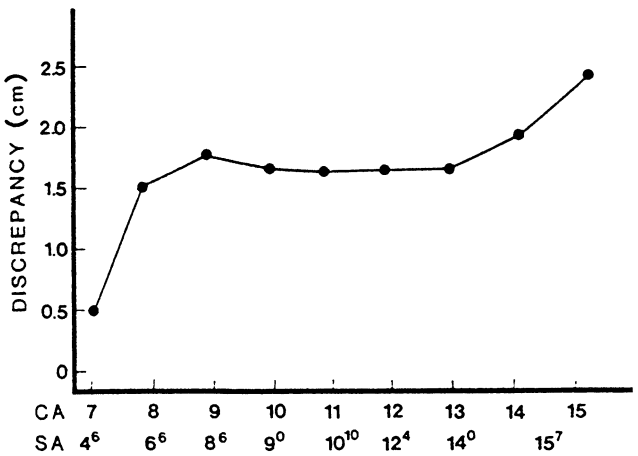


Fig. 6.14 Type IV pattern in a patient with Legg–Perthes disease who maintained proximal femoral growth for several years after the initial insult but then prematurely fused the proximal femoral capital epiphysis increasing the discrepancy (Reprinted with permission from Shapiro F, Developmental patterns in lower extremity length discrepancies. J Bone Joint Surg Am 1982;64A:639–651)

6.6.22 Thalassemia

Premature fusion of the epiphyses is a fairly common occurrence in thalassemia of the homozygous or major type. In a series of 79 patients with the disorder, 14 % showed premature physeal fusion almost always most marked in one growth plate [300]. All instances however were noted in those >10 years of age. When that age group alone was assessed, 23 % of 48 patients demonstrated the physeal arrest phenomenon. The commonest growth plate involved was that of the proximal humerus with frequent occurrence in the distal femur and also in the proximal and distal tibia and fibula. Currarino and Erlandson noted that the premature fusion was almost always focal and generally peripheral such that any shortening present was usually complicated by angular deformity. The growth plate arrest in the proximal humerus was almost always seen medially leading to varus tilt of the head in relation to the glenoid. The abnormality was not demonstrated in any of the 31 patients under 10 years of age. The incidence in males and females was approximately equal. There is very little documentation of the extent of the discrepancy or the nature of angular deformity and little also with any indication that surgical intervention was performed. No definitive cause of the disorder has been described.

6.6.23 Hemophilia

Lower extremity length discrepancies can occur in hemophilia [301]. The mechanism appears similar to that in juvenile rheumatoid arthritis in that a recurrent synovitis in a single joint, commonly the knee, leads to growth stimulation in the early years up to approximately 8 years of age following which continuing synovitis tends to cause a premature closure of the distal femoral and to a lesser extent proximal tibial physes. It is common for hemophilia to occur in a recurrent fashion in one joint, which is referred to as a target joint, with the three commonest affected regions being the ankle, knee, and elbow. Caffey and Schlesinger described overgrowth of the epiphyses themselves in all dimensions in joints with hemophilic arthropathy but they did not study overall bone length [302].

Kingma described overgrowth of an extremity affected with recurrent hemarthrosis in one joint [303]. Three patients, all <10 years of age, suffered repeat knee hemarthrosis and after straightening of flexion contractures were noted to be longer on the involved side. Each was still growing and report of the final discrepancy was not made. The overgrowth in an 11-year-old boy was 2.5 cm, in a 5-year-old boy 2 cm, and in a 7-year-old boy 2.5 cm.

Overgrowth in hemophilia was also described by Heim et al. who reported a 2.2 cm overgrowth on the side of the involved knee at 5 years of age [304]. Length discrepancy is seen less frequently now because of improved medical control limiting hemarthrosis and synovitis. Overgrowth discrepancies were often hidden and minimized by flexion contractures and articular cartilage degeneration of involved joints.

6.6.24 Synovial Hemangioma of the Knee Joint

Synovial hemangioma, a rare disorder, can occur with the most frequent site of involvement being the knee joint. Moon performed a careful review of the literature and documented 137 patients with synovial hemangioma of the knee [305]. There was equal occurrence in males and females with initial occurrence of symptoms concentrated in the childhood years from birth to late adolescence. Approximately, 75 % of patients were symptomatic prior to age 16. In those reports which mentioned limb length, only 14 cases were described as having increased limb length on the involved side with many showing only about 1 cm difference, in 8 cases the limbs were of equal length, and in 4 the involved limb was somewhat shorter. Limb length discrepancies were thus variable although a slight majority of patients had slight overgrowth.

6.6.25 Legg–Calve–Perthes Disease

The extent of lower extremity length discrepancy in Legg–Perthes disease was reported a large group of patients treated with a unilateral abduction brace [306]. Both the disease and the treatment used impact on length differentials. In 147 patients with a lower extremity length discrepancy associated with unilateral Legg–Calve–Perthes disease, the involved side was always shorter at some time during the period of assessment. The average maximum femoral discrepancy in this group of patients was 1.38 cm, none of whom had femoral or pelvic osteotomy. All five types of discrepancy pattern were seen. Femoral shortening occurs due to cessation of growth during the phase of necrosis of the secondary ossification center, due to subchondral collapse with the coxa plana deformity, and due to disuse in association with therapy, and it has long been recognized as part of the disease entity [307–309]. If proximal femoral varus osteotomy is performed shortening will be increased [310]. Innominate osteotomy tends to increase length on the operated side by 1 cm [308]. The femoral shortening was frequently associated with shortening of the ipsilateral tibia due to decreased use of the limb with unilateral brace therapy. The average maximum tibial discrepancy was 0.93 cm and the average maximum combined lower extremity length discrepancy was 2.14 cm. Once bracing was discontinued, the tibial discrepancy decreased. Twenty-one patients demonstrated a type I pattern; 8, a type II; 52, a type III; 10, a type IV; and 49, a type V. When only the femoral lengths were assessed, 14 patients (10 %) demonstrated a type IV pattern (Fig. 6.14). The occurrence of the type IV pattern was analogous to that seen in some patients with septic arthritis of the hip with only mild destruction. Premature fusion of the capital femoral epiphyseal growth plate occurred, with a late alteration of the femoral head-greater trochanter relationship. It is probable that the type IV pattern would have been seen more often, but the performance of distal femoral epiphyseal arrests in these patients made it difficult to document the type IV change. There was a good correlation between the age of the patient at onset of the disease and the final discrepancy pattern. The average age at onset in the patients who showed the type I pattern was 8.7 years, for type II 6.5 years, for type IV 5.6 years, and for type V 5.3 years. These numbers reflect the better healing that occurs in younger patients with Legg–Perthes disease, who have a longer time available for the slow repair process.

6.6.26 Slipped Capital Femoral Epiphysis

Clinically significant lower extremity length discrepancy is relatively infrequent in slipped capital femoral epiphysis. There are several reasons for this, the two most important being the relatively late age of occurrence in skeletal development and the fact that only 30 % of femoral and 15 % of lower extremity length is due to growth at the proximal femur. Even though treatment induces premature physeal fusion, there is insufficient growth remaining on the contralateral proximal femur to lead to clinically significant discrepancy. Other limiting factors include cases with bilateral involvement and the slight discrepancy caused by cases with only mild-to-moderate slippage. Concern about discrepancy is increased with unilateral disorders in those 11 years of age or younger in particular with moderate or severe displacement. This profile is often seen in the subgroup of slipped epiphysis associated with other medical disorders.

6.6.27 Infantile Cortical Hyperostosis: Caffey's Disease

In this disorder there is thickening of the periosteum and radiodensity of unknown etiology but the bone involvement is selective and can lead to increased length on the involved side [311]. In those instances where the tibia and fibula are involved overgrowth has been described. Jackson and Lyne

reported an unusual complication of Caffey's disease, however, which involved shortening on the involved side secondary to direct involvement of the distal tibial and fibular epiphyses [312]. Radiographs showed cortical hyperostosis of the entire length of the tibia and fibula on one side, as well as the left mandible. Synostoses eventually developed between the tibia and fibula proximally and distally. In addition the distal tibial epiphysis was wedge shaped. The fibula was shortened 1.1 cm relative to the opposite side and the tibia was shortened 0.7 cm. The authors felt that it was not the synostosis which caused the growth retardation but primarily the periosteal inflammation and scarring in the epiphyseal-metaphyseal regions which affected the vessels to the epiphyseal plates. In this report, the patient was followed only to 4 years of age.

6.6.28 Limb Length Discrepancies Due to External Causes

6.6.28.1 Burns

Lower extremity length discrepancies can occur following severe third-degree burns in particular about the lower part of the leg and ankle joint. Four cases were reported by Frantz and Delgado [313]. The growth slowdown was considered to be due primarily to scarring in the periphyseal region which could serve as a mechanical tether to growth and also limit the vascularization of the physeal area. The possibility of direct thermal damage to the epiphyseal plate was also raised. In two instances, there was premature closure of the distal tibial physis leading to a maximum discrepancy of 4.6 cm in one case and 4.7 cm in another as measured prior to contralateral epiphyseal arrest for correction of discrepancy. In a third patient, the discrepancy prior to epiphyseal arrest was 2.0 cm although premature closure of the distal tibial plate did not develop and it was felt that the periphyseal scar formation was limiting the growth. In a final patient, a discrepancy of 1.0 cm was noted with early central sclerosis of the distal tibial physis and the suspicion that growth would worsen with time since there were still several years of growth remaining.

Evans and Smith studied several cases of burn patients, many in the childhood years, and described bone and joint changes [314]. In spite of the fact that many children were assessed no specific comment on physeal changes was made. They defined skeletal alterations as falling into three groups: (1) alterations limited to bone with osteoporosis and periosteal new bone formation; (2) alterations involving pericapsular structures such as pericapsular calcification, osteophytes and heterotopic para-articular ossification; and (3) alterations involving the joint with progressive articular destruction and joint fusion. Tethering of the physis would clearly occur with alterations involving the pericapsular structures and in those instances where the articular cartilage is destroyed adjacent physeal cartilage would also have a high likelihood of destruction.

6.6.28.2 Epiphyseal Growth Arrest Secondary to Freezing

Severe frostbite in childhood has been shown to lead to epiphyseal damage with premature growth arrest following. The large majority of cases described involve the hands with the phalangeal epiphyses most commonly affected. Initial observation of this occurrence was made by Lohr who demonstrated physeal closure in several phalanges beginning several months post exposure [315]. Other instances of phalangeal destruction due to freezing were reported by Bennett and Blount in which there was complete destruction of the epiphyses of the distal phalanges of the second to fifth digits, and the middle phalanges of digits 2, 3 and 4 [316]. The physes in the less involved contralateral hand remained open. Thelander also reported a case of unilateral frostbite in a 6.5-year-old boy who demonstrated premature physeal closure at 9 years of age involving each of the epiphyses of the distal and middle phalanges from the second to the fifth digits [317]. An extensive study by Bigelow and Ritchie described 13 patients with frostbite of the hands during the childhood years all of whom had loss of one or more epiphyses [318]. The thumb was shown to be involved rarely and it was invariably the distal and then middle phalanges of the fingers which were affected first. In any instance where the proximal phalangeal epiphysis was affected, those distal to it were also affected. In most instances, shortening occurred without angular deformity but in some instances the growth arrest was partial and subsequent growth led to varus or valgus angulation. The epiphyses are damaged both by the direct effect of the freezing and then by vascular changes secondary to frostbite including thrombosis.

6.7 Projection of Limb Length Discrepancies by the Time Skeletal Maturity is Reached

The projection of limb length discrepancies that would be present at skeletal maturity became of practical importance with the demonstration by Phemister that surgical arrest of an epiphyseal growth plate on the longer limb with growth remaining allowed limb length equalization as the shorter limb continued to grow [299]. Accurate timing of an epiphyseal arrest procedure became feasible as documentation of the percentage of growth at each long bone epiphysis and the normal range of femoral and tibial bone lengths was obtained.

6.7.1 Percentages of Growth at Each End of Major Long Bones

Digby determined percentages of growth in human bones by measuring from the nutrient canal to either end taking the nutrient canal position as a standard and unchanging marker [319]. He documented proximal femoral growth as contributing 31.2 % of entire length and distal growth 68.9 %. Other measurements included: proximal tibia 57.1 %, distal tibia 42.9 %, proximal humerus 80.8 %, distal humerus 19.2 %, proximal radius 25 %, distal radius 75 %, proximal ulna 18.6 %, and distal ulna 81.4 %. Bisgard and Bisgard performed similar studies in goats and showed remarkable similarity of growth patterns [320]. Using the nutrient canal method their findings for the proximal femur were 32.7 %, distal femur 67.3 %, proximal tibia 56 %, distal tibia 44 %, proximal humerus 81.7 %, distal humerus 18.3 %, proximal radius 25.5 %, distal radius 74.5 %, proximal ulna 19.6 %, and distal ulna 84.4 %. The rounding off of numbers widely accepted for clinical use is proximal femur 30 % of growth, distal femur 70 %, proximal tibia 55 %, distal tibia 45 %, proximal humerus 80 %, distal humerus 20 %, proximal radius 25 %, distal radius 75 %, proximal ulna 20 %, and distal ulna 80 %. In terms of overall lower extremity growth, general percentages are upper femoral epiphysis 15 %, lower femoral epiphysis 35 %, upper tibial epiphysis 30 %, and lower tibial epiphysis 20 %. Two major studies in the American literature have provided data which remains valuable in terms of overall lengths of femurs and tibias throughout the childhood years. These are the reports by Maresh in 1955 [321] and 1970 [322], and Anderson, Green and Messner in 1964 [323]. Beumer et al. updated the femoral–tibial growh data studying 182 Dutch children by serial radiographic studies (orthoradiographs) from 1979 to 1994 [324]. They performed 596 measurements (mean 3.3/child, range 2–14) and established straight line growth curves for girls and boys, similar but not identical to those outlined by Moseley. Dimeglio and Bonnel have broken down the growth data to indicate the mean amounts of growth remaining in males and females at the distal femur and proximal tibia at varying ages [325].

6.7.2 Systems for Assessing Skeletal Development and Maturation

With the discovery of radiography in the first decade of the twentieth century there was almost immediate recognition of the value of childhood radiographs in demonstrating progressive bone ossification at each joint and body region and the application of this information to normal and abnormal development. Rotch of Children's Hospital, Boston presented a detailed article in 1909 studying "about a thousand" radiographs throughout the growth period [326]. He came "to the conclusion that in the process of development from birth to adolescence the normal changes which take place in the bones of the wrist correspond so closely to those of other joints that in the great majority of individuals the wrist may be accepted as a fairly correct index of general development." He then chose about 200 children of all ages with normal development of the joints and epiphyses who underwent radiographic assessment. The radiographic studies were accompanied by listings of chronologic age, sex, weight, height, and tooth development. The development of the ossific centers of the carpal bones and the lower epiphyses of the radius and ulna served as the milestones. He referred to the findings as the anatomic age and related them to the chronologic age and other criteria. He developed an alphabetical classification A to M which corresponded to increasing appearance of ossification of the particular cartilaginous bones and regions, their increased size, and their development toward mature shapes. While noting the varying times of appearance of bone of the metacarpal epiphyses and the epiphyses of all the phalanges he felt that they were "somewhat illusive as factors of development" and that "the most practical and reliable signs for the different periods of developmental age… were a combination of the carpal bones and the lower epiphyses of the radius and ulna." It was quickly recognized that girls developed ossific centers earlier than boys. He presented wrist and hand radiographs showing progressive stages of development from A to M which formed his preliminary anatomic index. Even at this period of time (1909) he cautioned that "we should, as a rule, use chronological age as little as possible in solving the problems of early life." He felt that "anatomic age as gauged by the epiphyses always means the same conditions, (while) chronologic age is very variable." Height and weight were also unreliable indicators of the status of bone development. His rough outline of anatomic age with the approximate correspondence of chronologic age was: A (1st year), B (2nd to 3rd), C(2nd to 3rd), D (2nd to 3rd), E (3rd to 4th), F (5th to 6th), G (6th), H (6th to 7th), I (6th to 7th), J (7th to 8th), K (9th to 11th), L (11th to 12th), and M (12th to 14th). He concluded that the best way of using the wrist as an anatomic index was to classify the carpal bones and the lower radial and ulnar epiphyses alphabetically in groups. Serial radiographic studies of developing regions were done extensively in the first half of the twentieth century. Acheson refers to at least nine detailed published radiographic studies between 1902 and 1952, including those of Todd and Greulich, and Pyle from Cleveland, Ohio. The atlases of skeletal development of the wrist and hand by Todd (1937) [51] and Greulich and Pyle (1950, 1959) [52], were based on radiologic studies done at Western Reserve in Cleveland, Ohio

under the auspices of the Brush Foundation. Atlases of regional skeletal development were also published by this group on the knee [327] and foot and ankle [328].

Acheson outlined the strengths and weaknesses of determining skeletal maturity from radiographs [329]. He referred to use of the atlases alone as the "inspectional technique." To improve analyses he devised the Oxford Method for grading skeletal development [330]. This was essentially a semi-quantitative system giving a point for each successive distinct shape change in a particular bone. The sum total of points (or units) scored by a bone at any stage in development would be an exact measure of maturity. The technique could be applied to any bone or region of the body once the maturity pattern was established for those bones/regions being assessed. Advantages were: every round bone and epiphysis could be graded, small increases of maturity were recorded, the same standards applied to both sexes, and maturation was quantitated by the units/points referred to as Oxford maturity units. Acheson demonstrated the method for the first 5 years of life on the left wrist and hand using a posteroanterior film and the left knee on an anteroposterior film [329]. For the wrist and hand, the scoring system was as follows: distal radius (3 units), distal ulna (2), each of eight carpal bones (3), metacarpal [1 for each epiphysis (secondary ossification center)], and phalanges (1 for each epiphysis). The maturity development score for the knee was also outlined: distal femur (1–5 units), proximal tibia (1–5 units), fibula [1 (presence of epiphysis)], and patella (1). For each bone/region the skeletal maturity in units was plotted along one axis and the age in years along the other to provide the developmental curve.

Acheson also applied the Oxford method of assessing skeletal maturity to hip and pelvis of over 500 boys and girls assessing the proximal femur-head 0 → 8, greater trochanter 0 → 7, and lesser trochanter 0 → 5; and pelvis-ilium 0 → 7, ischium 0 → 8, acetabular lip 0 → 1, junction of ischial and pubic rami 0 → 4, pubis 0 → 2, and triradiate cartilage 0 → 3 [330].

6.7.3 Systems for Projecting Limb Length Discrepancy at Skeletal Maturation

Many systems for predicting limb length discrepancy at time of skeletal maturity have been outlined. Accurate knowledge of the amount of growth remaining in femoral and tibial physes at any particular age became of practical importance after Phemister demonstrated the relative ease and value of arresting physeal growth in the longer bone [299].

6.7.3.1 Hatcher

Hatcher developed the initial approach for timing epiphyseal arrest procedures at the femur and proximal tibia [331]. Although his figures were based on averages at chronological age periods, they provided the first quantitative information on expected growth increments. Hatcher compiled data from studies which included percentages of growth of the bones of the lower extremities from the proximal and distal epiphyses as follows: femur 23 % proximal and 77 % distal, tibia 56 % proximal and 44 % distal. Growth percentage contributions of each of the 4 major lower extremity epiphyses to overall lower extremity length were then determined as proximal femur 12 %, distal femur 40 %, proximal tibia 20 %, and distal tibia 21 %. From available growth tables, Hatcher was able to calculate and chart the averages of normal growth to be expected from the femur and tibia for males and females from age 4 to age 17 years. Although the length numbers were averages, they provided the initial information in terms of final projected length of the femur and tibia and the average increment per year. Hatcher's growth increment curve was published in the first edition of Campbell's Operative Orthopaedics in 1939 [331]. With the three above-mentioned pieces of information, one could make a relatively accurate estimation of the appropriate timing for any epiphyseal arrest.

6.7.3.2 White

White timed all epiphyseal arrests on the basis that the distal end of the femur grew 9.5 mm (3/8 of an inch) per year and the proximal ends of the tibia and fibula grew 6.4 mm (1/4 in.) per year [99]. White and Warner described their technique for epiphyseal arrest by slightly modifying Phemister's approach [332]. They credited him, however, with the original idea of epiphyseal arrest and confirmed its great value in treating lower extremity length discrepancies. They used a square chisel which, at the distal femur, was placed in the midline medially and laterally. The square chisel was to straddle the growth plate diagonally so that two of the diagonal points were forced into the epiphyseal line and two into bone on either side. The chisel was driven into the femoral condyle to a depth of approximately 3/4 of an inch and the square of bone and interposed physeal cartilage tissue was removed in one piece. The metaphysis and physis were further damaged by a curette and the plug of bone and cartilage removed by the chisel was rotated 90° and replaced in the femur so that the contained portion of the epiphyseal line was directed in the long axis of the femur and solid bone bridged across the physis. A light plaster cast was used to immobilize the leg for 2 weeks after which physiotherapy was started with weight bearing allowed in 4 weeks. They

reported successful transphyseal bone bridging bilaterally with no deformities produced in 30 cases.

White and Stubbins reported on additional cases a few years later, again stressing the relative ease and effectiveness of the square chisel approach to epiphyseal arrest [333]. As the operation came to be more widely used they stressed (i) the importance of recording lower extremity length discrepancies more accurately than by tape measurements and (ii) use of a simple method of calculation to project the appropriate timing for the intervention. In a short period of time, the epiphyseal arrest dramatically limited use of the more involved femoral shortening procedure. They felt that the bone block removed by Phemister did not [299], in many instances, include sufficient depth of bone and that the technique they had developed favored solid bony union since there was more extensive bone surface opposed. Phemister had mentioned chiseling out the epiphyseal plate to a depth of 1 cm anterior and posterior to the block of bone and cartilage removed but apparently some surgeons were somewhat lax in doing this. The square mortising chisel was 0.5 in. in size. With 90° rotation of the square bone plug, the contained epiphyseal cartilage was at right angles to the persisting physis and on either side of it bone tissue crossed the physis. With healing metaphyseal bone became continuous with epiphyseal bone. White and colleagues began using standardized radiographic projections to document length discrepancy using a standard tube distance. A formula for calculating growth remaining in the femur and tibia was also established. Regardless of the age and size of the child, a growth arrest operation at the distal femoral epiphysis would retard growth at the rate of 3/8 of an inch a year, while at the proximal end of the tibia and fibula it would retard growth by ¼ in. a year. They accumulated a series of 202 separate growth arrests; of these 57 % were for poliomyelitis and 11.5 % for osteomyelitis.

6.7.3.3 Wilson and Thompson

Wilson and Thompson also derived a guide for timing epiphyseal arrest based on the expected amount of growth from each of the epiphyses [121]. Several years of documented lower extremity lengths were needed for each individual. If a discrepancy had not been increasing with growth, the present discrepancy would equal the expected discrepancy. If the rate of growth in the longer leg had been greater than in the shorter extremity a discrepancy would continue to increase proportionately. They calculated the expected discrepancy, related it to the expected growth in the longer extremity, and chose the appropriate physis for ablation. Fourteen patients averaging 12.5 years of age at time of surgery had been observed from 1 to 4 years postsurgery. Seven of these showed a lessening in discrepancy of 1 to 1.75 in.; in 3 the decrease was 0.5 to 1 in.; in 2 the difference between the 2 legs remained the same; while in 2 the discrepancy increased slightly. Even in those cases where no limb length equalization occurred there was at least stabilization of any progressive discrepancy.

6.7.3.4 Gill and Abbott

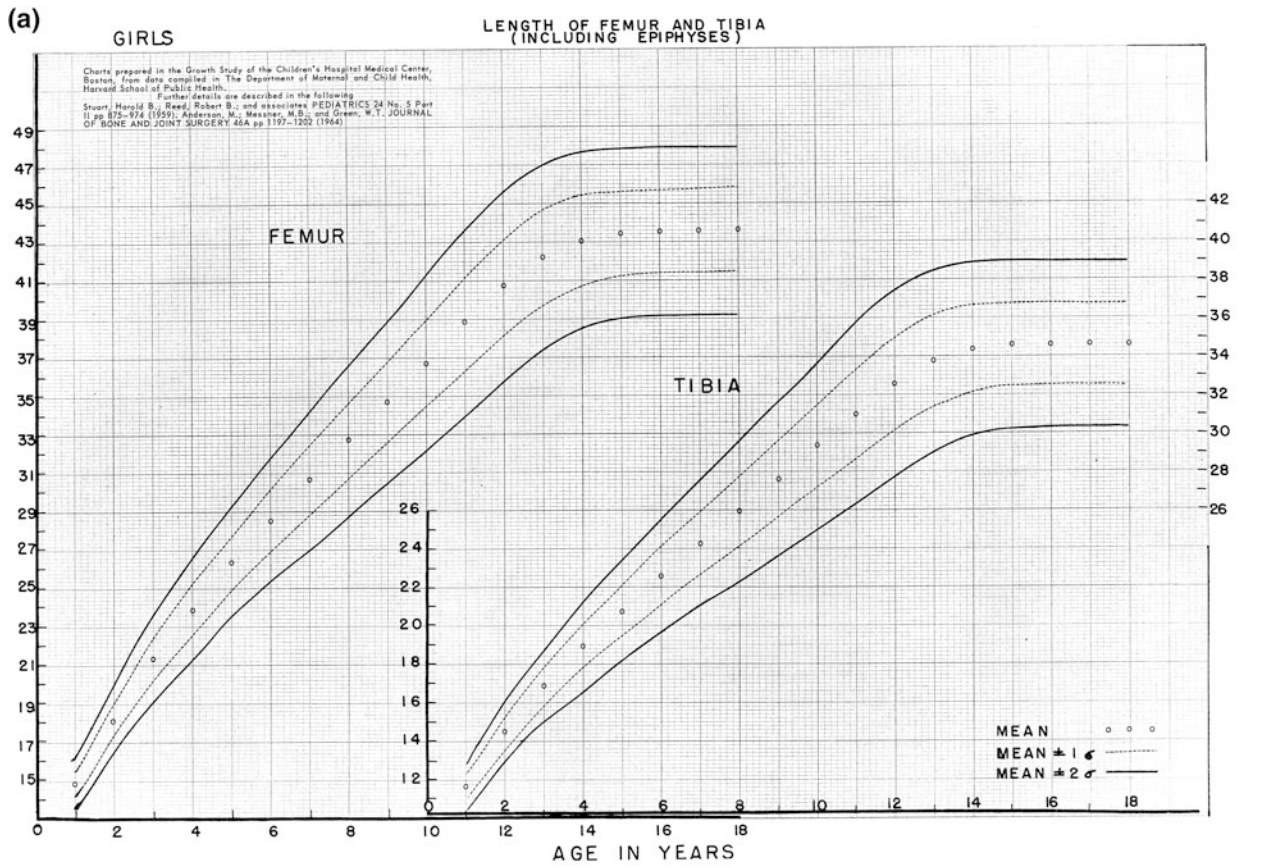
Gill and Abbott improved the accuracy of growth projections greatly by using percentile height tables and determinations of skeletal age [334]. Their method took the individual's relative growth and maturation rate into consideration rather than using average values, as had been done previously, although the limb lengths were based on percentage determinations from data for total body height. Gill and Abbott pointed out five major criticisms in relation to the methods used by Phemister, Hatcher, White and colleagues, and Wilson and Thompson. Their work began the era of accumulation and use of more accurate growth data. They pointed out that: average figures for the length of legs should not be applied because of the wide variations in the final length of individual children; leg lengths determined as proportions of overall height were far less reliable than radiographic measurements that they were beginning to use; no allowance had been made previously for variations in sexual and skeletal development in children of the same age; use of parents' measurements was not reliable in determining future growth of the child; and the numbers used by Digby presupposed that the femur and tibia grew at the same relative rate during the entire period of growth. Many studies, even then, showed this latter point to be untrue with some data showing that the tibia obtained its final growth before the femur. Their method was based on three major principles: (i) the final stature of a child could be predicted by use of the percentile method; (ii) the accuracy of growth projection would be increased if the bone maturation age of the child was considered; and (iii) the relative proportions of the length of the femur and the tibia to overall stature were maintained with only small variations throughout the adolescent period. Among the principles of general and limb development that they utilized were the relationship of overall patient height to the age and percentile, utilization of separate tables for males and females and assessment of skeletal maturation using Todd's Atlas of Skeletal Maturation. They began to utilize skeletal maturation ages for growth calculations if skeletal development was >6 months advanced or retarded from the chronologic age. Length data were then placed in a specific percentile range to allow final length to be determined relatively early. Femoral and tibial lengths were quantitated radiographically using either teleoroentenograms or scanograms. The expected final lengths of each bone were calculated. By subtracting the present length of the normal femur from its expected final length, the future expected growth of the bone was obtained. This was done separately for femur and tibia. It was then possible to determine growth from the distal part of the femur which

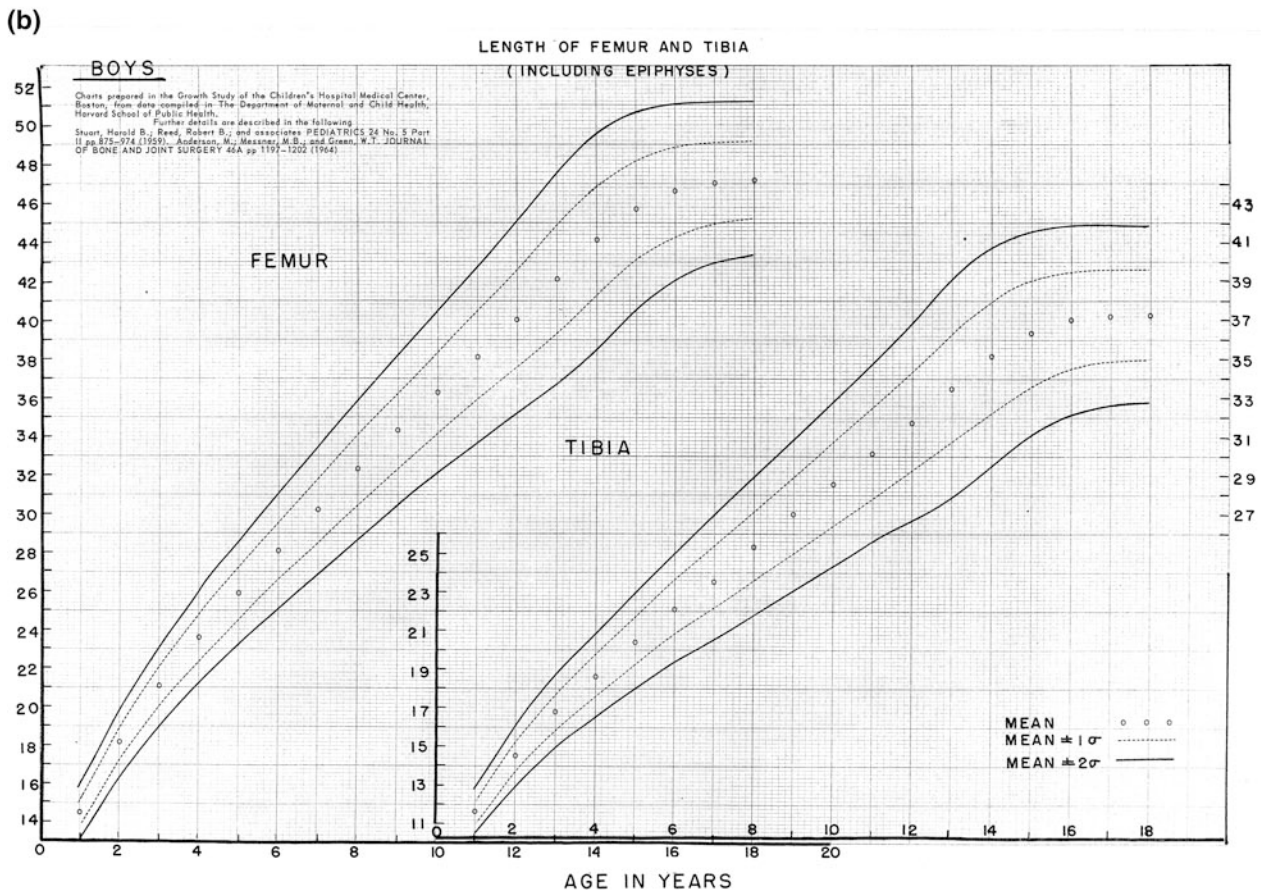
would be 70 % of expected femoral growth. Similar approaches were used for the proximal tibia: the expected proximal tibial growth was 55 % of the expected tibial growth. They calculated expected final lengths of femur and tibia by relating them to projected adult stature since numbers with appropriate percentiles were available for overall stature but not at that time for femoral and tibial lengths. Direct femoral and tibial length measurements were eventually determined by Maresh [321, 322] and by Anderson et al.[323]. The relationship of the femur and tibia to overall stature, however, was felt to be stable with growth. Based on a femoral radiograph and total body height measurement, they were able to determine the femoral percentage of stature which, for example, was frequently 28 %. They then determined the patient's final overall stature from the charts and calculated the final femoral length as being 28 % of that. The remaining expected growth of the femur and tibia could also be calculated as could the growth at proximal and distal ends of each of the major long bones. The accuracy of their predictions was dependent on the exactness with which height could be predicted by the percentile method. The method was felt to be valuable since any given child tended to maintain his or her rank in stature from one age to another. Much data was also presented to indicate that the relative proportions of femoral and tibial length to overall stature were maintained throughout growth with only small age variations. The percentage of growth from each end of the bone could then be calculated based on the proximal femur 30 %, distal femur 70 %, proximal tibia 55 %, and distal tibia 45 % numbers. The growth remaining could be further calculated. Gill and Abbott showed the reasonably high accuracy with which they could estimate expected growth of the normal limb. The next problem in terms of treatment of lower extremity length discrepancies involved estimates of the expected growth of the abnormal limb. In experimental efforts to determine how much growth was occurring in physes which were open but growing at a slower than normal rate, for example with poliomyelitis, Gill and Abbott inserted small metallic markers in the affected bones through a special hypodermic needle, although this method could not be used widely in a clinical setting.

6.7.3.5 Green and Anderson

Shortly after Phemister demonstrated the value of epiphyseal arrest in the longer extremity to allow for relatively straightforward correction of lower extremity length discrepancies during the final years of skeletal growth, it became evident that more accurate growth data would greatly enhance the timing and thus the accuracy of the procedure. Green, Anderson and Messner of the Children's Hospital, Boston played a major role in developing femoral and tibial growth data [323, 335]. They worked in conjunction with Stuart and Reed and associates at the Harvard School of Public Health who were performing a longitudinal series of child health and development studies from 1930 to 1956 [336]. The patients assessed involved 134 healthy children, 67 boys and 67 girls, who were followed from birth to 18 years of age. Assessments began in 1930 when the first mother was enrolled in the study and continued until 1956 when the last child was discharged from assessment at 18 years of age. Part of the study involved a completely longitudinal series of radiographs of the lower extremities in the 67 boys and 67 girls who had annual lower extremity radiographs as part of the observations in the comprehensive longitudinal study program. Very early in the program the standardized lower extremity radiographs utilized the orthoroentographic technique which ensured a high degree of accuracy with each assessment. Radiographs were performed once yearly. In 1964 Anderson, Messner, and Green published their normal femoral and tibial growth charts [323]. Separate assessments were made for the femur and the tibia in both boys and girls. Values at each year included the mean length of the bone including the epiphyses and publication of growth charts in which the mean value was indicated as well as those values 1 and 2 standard deviations above and below the mean. Values were listed from 1 year of age to 18 years of age. These are printed as Fig. 6.15a, b.

The socioeconomic status and national origin of the patients in this study were defined by Stuart and Reed [336]. Enrollment was limited to white males and females of predominantly North European stock and all but 48 of the 592 parents of the children initially enrolled were born in the United States, with most of the others born in Ireland and brought to the United States early in life. The vast majority of children therefore were born in North America and family origin was from North America, the British Isles, or Northern European countries. The predominant national origin of the families enrolled was Irish. The patient population was drawn from the clinics at the Children's Hospital such that it tended to exclude those of high economic status and the indigent. Additional growth data generated by the study allowed for charts to be constructed indicating recumbent and erect overall height in boys and in girls. Recumbent height was measured between 1 and 6 years of age and standing height between 6 and 18 years of age. Charts incorporating the data outlined the mean values and also those 1 and 2 standard deviations above and below the mean. Sitting height charts were also produced for boys and girls. In a separate publication, Anderson, Green, and Messner derived charts indicating the growth remaining in the normal distal femur and proximal tibia observed in a longitudinal series following given skeletal ages [335]. The "growth remaining" data were derived from 100 children, 50 girls and 50 boys, measured at least once a year over the 8 years before growth terminated in their lower extremities. Of this number, 51 children were normal (25 girls and 26





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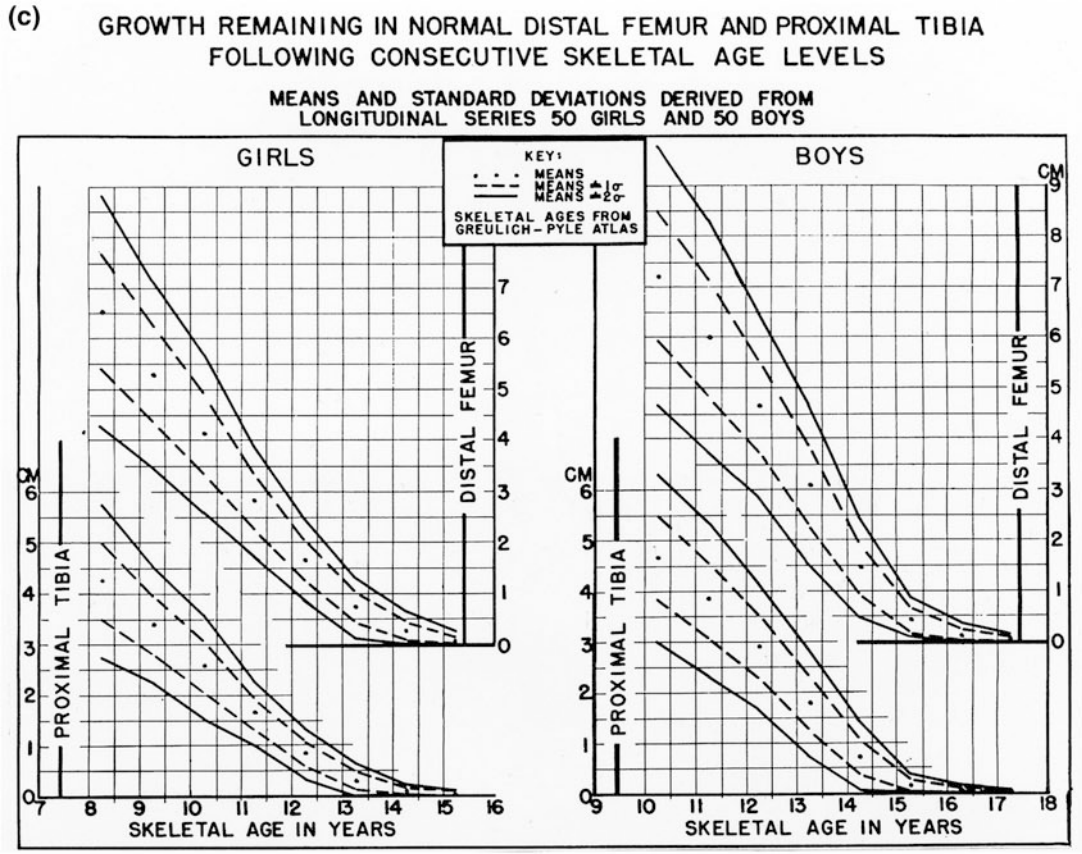


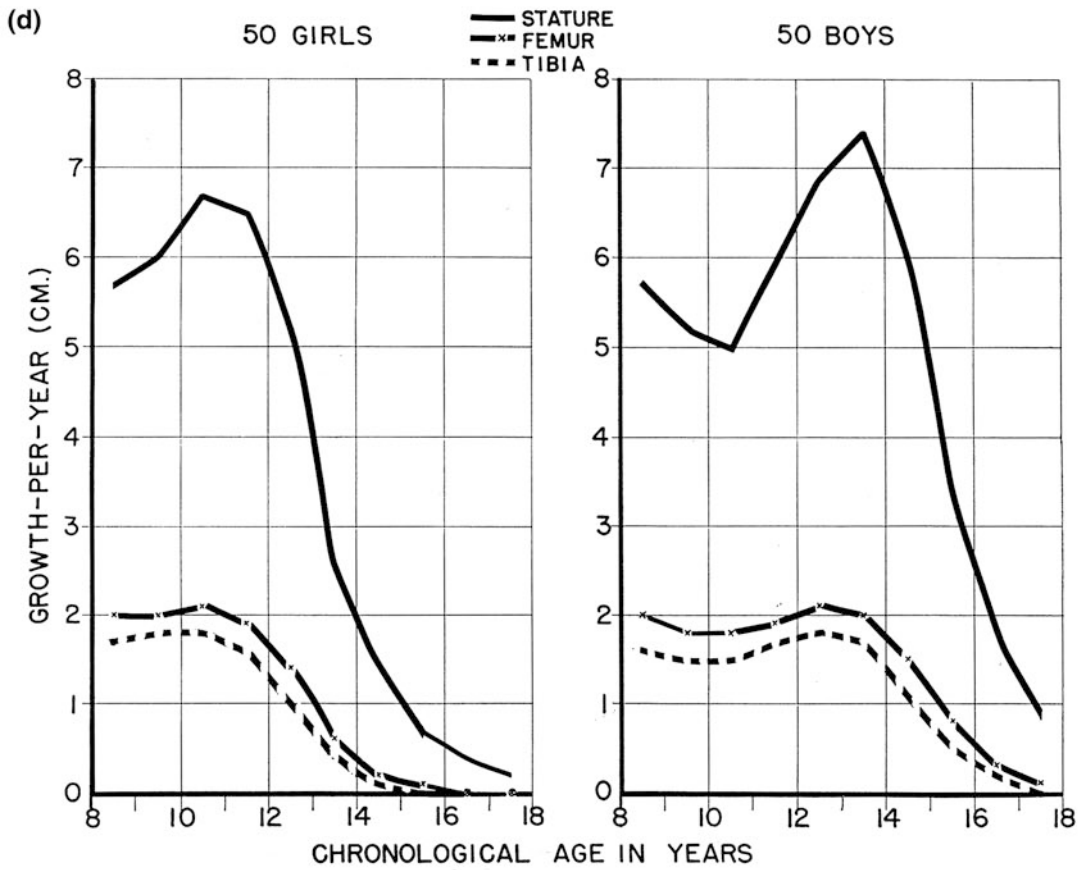


Fig. 6.15 (continued)

boys) and 49 children (25 girls and 24 boys) had poliomyelitis which affected only 1 lower extremity with the opposite normal extremity used for data accumulation. The maturity of each child was evaluated from the radiographic appearance of the bones in the hand and wrist with the skeletal ages being read from Greulich and Pyle Atlas. The normal children were part of the longitudinal study from the Harvard School of Public Health whose radiographic studies were also used to derive the normal femoral and tibial length charts. The normal and poliomyelitis groups were analyzed separately before the data were combined. No statistically significant differences were found between the two at any age either in the patterns of maturation or in the average amounts of growth that occurred after specific skeletal ages. The growth remaining charts indicate values for the distal femur and proximal tibia in boys and girls with data in the girls beginning at 8 years of age and in the boys at 10 years of age. Values are listed as the mean amounts plus those in the first and second standard deviations above and below the mean (Fig. 6.15c). Annual increments in lengths of femur and tibia in males and females are illustrated compared to total height above (Fig. 6.15d). The Growth Study unit at the Children's Hospital, Boston was founded by Green in 1940 at which time the major cause of lower extremity length discrepancies was poliomyelitis. The unit was initiated with support from the National Foundation for Infantile Paralysis. Details relating to the use of the Green-Anderson method for projecting timing of epiphyseal arrest will be described below and in the following Sects. 6.6, 6.7 and 6.8.

In a study of 125 epiphyseal arrest procedures in their unit followed to skeletal maturity correction to within 1.2 cm (½ in.) of prediction occurred in 89 % of cases [337].

6.7.3.6 Menelaus

Menelaus developed a simplified approach for projecting eventual length discrepancies based on chronological rather than skeletal age [338]. It was assumed that the lower femoral epiphysis provides 3/8 of an inch and the upper tibial epiphysis 1/4 of an inch of growth each year. It was further assumed that growth of these epiphyses stops at the chronological age of 16 years in boys and 14 years in girls. Skeletal age is estimated but primarily to allow for a calculation of the predicted adult height. Epiphyseal arrest is then resorted to only if this adult height will be acceptable. In addition, a marked difference between skeletal and chronological ages indicates that any calculation for the timing of the epiphyseal arrest is likely to be inaccurate.

In a study of 44 patients having had 53 epiphyseal arrests who were followed to skeletal maturity, Menelaus indicated that 52 % were within 1/4 in. of calculated discrepancy and an additional 41 % were within 3/4 of an inch [338]. Those with more than 3/4 of an inch error were only 7 % of the operative cases. He felt that this approach compared quite favorably with the use of skeletal age as proposed by Green and Anderson. In their 1957 report of patients with poliomyelitis, 89 % were within 0.5 in. of calculated discrepancy while in Menelaus' series those with poliomyelitis showed an 85 % effectiveness within 0.5 in. [338].

In a later study of 94 patients described by Westh and Menelaus, 85.1 % were within 0.5 in. of that calculated and 94.1 % of those had final discrepancy within 3/4 of an inch of that calculated [339]. The values are expressed in that fashion since equalization was not specifically sought in many of the patients who had poliomyelitis since the weakened limb was often deliberately left somewhat shorter than the stronger.

6.7.3.7 Moseley

Moseley, using the Anderson et al. data, developed a straight-line graph for leg length discrepancies by converting the normal growth curve using logarithmic methods into a straight line (Fig. 6.16a, bi, ii) [340, 341]. Moseley based his straightline graph method on 2 concepts not previously used in growth projections. The first was that the growth of the legs could be represented on a graph by straight lines and that a nomogram relating leg length to skeletal age could provide a mechanism for taking the child's growth percentile into account in predicting at what lengths the growth of the legs will stop. The first concept simply involved converting the exponential curve of normal growth to a straight line by plotting the data against a logarithmic scale. The Anderson, Messner and Green data were used to construct the chart. Moseley pointed out several of the important consequences of this way of depicting the growth data: (i) the growth of the short leg was also represented by a straight line which was positioned below that of the longer leg and tended to have a different slope; (ii) the leg length discrepancy is represented by the vertical distance between the two lines; (iii) the percentage inhibition of growth of the short leg is represented by the difference in slope of the two growth lines designating the slope of the normal leg as 100 %; (iv) the growth of the leg that has undergone surgical lengthening thereafter follows a straight line of the same slope which is displaced upward on the graph by an amount equal to the lengthening

◀ **Fig. 6.15** Femoral and tibial length charts presented by Anderson, Messner and Green. **a** Femoral and tibial length chart for girls is shown. **b** Femoral and tibial length chart for boys is shown. **c** The growth remaining chart documenting distal femoral and proximal tibial growth remaining in relation to skeletal age for boys and girls is shown. **d** Annual increments in length of femur and tibia in males and females are shown below compared to total height above

achieved; and (v) the length of a leg that has undergone epiphyseal arrest will follow a straight line of decreased slope where the decrease in slope exactly equals the percentage contribution that the fused growth plate would otherwise have made to the total growth of the extremity. Since the contributions of the proximal tibial and distal femoral growth plates are 28 and 37 %, respectively, of the total growth of the leg it is possible to predict the amount of inhibition to be introduced by an epiphyseal arrest. The Moseley approach was widely adopted.

6.7.3.8 Beumer et al

Beumer et al. performed radiographic length documentation of femurs and tibias in 182 Dutch children to address concerns that different groups than those assessed in North America might have different growth results and that children now grow taller than those of 50 years ago due to improved socioeconomic trends [324]. They then used the data to construct a straight line graph, similar but not identical to the way Moselely worked with length data. They developed the Rotterdam Straight Line Graph (R-LSG), referring to the Moseley graph as the M-SLG method. At most ages, Dutch children had longer femurs and tibias than in the data of Anderson et al. although the differences appear so slight that growth projection should not differ in clinically significant ways, especially since in any individual patient right and left legs are compared.

6.7.3.9 Hechard and Carlioz

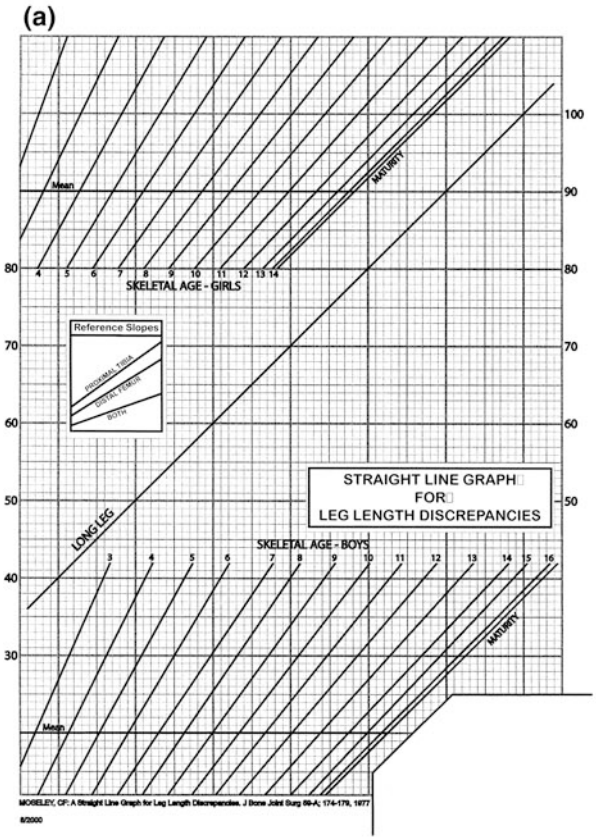
Hechard and Carlioz also developed a growth chart for the long bones based on the data of Anderson, Green and Messner (Fig. 6.16c) [342]. The limb lengths from 15 cm to 54 cm were listed on a single chart as were the bone ages for both females and males. Since, in the vast majority of instances, normal growth persisted along its same percentile projections were readily made at a glance. In addition by plotting the length of the abnormal extremity with time its pattern of change in relation to the normal side could be viewed easily and projections readily made. The method for projecting the inequality in length provided a document which could follow the growth evolution at a glance. Before 4 or 5 years of age the rate of growth per year increased from year to year; between 4 and 13 years for girls and 5 and 14 years for boys the rate of growth annually was constant; while toward the approach of skeletal maturity the rate of growth diminished in a regular fashion. It was evident therefore that the majority of children examined for a lower extremity length discrepancy were seen during the period of linear increase in growth. By eliminating the extremes of age at either end, a linear depiction of growth was felt to be acceptable in terms of accuracy for the clinical situation. The values for bone ages and femoral–tibial lengths were listed in girls from 5 to 14 years of age, and for boys from 6 to 16 years of age (Fig. 6.16c).

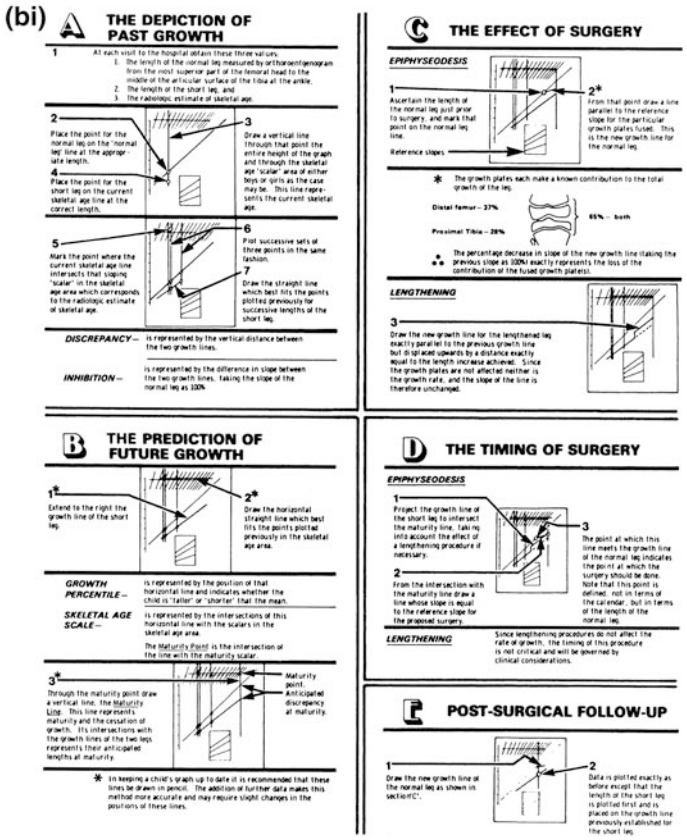
6.7.3.10 Eastwood and Cole

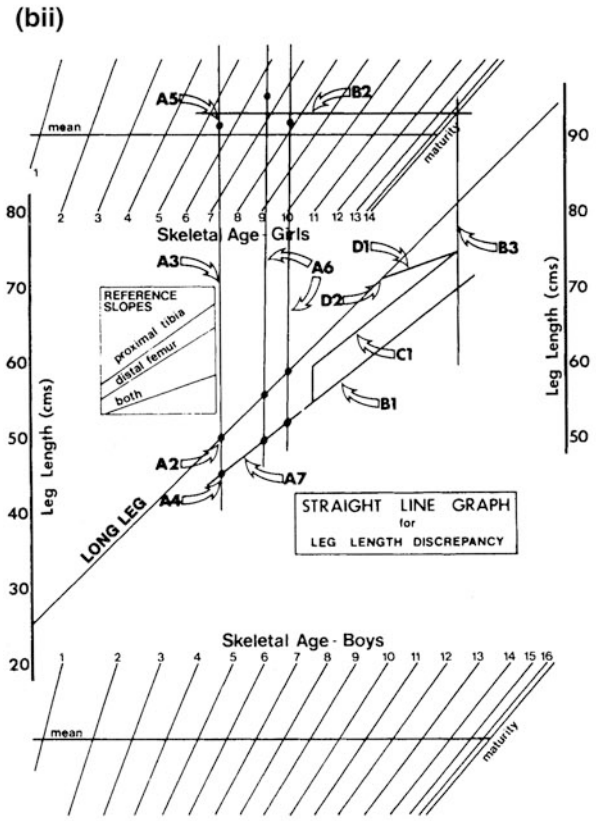
Eastwood and Cole described a clinical method for the graphic recording, analysis and planning of lower extremity length discrepancies during the growth years [343]. Their chart lists length discrepancy in cm along one axis and chronological age in years along the other (Fig. 6.17). The average maturity lines were marked for girls at 14 years and for boys at 16 years. Superimposed on the graphs are epiphysiodesis reference slopes (slopes 1–3) which converge to the skeletal maturity lines at zero leg length discrepancy. The slopes of these lines are based on the average annual growth of 1.0 cm from the distal femoral growth plate and 0.6 cm from the proximal tibial growth plate after the age of 8 years in girls and 10 years in boys. These approximate values (3/8 and ¼ in. respectively) were also used by White and Stubbins, Anderson et al. and Westh and Menelaus. The graphs depict the estimated mature discrepancy and timing of surgery. Eastwood and Cole indicate that the pattern of differential growth of the legs is determined from the graph such that the developmental patterns defined by Shapiro are documented and then used to predict the pattern of further differential growth and eventual leg length discrepancy projected for skeletal maturity. The observed discrepancy line (line 2) is projected to the skeletal maturity line (line 3). The point of intersection (*Y*) gives the estimated mature discrepancy. The mature discrepancy line (line 4) is drawn horizontally from point *Y* and may intersect one or more of the epiphysiodesis references slopes. The slopes are for proximal tibial arrest alone, distal femoral arrest alone, or a combination of the 2. Vertical lines are dropped from these points of intersection to give the chronological ages for epiphysiodesis of the appropriate growth plates (*X* and *X*1) (Fig. 6.17). This method incorporates the different patterns of discrepancy into the plotting of the appropriate time for surgery without the need for specific calculation of the growth inhibition rate as is done in the Green-Anderson method.

6.7.3.11 Paley et al.

Paley et al. developed the multiplier method for predicting limb length discrepancy at skeletal maturity [344]. It is applicable to congenital or developmental limb length discrepancy where the short limb grows at a rate that is always proportional to the normal long limb. These disorders are the most frequent causes of limb length discrepancies and also lead to the most severe or extensive deformities. The method is thus applicable to the type I developmental length discrepancy pattern. The multipliers are derived from the Anderson et al. data for femoral and tibial growth from 1 to 18 years of age and from the Marsh data from birth to







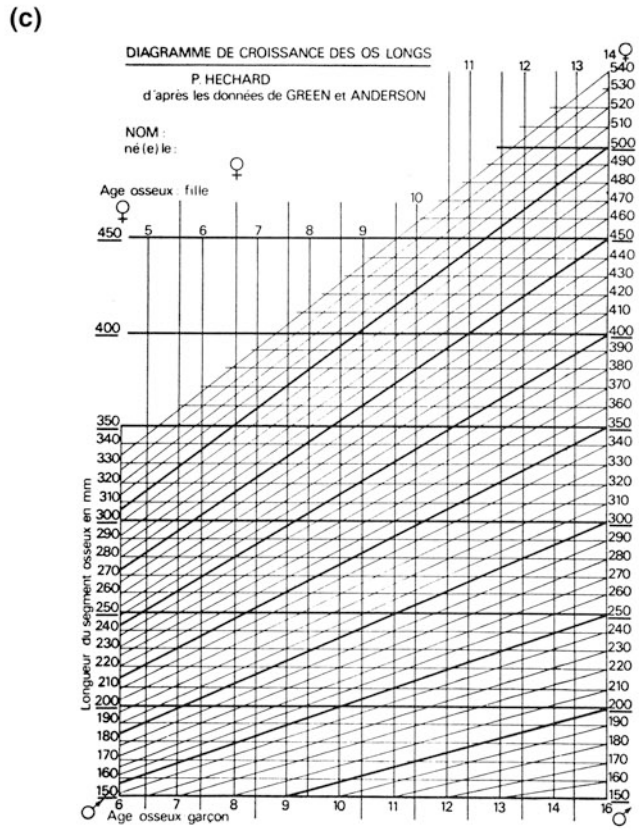


Fig. 6.16 (continued)

skeletal maturity. Data in both studies was obtained by standardized radiographs. Using these databases, they divided the femoral and tibial lengths at skeletal maturity by the femoral and tibial lengths at each age for each of the five percentile groups in boys and girls. The resultant number is the multiplier. The multipliers for the femur and tibia are equivalent in all percentile groups, varying only by age and gender. Because congenital limb length discrepancy increases at a rate proportional to growth the discrepancy at maturity can be calculated as the current discrepancy times the multiplier for age and gender. One measurement alone can allow for an accurate projection of eventual discrepancy. The percentile groups are the mean, mean plus one standard deviation, mean plus two standard deviations, mean minus one standard deviation, and mean minus two standard deviations. The values thus correspond (from lowest to highest) to the 5th (−2.5D), 33rd (−15D), 50th (mean), 67th (+15D), and 95th (+25D) percentile.

Paley et al. also obtained femoral and tibial growth data and calculated age and gender-related multipliers from additional databases. Overall they assessed 20 databases, 11 based on radiographic or clinical measurements of living children and 9 based on anthropological measurements of femoral and tibial bones. The multipliers derived from radiographic, clinical, and anthropological measurements of femurs and tibias were all similar. Femoral and tibial multipliers at the same age were also nearly identical, allowing them to average the mean multipliers to obtain overall lower limb multipliers for boys and girls. A more recent radiological study in Dutch children between 1979 and 1994 allowed Beumer et al. to demonstrate that their population was taller than the American groups studied in the 1930s–1950s [324]. In spite of this, the multipliers were "approximately the same" in the two databases. The lower limb multipliers for boys and girls are shown in Table 6.2.

Multipliers have also been determined for upper extremity lengths (humerus, radius, and ulna) [345], the foot [346], fetal prenatal lengths for prediction of bone length at birth [347], and adult height [344]. The study by Paley et al. on the upper extremity used a wide range of radiographic, clinical, and anthropological databases, similar to their approach with the earlier lower extremity studies [344]. Studies separated males from females and also determined multipliers for various percentiles. The multipliers for different national and racial groups were the same.

6.7.4 Discussion of Methods Used

The previous Sect. (6.7.3–6.7.3.10) have shown the evolution of approaches to determining the expected discrepancy at skeletal maturity and the appropriate time for epiphyseal arrest to allow for diminution of the discrepancy during the remaining years of growth either to make both limbs equal at skeletal maturity or, as may be the case in certain instances of weakness of the short limb, to minimize but not completely eliminate the discrepancy at skeletal maturity. The most detailed conceptual advance and practical work was done by Gill and Abbott who developed the concepts needed for accurate growth determination [334]. The studies of Green and Anderson and colleagues provided the data needed to construct the appropriate growth charts for femoral and tibial lengths, from which the growth remaining charts were also derived [323, 335]. Both Anderson et al. and Menelaus derived formulae to aid in determination of the appropriate time for epiphyseal arrest. Green and Anderson based their determinations on skeletal age while Menelaus used chronologic age for most patients. Green and Anderson were able to derive a method utilizing their growth charts. They incorporated the concept of a growth inhibition formula to aid in ultimate timing for epiphyseal arrest. Growth inhibition was calculated as a formula: [(growth of the long leg–growth of the short leg)/growth of the long leg]. This formula enabled them to determine a rate of growth inhibition which then served to indicate how much the discrepancy would increase over the remaining years of growth. For example, from any time period reference to the normal growth charts would indicate how much growth of the longer or normal leg was expected prior to skeletal maturity. Growth inhibition was then calculated from a time period of sufficient length to provide accurate data. The assumption was then made that the growth inhibition would be constant throughout the period of growth. It is evident that this is not true for all discrepancies. In practice, however, the Boston Children's Hospital Growth Study unit frequently took a slowing of growth inhibition into account although there was no specific formulaic method for this. If the growth inhibition was calculated as 0.4 and the future projected growth of the normal leg was 10 cm, then the future increase in discrepancy was considered to be 10 × 0.4 or 4 cm. This would be added to the discrepancy at the time that the projection was made to yield the final discrepancy at skeletal maturity.

◀ **Fig. 6.16** **a** The Moseley straight-line graph is shown in both Figures **ai**, **ii** (Reprinted with permission from Moseley CF, A straight line graph for leg length discrepancies. Clin Orthop Rel Res 1978;136:33–40. Copyright 1978 Wolters Kluwer Health). **bi**, **ii** Detailed presentations explaining use of the *straight-line graphs* are shown. The step-by-step method is illustrated and described in **bi** and a case example is outlined in **bii**. **c** The Hechard-Carlioz growth chart depicts the length of the lower extremity bones from 150 to 540 mm and allows for representation of boys and girls with bone age in girls going from 5 to 14 years and in boys from 6 to 16 years (Reprinted with permission from Hechard and Carlioz, Methode pratique de prevision des inegalities de longeur des membres inferieures. Rev Chir Orthop 1978;64:81–87. Copyright 1978 Masson Editeur)

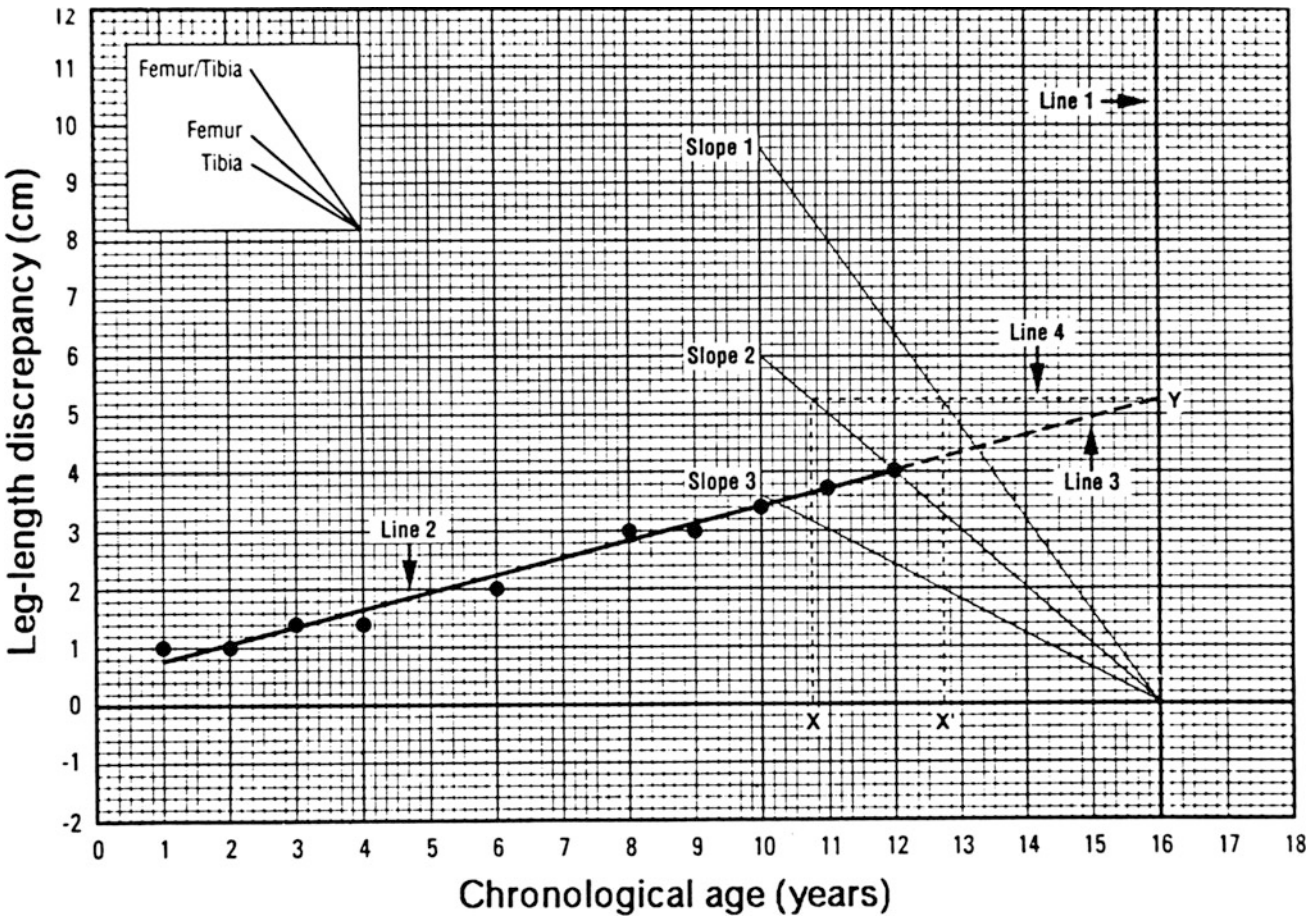


Fig. 6.17 The clinical leg length discrepancy graph for boys derived by Eastwood and Cole is shown. *Line 1* shows the skeletal maturity line which for boys is 16 years of age and for girls 14 years of age. *Line 2* documents the observed discrepancy in chronological years. *Line 3* is the projected discrepancy. *Line 4* is the mature discrepancy *line*. It is drawn horizontally from point *Y*. *Slope 1* is the femoral and tibial epiphyseal arrest reference slope, *slope 2* the femoral epiphyseal arrest reference slope and *slope 3* the tibial epiphyseal arrest reference slope. *Y* is the estimated mature discrepancy with *X* and X^1 representing the chronological ages for femoral or femoral and tibial epiphyseal arrests respectively (Reprinted with permission from Eastwood and Cole, A graphic method for timing the correction of leg length discrepancy. J Bone Joint Surg Br 1995;77B:743–747)

The appropriate timing for epiphyseal arrest would then be determined from the growth remaining charts. Since the correction would be made by the shortened leg the percentile along which the shortened leg was growing was determined from the normal femoral and tibial length charts. If this was a standard deviation below the mean, then that particular line was referred to on the growth remaining chart and the appropriate skeletal age to make up the specific discrepancy was decided upon. The conceptual changes introduced by the Moseley, Hechard and Carlioz, and Eastwood and Cole graphs primarily involved depiction of the growth data graphically such that growth inhibition would not have to be specifically calculated but was simply taken into account by plotting the growth of the normal and affected limbs on the chart which allowed the discrepancy to be read directly. These methods, each of which have their advocates, are indeed simpler than calculation of the growth inhibition itself and have been adopted by many.

All these studies are made more accurate by plotting 3 or more time points. Paley et al. recognized that for Shapiro type I discrepancies which do increase at a constant rate with time a multiplier can be determined for each sex, age, and percentile from the established growth charts in which the current length is multiplied by the multiplier to determine the final length. This method, in effect, needs only one measurement for the final determination.

It has been recognized for some time that the length parameter of normal growth can be represented accurately by logarithmic plotting [348, 349]. It is incorrect, however, to assume that pathological processes are as readily predictable by logarithmic plotting or any other formula. The straight-line graph of Moseley [340, 341] or the

growth-inhibition method of Green-Anderson [337, 350] or any of the methods described might well lead to inaccurate projections, particularly if the assessments are done too early in patients with conditions in which type II, late plateau type III, type IV, or type V patterns may be evolving. The types of pattern that occur in each disease category have been delineated. Knowledge of the developmental pattern classification, the natural and specific history of the condition causing a particular discrepancy, and the pattern type or types that occur in the condition allow the physician to project the ultimate extent of the discrepancy with clinically acceptable accuracy. The frequency with which clinical and radiographic evaluations of the discrepancy should be done must strike a balance. The evaluations should not be terminated too early or done too frequently on the expectation that straight-line graph or growth-inhibition projections always will suffice, and on the other hand they should not be done unnecessarily often, as though the eventual outcome were totally in doubt. The developmental patterns themselves cannot be used to make accurate mathematical projections, since growth, particularly during growth spurt periods and immediately prior to skeletal maturity, is not linear with time. The patterns do, however, permit accurate projections of discrepancy to be made using the femoral and tibial length charts and the femoral and tibial growth remaining charts which do take the nonlinearity of growth into consideration. The method of Eastwood and Cole incorporates both the discrepancy pattern classification and the Menelaus method.

The length and growth remaining charts were developed from information obtained by making yearly orthoradiographs of 67 boys and 67 girls between the ages of 1 and 18 years. Their value lies in indicating the lengths of the femur and tibia and the growth remaining in those bones plotted along percentiles in relation to the standard deviation position. Smooth curves of growth are shown, with the individual growth spurt that occurs between the ages of 10 and 14 years blurred by averaged data. When an individual child's growth is plotted, the growth spurt will often change the standard deviation position of the limb lengths. If maturation is relatively early the limb length will be on a higher percentile; if maturation is late the limb length will be on a relatively lower percentile. Awareness of this factor is important in determining the amount of growth remaining in a bone and in projecting its final normal length. Growth is generally linear between the ages of 4 and 10 years, and if a child is on the first standard deviation above the mean at the age of 7, at skeletal maturity limb length will also rest along that percentile. Thus, length data obtained before the adolescent growth spurt are of great value in indicating what the child's projected mature level will be. If information is available only from the period between 10 and 14 years,

Table 6.2 .

Age (years + mos.)	Multiplier	
	Boys	Girls*
Birth	5.080	4.630
0 + 3	4.550	4.155
0 + 6	4.050	3.725
0 + 9	3.600	3.300
1 +0	3.240	2.970
1 + 3	2.975	2.750
1 + 6	2.825	2.600
1 +9	2.700	2.490
2 + 0	2.590	2.390
2 + 3	2.480	2.295
2 + 6	2.385	2.200
2 + 9	2.300	2.125
3 + 0	2.230	2.050
3 + 6	2.110	1.925
4 + 0	2.000	1.830
4 + 6	1.890	1.740
5 + 0	1.820	1.660
5 + 6	1.740	1.560
6 + 0	1.670	1.510
6 + 6	1.620	1.460
7 + 0	1.570	1.430
7 + 6	1.520	1.370
8 + 0	1.470	1.330
8 + 6	1.420	1.290
9 + 0	1.380	1.260
9 + 6	1.340	1.220
10 + 0	1.310	1.190
10 + 6	1.280	1.160
11 +0	1.240	1.130
11 + 6	1.220	1.100
12 + 0	1.180	1.070
12 + 6	1.160	1.050
13 + 0	1.130	1.030
13 + 6	1.100	1.010
14 + 0	1.080	1.000
14 + 6	1.060	NA
15 + 0	1.040	NA
15 + 6	1.020	NA
16 + 0	1.010	NA
16 + 6	1.010	NA
17 + 0	1.000	NA

**NA* not applicable

however, awareness of the relationship of skeletal age to chronological age is important. If the skeletal age is retarded or advanced by 6 months or more in relation to chronological age, the correct growth percentile can best be determined by plotting the femoral and tibial lengths in relation to skeletal age, not chronological age. The Anderson et al. growth charts are derived from studies of white North American and northern European children during the time frame from 1930 to 1956. They thus reflect the growth characteristics and height variations of that group which would differ slightly from different racial groups and even from similar racial groups at differing time periods under altered socioeconomic climates. Even if the absolute height values between groups are slightly different, however, the pattern and percentile distribution would be unlikely to change in any meaningful clinical way. Since the values are read from the appropriate percentile and not simply determined as means or averages placing of any individual on his or her percentile, even if this were somewhat higher than the percentile placements for other groups of relatively smaller stature, would still lead to the appropriate projections with time. Beumer et al. have documented femoral and tibial growth radiologically in Dutch children from 1979 to 1994 [324]. Pritchett and Bortel studied individual bones creating single bone (femur and tibia) straight line graphs (using the Anderson et al. data) as well as single line growth remaining graphs. The mean, 10th, and 90th percentiles were recorded on the skeletal age nomogram [351]. This approach with multiple plottings of the normal and abnormal limb allowed for timing of interventions for epiphyseal arrest by comparing curves and growth remaining data by superimposing the normal and abnormal graphs. The ability to perform accurate imaging assessments without radiographic means, for example by use of ultrasonography, should enable newer charts of differing racial groups and in differing socioeconomic settings to be established.

The assessment of skeletal age is important in using the Green-Anderson method. While a wide variation in skeletal-age reading can be demonstrated among readers who do it infrequently, the assessments become much more reproducible when done by readers who do many. Although the Greulich and Pyle atlas has certain limitations, it still serves as a clinically reliable guide to the rate of skeletal maturation. The use of skeletal age versus chronologic age in growth studies will be addressed below in Sect. 6.9.2.2.

Management of the growing patient with a limb length discrepancy can be improved by knowledge of the classification of developmental patterns; the type or types of patterns that can occur with the particular disease process; radiographic documentation of the lengths of the lower extremities; a chart of the relationship between discrepancy and age, to outline the developmental pattern that is evolving; the percentile of the normal limb and the abnormal limb; and the patient's skeletal age.

6.8 Use of the Developmental Pattern Classification in Projecting Limb Length Discrepancies

Type I. The type I discrepancy increases at a constant rate with time, as the rate of inhibition or stimulation remains uniform throughout the growth period [50]. If one is certain that a type I pattern will evolve, one radiographic assessment of length, especially after the age of 2 years, will suffice for accurate determination of the final discrepancy, although more determinations are always performed. In the first 2 years of life there can be considerable shifting of length between various percentiles, whereas afterward the distinct tendency is for normal growth to persist along the same percentile. For example, if at the age of 4 years the involved femur in a child with proximal femoral focal deficiency is 63 % as long as the normal femur, one can project the final discrepancy by determining the length percentile on which the normal femur lies from the femoral and tibial length charts and noting the femoral length at maturity for that percentile. Sixty-three percent of the value represents the projected final length of the involved femur, and the difference between the 2 lengths represents the projected femoral length discrepancy. The length differential using the multiplier tables would also be accurate.

When the type I pattern is due to physeal destruction the femoral and tibial growth remaining data can be localized accurately to the involved physis, and the values for the distal end of the femur and proximal end of the tibia can be read directly from the chart. If the proximal femoral physis has closed, the projected growth loss is determined on the basis that 30 % of the remaining growth of the normal femur would occur at the proximal physis and 70 % at the distal physis. Similarly, if the distal tibial plate has fused, projected growth loss is determined on the basis that 43 % of the remaining growth would occur at the distal tibia and 57 % proximally. The amount of growth remaining in the entire femur or tibia is determined from the line that corresponds to the standard deviation position of the normal bone on the femoral and tibial length charts. Thirty percent of the difference between the present normal femoral length and the projected final length along the patient's percentile is the growth remaining in the normal proximal femoral physis.

Type II. This can be a difficult pattern to project because the discrepancy shows a decremental rate of increase which varies from patient to patient and from condition to condition. The information available from the period of constant increase has no predictive value, as the discrepancy values themselves cannot "be aware" that a change in discrepancy pattern is about to occur. This group therefore requires especially careful monitoring. An example follows: at the age of 11 years if a child's femoral discrepancy measures 5.0 cm the length on the short side is a cumulative 87 % of normal. The growth percentile on which the normal femur lies allows one to project its final length. The growth rate in the most recent six-month period however indicated that the short femur has shown 93 % growth in relation to the normal side, thus demonstrating the deceleration in the development of discrepancy. The growth remaining in the normal femur is 8.6 cm, as indicated by the femoral and tibial length chart. A projection of the change in discrepancy with time indicates that growth on the shorter side, based on the recent 6 month deceleration, would be at least 93 % of 8.6 cm, such that the discrepancy would increase only by 7 % of 8.6 cm, or 0.6 cm, yielding a final maximum projection of 5.6 cm of discrepancy. If there is more time before surgical intervention, a further 6 month growth assessment might allow for an additional calculation. By this time, projections that allow for a clinically acceptable result (discrepancy of <1.0 cm) can be made.

Type III. Once a plateau has been reached, the lower extremity length discrepancy will not change throughout the remaining period of growth. The prototypical type III pattern is seen with overgrowth following fracture of a femoral diaphysis. The timing for the corrective physeal arrest is arrived at by using the femoral and tibial length charts and the femoral and tibial growth remaining charts. The final discrepancy is known once the plateau phenomenon has been documented to have occurred, as neither further stimulation nor inhibition will occur.

Type IV. Type IV discrepancies characteristically are seen after hip diseases in childhood that affect the proximal femoral capital epiphysis, such as septic arthritis of the hip with mild-to-moderate damage, Legg–Perthes disease, and avascular necrosis of the femoral head in association with treatment of congenital or developmental dysplasia of the hip. Premature closure of the proximal femoral capital epiphysis can occur after the discrepancy has remained in a plateau phase for as long as a decade. Radiographic indication of premature fusion of the proximal femoral capital epiphysis is demonstrated by a change in the relationship of the femoral head to the greater trochanter due to relative overgrowth of the latter. The growth discrepancy to be expected from premature fusion, once it has occurred, is obtained by determining the growth remaining in the entire normal femur, determining 30 % of that valueto give the amount of overgrowth expected from the proximal end of a normal femur, and, since growth is not occurring, adding this value to the pre-existing discrepancy to give the projected final discrepancy.

Type V. If a discrepancy is beginning to correct itself, the growth charts are used to see how much growth remains. A determination can then be made as to whether the spontaneous correction will be insufficient, will result in equal limb lengths, or might result in overcorrection. The type V pattern is seen characteristically with chronic inflammatory disorders not fully responsive to therapy which stimulate growth under 10 years of age but lead to premature growth cessation toward the end of skeletal growth. The type V pattern is well documented in juvenile rheumatoid arthritis and appears to occur in many cases of hemophilia and tuberculosis where therapy is less than fully effective.

The developmental pattern classification provides a visual representation of the varying directional changes that can occur with time in lower extremity length discrepancies (Fig. 6.3a). The dependence of the patterns on the causes of the discrepancies and on the time and anatomical locations of their occurrence is stressed. The demonstrated relationships between the pattern type and the particular disease entity (Fig. 6.3b) should aid in planning the nature and frequency of discrepancy assessments. In those conditions in which several pattern types occur, the classification serves mainly to point out that variability. Some of the contributing factors to the various patterns within each disease entity have been assessed further. The patterns provide for an accurate projection of a final discrepancy in type I and in type III but not in types II, IV, and V. The patterns do, however, permit accurate projections of discrepancy to be made using the femoral–tibial length and growth remaining charts of Anderson and colleagues.

6.9 Management of Lower Extremity Length Discrepancies

6.9.1 General Considerations

As a general guideline, any discrepancy projected to be <2.0 cm at skeletal maturity should not require limb equalization; those discrepancies between 2.0 and 5.0 cm are usually treated with contralateral epiphyseal arrests to shorter the longer side; those >5.0 cm warrant consideration for ipsilateral lengthening; those beyond 8 cm often benefit from a combination of ipsilateral lengthening and contralateral shortening; and massive discrepancies in the 15 cm range or beyond might require prostheses with or without partial amputation. The aim of management is to ensure a discrepancy of <1.2 cm at skeletal maturity. This goal can be achieved in five basic ways: (i) by epiphyseal growth plate arrest in the longer limb at the appropriate time before

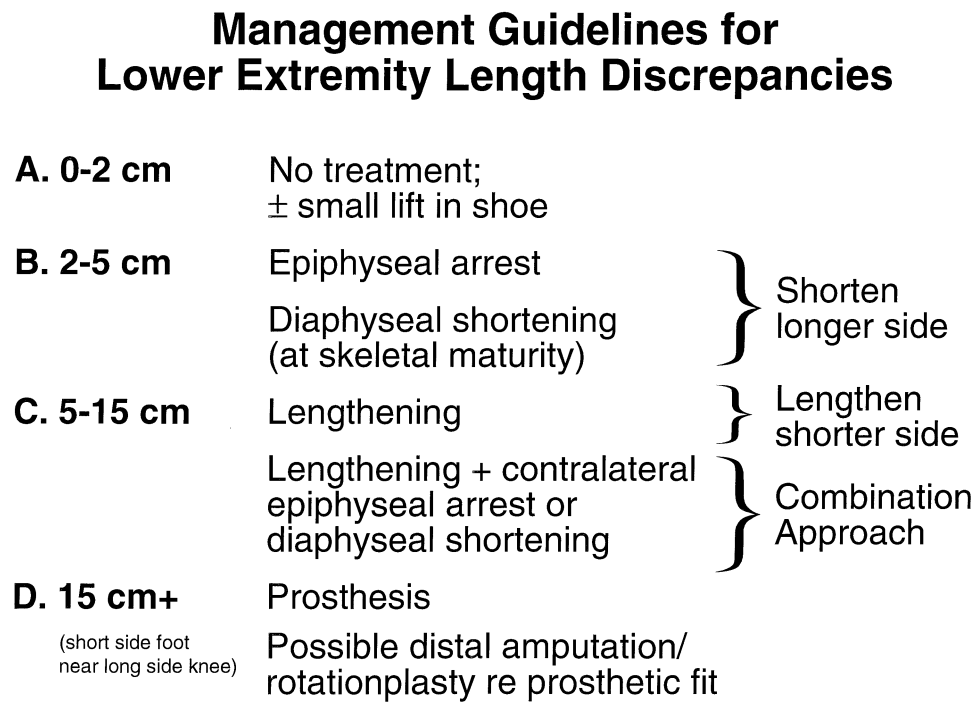


Fig. 6.18 Management approaches to discrepancies of increasing magnitude is shown. The management profiles *A–D* in each of the defined disorders leading either to stimulation or retardation of growth are shown in Table 6.1

skeletal maturity; (ii) by metaphyseal or diaphyseal shortening in the longer limb, removing a segment of bone at skeletal maturity; (iii) by lengthening the shorter extremity using metaphyseal or diaphyseal osteotomy and gradual distraction, transphyseal distraction, or transiliac osteotomy; and (iv) by combinations of shortening and lengthening cases with the more extensive discrepancies; and (v) for relatively massive discrepancies which leave the foot on the shortened side in the region of the midleg or knee of the longer side, prosthetic fitting and some or all of correction of angular deformity, joint stabilization, limb lengthening, distal limb rotationplasty or amputation fit may be required (Fig. 6.18). Several excellent reviews of the lower extremity length discrepancy entity were published [309, 352–355].

6.9.2 Procedures to Shorten the Longer Limb

6.9.2.1 Therapeutic Arrest of Growth Plate

Therapeutic arrest of the growth plate requires knowledge of the amount of further growth to be expected in each of the growth plates at a particular age and an accurate projection of the expected discrepancy at skeletal maturity. The lengths of the femur and tibia have been documented radiographically and plotted in percentile charts showing standard deviations, and charts of the amount of growth remaining in these bones have been developed. The approximate contributions of each of the major long-bone epiphyses to growth have been known for some time. In patients with a discrepancy in the length of the lower extremities, Green and colleagues used an index of the rate of growth inhibition to project the final discrepancy [97, 335, 337, 350, 356]. Moseley developed a straight-line graph for projecting length discrepancies by using logarithmic methods to convert the normal growth curve [340, 341].

Paley et al. derived the multiplier method for determining extent and timing of treatment for lower extremity length discrepancies [344]. Aguilar et al. subsequently showed the clinical value and accuracy of the method both for predicting limb length at maturity [357] and predicting limb length discrepancy and outcome of epiphysiodesis [358]. Each method can lead to inaccurate projections, in patients in whom the rate of change varies over time, if the assessments stop too early. The five patterns of discrepancy and their prevalence in each of the major conditions causing discrepancies in length have been delineated. Not all discrepancies increase at a constant rate, but the discrepancy at skeletal maturity can still be projected if the disease and the pattern of development are assessed carefully. The growth of the distal femoral, proximal tibial, and proximal fibular growth plates may be arrested when discrepancies are projected to be <5 cm at skeletal maturity. The function of the growth plate can be arrested surgically by inducing premature fusion between the epiphyseal bone of the secondary ossification center and the metaphysis; length discrepancy is then corrected by continuing growth of the shorter side.

Complete growth plate arrest of a normal functioning physis, if the contralateral affected epiphysis is still functioning, allows the shorter side to catch up in terms of growth. If the affected contralateral epiphysis no longer has

any growth, normal side epiphyseal arrest prevents any discrepancy from worsening but does not lead to any correction of the discrepancy. Complete epiphyseal arrest is most commonly used in treatment of lower extremity length discrepancies. The timing of the procedure is crucial to its success but can be determined effectively using any of several prediction systems. The most common sites for elective growth plate epiphysiodesis are at the distal femur and proximal tibia and fibula. In limb segments with 2 long bones (the leg and forearm) complete arrest of one growth plate often mandates arrest of the adjacent growth plate to prevent worsening of deformity and to maintain articular alignment.

Five technically effective ways of inducing premature epiphyseal arrest have been used.

(a) *Phemister technique*: At open operation a periphyseal rectangle of bone and cartilage is removed, rotated 180°, and replaced at both the medial and lateral sides of the involved bone end (Fig. 6.19a) [299]. The rectangle of tissue removed involves metaphyseal bone, epiphyseal bone, and the intervening growth plate with 2/3 of the length of the resected block on the metaphyseal side and 1/3 on the epiphyseal side. The size of the segment removed and then repositioned varies depending on the size of the bone. Phemister defined a 3 cm × 1.5 cm × 1 cm block of tissue with curettage of the physis anterior and posterior to the block of tissue removed to a depth of 1 cm. Once removed the block is rotated 180° so that the larger metaphyseal fragment bone completely bridges the remaining epiphyseal growth plate. The medial and lateral transphyseal bone bridges stop growth as soon as bone repair occurs and their peripheral tethering effect induces central physeal fusion. The White and Warner modification was popular with many (Fig. 6.19b) [332].

(b) *Green-Phemister technique*: Green, in his modification of the Phemister approach, removed a larger and deeper block of bone and cartilage medially and laterally, obliterated the remaining growth plate cartilage with drills and a curette and packed adjacent metaphyseal bone into the physeal defect [337, 350]. The rectangle of bone removed was approximately 1.5 in. long (1 in. diaphyseal; 0.5 in. epiphyseal), 1 in. wide and 3/4 in. deep. At the end of the procedure it was reversed 180° as in the Phemister approach, replaced into the defect, and the periosteum resutured in place. Metaphyseal–epiphyseal bone fusions leads to immediate growth cessation.

(c) *Blount stapling technique*: Blount used three large metallic staples placed medially and laterally at the anterior, middle, and posterior aspects of the physes to halt growth [359–362]. The principle involved is different from the two techniques described above; growth cessation is gradual since the physis must continue to grow until the prongs of the staple mechanically prevent further expansion. The original reason for this approach was to allow for subsequent removal of the staples and the resumption of growth if the timing of epiphyseal arrest proved to be too early such that the discrepancy was not only eliminated but continuing growth from the shorter side was about to reverse the discrepancy. This rationale was not always realized since in some cases the staples had caused complete cessation of growth and there was often no continuing growth of the physis once the staples were removed.

Blount and Clarke in their initial report on control of bone growth by epiphyseal stapling clearly laid out the principles of the approach [359]. They pointed out that Haas proposed and demonstrated retardation of physeal growth by a circumferential wire loop; a discovery of "the principle of temporary arrest of epiphyseal growth." [363, 364]. This approach utilized the principle of mechanical diminution of growth and was attractive to Blount since when Haas either removed the wire or the wire broke growth continued. Pressure inhibition of growth had also been demonstrated experimentally by Arkin and Katz [365].

Haas had utilized a mechanical principle of limiting physeal growth by passing a wire around the epiphyseal plate with one transverse path across the metaphysis and the other across the secondary ossification center with the ends twisted together to provide a continuous loop [363]. Several experiments in the dog were done each of which showed a definite loss in length growth of the bone. In some instances, the wire either broke or came loose at which time growth continued indicating that physeal growth while restrained by the intact wire did not lose its full potential which could be realized once the restraint was released. A few similar procedures were performed on patients with definite evidence of growth retardation noted. In the human growth also continued after breakage of the wire. Haas performed additional investigations in efforts to make the technique of clinical value [363]. In a second series of studies, staples were used instead of wire loops. The staples applied unilaterally across the physis arrested growth on the side of insertion and also restricted it on the opposite side to a lesser degree. In many instances, there was evidence of complete cessation of physeal growth. Enormous forces generated by the growing physis were readily apparent since either a single staple or the wire loop often broke allowing growth to continue. Even when two staples were placed, there was often separation of the tips or widening of the staples again indicating the powerful forces of growth not fully controlled by the staple.

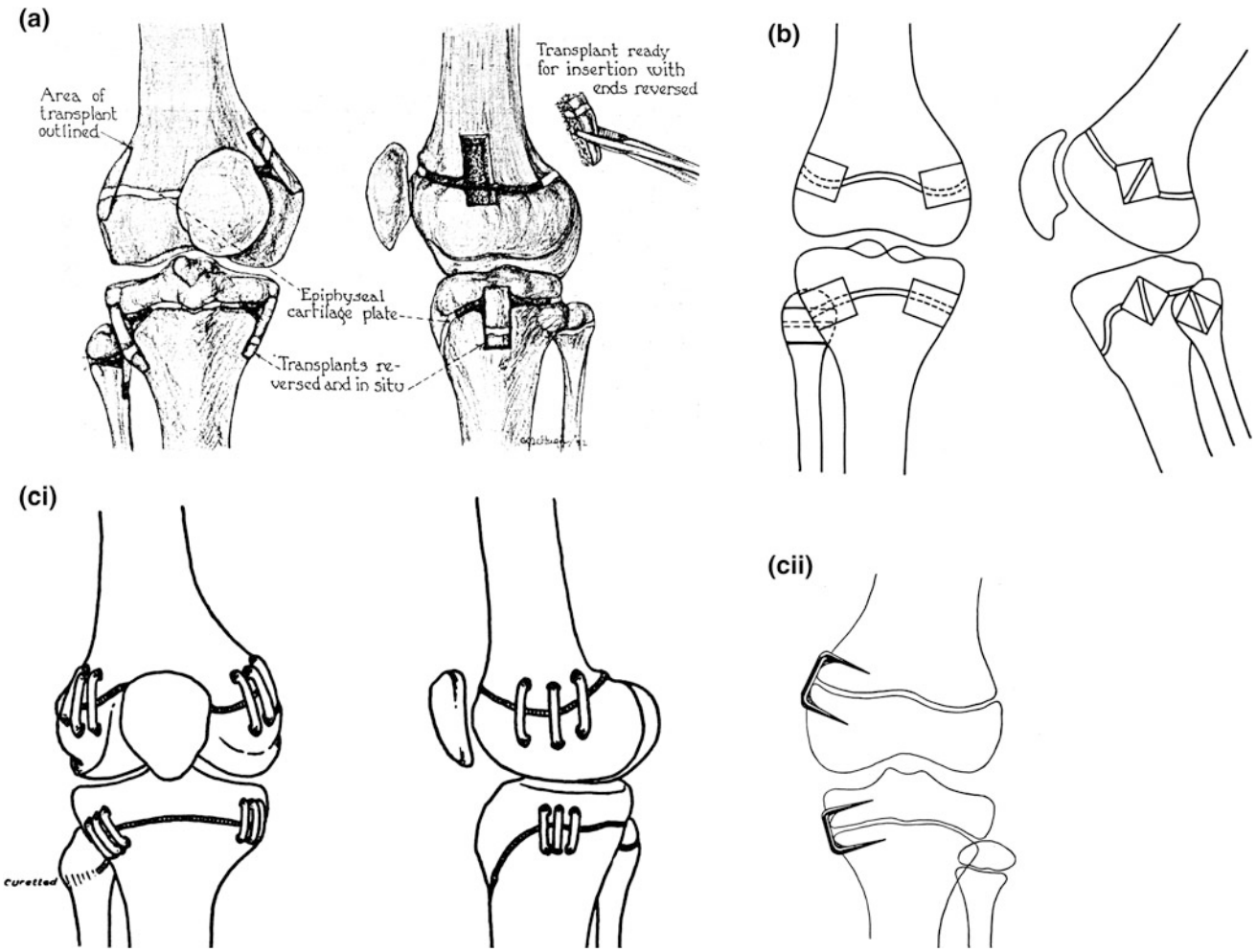


Fig. 6.19 Technical approaches to epiphyseal arrest are illustrated. **a** Drawing from Phemister's original work shows his outline of the reversed bone block technique. **b** The White modification of the Phemister technique is illustrated. At left the medial and lateral distal femoral and proximal tibial blocks to be removed are outlined. Once removed the ½ in. plugs containing epiphyseal bone, the epiphyseal growth plate cartilage and metaphyseal bone are rotated 90° and reinserted. Bone tissue now completely covers the physis and the bone bridge formed bilaterally tethers growth and leads to its cessation. The fibular block was soon recognized as being unnecessarily large and for fibular arrest most now simply curette the physis which also minimizes the chance of damage to the peroneal nerve. **c** Surgical approaches for the Blount stapling technique are shown in this figure **ci**. The medial approach is shown at *left* and the lateral approach at *right*. In this figure **cii** the correct insertion for the distal femoral and proximal tibial medial staples is shown. Each prong is equidistant from the physis and the alignment of the staple is parallel to that of the epiphyseal growth plate with the cross bar at right angles to the physeal cartilage and parallel to the bone surface. Three staples were placed medially and three laterally in each bone requiring arrest (Reprinted with permission from Blount WP, Unequal leg length, in Reynolds FC (ed): Instructional Course Lectures 17. Rosemont IL, American Academy of Orthopaedic Surgeons 1960; pp. 218–245)

Blount and Zeier pointed to the work of Strobino and Colonna that a force >120 pounds was needed to halt proximal tibial growth in a calf [360]. The routine use of three staples on medial and lateral sides of the physis was then adopted for clinical cases and the procedures used for distal femoral and proximal tibial growth arrests which during that era were generally for poliomyelitis. The procedure, which appeared technically quite simple, was adopted widely with relatively less consideration for timing since it was expected that any imperfect timing could be remedied simply by removing the staples at which time growth would resume. In a second report, Blount and Zeier reviewed 117 staplings noting few complications [360]. They concluded that staples could be left in place at least 2 years and still removed with the expectation that growth would be resumed. After removal of staples, there was usually a local growth spurt lasting a few months.

Frantz reviewed 10 clinical papers summarizing the first 2 decades of work with this technique [366]. Benefits and drawbacks became more clearly defined. One of the

problems, which was basically present in any epiphyseal arrest operation, was that of timing. The complications reported which tended to appear early in any series, included buried staples, metal reaction, overcorrection, premature physeal closure, peroneal palsy, knee joint laxity, misplaced staples, fractured staples, extrusion of staples, angular deformity, infection, genu valgum, and false aneurysm. It was widely agreed that stapling was not warranted under the age of 8 and preferably 9 years. Green and Anderson reported on both formal epiphyseal arrest and stapling and felt that both procedures were satisfactory with the incidence of complications relatively insignificant, although they used the stapling for definitive growth cessation [366]. In an experimental series of studies, Heikel demonstrated that epiphysiodesis of the proximal tibial plate had no effect on subsequent longitudinal growth distally [367]. Siffert performed asymmetric stapling of the distal femoral epiphysis in rabbits and noted production of the varus deformity with gradual histologic thinning of the physis and eventual transphyseal bone arrest [368]. Goff studied 120 biopsies of children at various stages of growth deceleration and arrest following stapling [369]. He observed that the direct compression by staples served to inhibit the proliferation stage of the physis. The thinness of the disk increased with time. The most sensitive sign of diminished growth was increased degeneration and shortening of the hypertrophic region. Eventually all the hypertrophic cells disappeared and new bone formation crossed from metaphysis to epiphysis. Bone bridge formation was present invariably after 4 years or 48 months although the markedly abnormal structure prior to that time would appear to have had little potential for regrowth. Bylander et al. studied growth of the physeal regions following stapling using highly accurate radiographic stereophotogrammetric analysis [370]. There was a uniform pattern of growth retardation following stapling which lasted over a period of several months to years. This pattern was evidence of the applicability of the original theory of stapling since it indicated slowing of physeal growth to basal levels rather than complete cessation of growth. They calculated that growth at the distal femur and proximal tibia in human patients continued at a low basal level of about 5–10 μm/day, in particular when stapling was performed at younger skeletal ages.

Blount pointed out the need for precise placement of the staples feeling that many of the imperfect results reported were due to improper timing or less than ideal technique [362]. The upper and lower prongs of the staple were to be equidistant from the physis and the cross member was to be perpendicular to the growth plate and parallel to the surface of the bone into which it was being driven (Fig. 6.19ci, ii). The staples were to be angled such that the tips of the prongs pointed toward the central axis of the distal femur or proximal tibia. Stapling was best performed after the patient had reached the skeletal age of 8 years. It was inappropriate to perform the stapling procedure according to a timing schedule set up for epiphyseal arrest since the stapling procedure was based on a different principle. Staples allowed for correction with growth but were not designed to cause complete immediate cessation of growth. Staplings needed to be done somewhat earlier than epiphyseal arrests. It was important not to bury the staples under the periosteum since they would be difficult to find at time of removal and were more likely to cause periosteal new bone formation and growth plate bridging. Blount indicated that "stapling of an epiphysis retards growth 80–90 % for the next few years. It causes a temporary growth spurt at the other end of the bone. At the stapled epiphysis, elongation is decelerated only 50 % during the first 6 months. Some growth continues until a year or less before the normal time for epiphyseal closure."

Sengupta and Gupta used two staples on each side of the distal femur effectively in the large majority of cases rarely resorting to three per side [371]. The two staples on each side were equidistant from each other with their tips pointing toward the center of the physis. Seventy-one percent of the 503 procedures led to a discrepancy of 0.5–1.0 cm shortening at the end of growth with only 3 % showing more than 2 cm shortening. The staples should be removed at skeletal maturity.

Gorman et al. have noted that mechanical axis deviation following staple epiphysiodesis for limb length inequality is significantly greater than was previously recognized [372]. They used final long standing anteroposterior radiographs of 54 patients at skeletal maturity to assess mechanical axis shifts from the preoperative state in patients undergoing distal femoral or proximal tibial or both sites medial and lateral (complete) epiphyseal arrests for limb length discrepancy. Fifty percent (27/54) of the patients showed a shift in the mechanical axis of 1 cm or greater compared with the preoperative measurement. Varus was the direction of deformity in 89 %. The most frequent sites of epiphyseal arrest causing the problem were isolated proximal tibial or combined distal femoral/proximal tibial procedures. The problematic region for attaining physeal fusion was the lateral proximal tibia; limited effect there compared to effective medial tibial physeal fusion led to the varus deformity. Distal femoral procedures alone were safest and most effective due to the more uniform anatomy. Six patients of the 54 (11 %) eventually underwent corrective osteotomy to improve alignment. Although occasional occurrence of angular deformity as a complication had been mentioned previously, only Brockway et al. in 1954 had specifically commented on the problem [373]. They noted 4/42 patients (9.5 %) who developed poststapling varus and 3 of whom had osteotomy for correction. The possibility of this occurrence leads to the recommendation of transphyseal epiphysiodesis, limiting stapling to femoral arrests or (if stapling was to be done) very careful placement of staples at the proximal lateral tibial physis due to its nonuniform structure.

(d) 8-*Plate*: The 8-plate was designed by Stevens primarily for unilateral growth plate slowdown to allow for correction of angular deformity without resort to osteotomy [374]. It uses the same principle as the Blount staple but is considered to be more reliable. It is used by some on both sides of the bone for physeal arrest. There have not yet been long-term studies of its effect specifically in relation to use for complete epiphysiodesis but many of the concerns noted in long-term studies of stapling will need to be assessed. If done for length equalization it is important to note that it slows down growth only as growth occurs since it is the extrinsic pressure applied to the physis that retards physeal elongation. Bone block epiphysiodesis with physeal curettage halts growth immediately with transphyseal bone bridging developing within a few weeks.

(e) *Percutaneous epiphysiodesis technique*:

(i) *Transphyseal drilling/curettage*: In this procedure, growth plate obliteration is performed through a small incision with physeal visualization by fluoroscopic imaging [375, 376]. Lateral and medial incisions are made over the physis to be ablated, but some surgeons use an approach only from one side. The soft tissues are dissected down to the physeal region at which time a guide wire and cannulated 4–6 mm wide drill bit is inserted. Under radiographic control drilling is performed across the physeal region anteriorly, at the midline and posteriorly. This serves both to destroy the cartilage and to allow for communication between epiphyseal and metaphyseal vessels thus leading to transphyseal bone bridge formation. The postoperative scars are smaller and rehabilitation is quicker than in the previous physeal ablation techniques.

The procedure was reported by Bowen and Johnson [375] in 1984 and by Canale, Russell and Holcomb [376] in 1986. Ogilvie provided an experimental report in 1986 [377] and a clinical assessment in 1990 [378]. Small differences in technique are used although the principles of small incision, percutaneous surgery, and growth plate obliteration under fluoroscopic control are common to all. The physis has been damaged with the use of a drill, drill and curette, drill and burr, or osteotome and curette. Ogilvie has demonstrated well the importance of several passes through the physeal plate in a fanlike pattern to assure complete obliteration [377, 378]. Excellent long-term results by the original authors and by others subsequently adopting the technique have been reported.

In the original report of Bowen and Johnson, the results of 12 percutaneous epiphyseal arrests noted no complications [375]. In their later series, complications were uncommon. Canale et al. in their initial report on 13 percutaneous epiphysiodesis operations reported that all growth plates appeared fused with no major complications and no clinical evidence of subsequent angular deformity [376]. There were no fractures, no neural or vascular complications and no angular deformities. A later report by Canale and Christian on 22 children with percutaneous epiphyseal arrest noted that arrest was achieved in all with no patient developing angular deformity [379]. Ogilvie and King in 7 epiphyseal arrests reported no failures of fusion, postoperative infections, restricted joint motion, or angular deformities [379]. Horton and Olney reported 42 percutaneous epiphyseal arrest procedures in which all patients achieved physeal arrest radiographically and clinically and no patient developed angular deformity from an incomplete arrest [380]. There were no neurovascular complications or fractures. Timperlake et al. in a detailed study from the DuPont Institute reported on 53 consecutive percutaneous epiphysiodeses in which the medial and lateral thirds of the growth plate are ablated, but the central third is preserved for stability [381]. They approach the physis from both sides, use a 3 mm wide osteotome driven 1 cm into the growth plate and rotated 180° to create a hole in the cortex, and then use a 3 mm wide oval curette which is swept across the growth plate to ablate it. Statistical analysis demonstrated no significant difference in the actual discrepancy at follow-up and the discrepancy at maturity as demonstrated by standard growth charts. Gabriel et al. recorded the results of percutaneous epiphyseal arrest in 56 physes using a cannulated 10 mm drill bit over a guidepin followed by curettage [382]. There were no severe complications of angular deformity, deep infections, or neurovascular problems.

(ii) *Transphyseal screws (PETS)*: Another method for epiphysiodesis by minimally invasive surgery was described by Metaizeau et al. in 1998 using screws across the physis [383]. Percutaneous epiphysiodesis using transphyseal screws (PETS) was introduced both for epiphyseal arrest for limb length discrepancies and hemiphyseal arrest for angular correction without osteotomy in growing children. Metaizeau et al. used two crossed screws for full epiphyseal arrest. One screw started at the medial femoral metaphyseal cortex and angled distally and laterally to cross the physis lateral to the midline and enter the epiphysis ossification center and stop just short of the articular surface of the lateral femoral condyle. The other screw went from the lateral metaphyseal cortex distally and medially to the medial subarticular region. Each screw passed through the physis at the junction of its middle and inner/outer thirds. An alternative placement used two nonintersecting screws from metaphysis through physis

into the epiphyseal bone not crossing the midline. The placement at the physeal area had one screw at either end of its (physis) middle third. The alignment was more longitudinal than with the two oblique crossed screws.

Metaizeau et al. used fully threaded cancellous screws with long threads. In other reports of this technique Nouh and Kuo [384] used cannulated partially threaded cancellous screws 6.5–8 mm with the threads across the physis with at least four threads protruding into epiphyseal bone and Khoury et al. [385] used 7.3 mm cannulated fully threaded cancellous screws.

Good results were reported for both limb length discrepancy and angular correction in each of the 3 studies. The authors felt that the screws provided a tether to limit growth rather than doing so by a lag effect to inhibit growth. Metaizeau et al. felt that growth would resume once the screws were removed although this was not attempted in their study [383]. Khoury et al. noted growth resumption in all 13 cases where screws were removed at completion of angular correction [385].

Similar to use of staples or the eight plate, growth cessation only occurs when some additional growth has occurred to allow the compressive effect of the hardware to occur. At the other end of the process, growth retardation may sufficiently damage the physis such that it either does not resume growth or does so at a diminished rate when the hardware is removed. It is advisable to indicate in advance that growth resumption may not occur with hardware removal.

6.9.2.2 Timing for Epiphysiodesis

The timing of epiphyseal arrest is still an imperfect science and studies continue to appear indicating a range of discrepancies at skeletal maturity from acceptable to amounts still leaving lower extremity length discrepancy out of the desired therapeutic range. It is not essential in a clinical sense for limb lengths to be equalized since a fully acceptable result by current criteria is to diminish the discrepancy to under 0.5 in. or 1.2 cm. Even those patients with a discrepancy moved to within 3/4 of an inch or <2.0 cm, would appear to have few long-term problems. There are relatively few problems reported with the various surgical techniques used to bring about the epiphyseal arrest.

There is widespread recognition of the relative inaccuracy of the skeletal maturation determinations used as a key indicator of timing for epiphyseal arrest in most systems. Several radiographic approaches to determine the stage of skeletal maturation have been developed.

(a) *Greulich and Pyle Atlas*: The Greulich and Pyle Atlas using postero-anterior radiographs of the left wrist and hand remains the most widely used indicator of skeletal age. There is still considerable subjectivity needed, however, with this system. The radiographs used are spaced at either 6 month or one-year intervals which represents a considerable margin of difference between age gradings. In particular, there are no radiographic data corresponding to 12 and 14.5 years of age in boys and 9.5, 10.5, 11.5 and 12.5 years of age in girls which are very important time periods for consideration of timing for epiphyseal arrest. The Greulich and Pyle atlas is based on radiographs covering the following ages in males: newborn, 3 months, 6 months, 9 months, 1 year, 1 year and 3 months, 1 year and 6 months, 2 years, 2 years and 8 months, 3 years, 3 years and 6 months, 4 years, 4 years and 6 months, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, 11 years and 6 months, 12 years and 6 months, 13 years, 13 years and 6 months, 14 years, 15 years, 15 years and 6 months, 16 years, 17 years, 18 years, and 19 years.
In females ages are: newborn, 3 months, 6 months, 9 months, 1 year, 1 year and 3 months, 1 year and 6 months, 2 years, 2 years and 6 months, 3 years, 3 years and 6 months, 4 years and 2 months, 5 years, 5 years and 9 months, 6 years and 10 months, 7 years and 10 months, 8 years and 10 months, 10 years, 11 years, 12 years, 13 years, 13 years and 6 months, 14 years, 15 years, 16 years, 17 years, and 18 years.

(b) *SauvegrainMethod for Determining Skeletal Age during Puberty*:

Dimeglio et al. [386] have used a modified version of the method described by Sauvegrain et al. [387] in 1962 to determine skeletal age and development using elbow radiographs. Four regions are assessed with each progression of ossification graded using anteroposterior and lateral radiographs of the left elbow beginning at the onset of puberty and during the first 2 years of puberty. This is effectively between 10 and 13 years of age in girls and 12 and 15 years in boys. This, however, is the main time period for performing epiphyseal arrests for limb equalization. The regions used for grading are the lateral condyle and epicondyle of the humerus, the trochlea of the humerus, the olecranon apophysis of the ulna and the proximal radial epiphysis. The original 27 point scoring system was modified for greater accuracy by Dimeglio et al. by adding 3 additional reference points. The lateral condyle has 9 points of inclusion at skeletal maturity, the trochlea 6, olecranon 8, and the proximal radial epiphysis 7. Once each area has been graded, the 4 scores are totaled and the values placed on a graph for boys or girls. This provides an indication of skeletal age. The system was used to assess skeletal age by 3 observers on radiographs from 60 boys and 60 girls all

healthy and to compare values with determinations made on AP wrist-hand radiographs using the Greulich and Pyle atlas from the same subjects at the same time. There were excellent correlation coefficients among the 3 observers at both assessments and at each elbow region. The same was found using the Greulich and Pyle atlas but when the 2 were compared the Sauvegrain method was considered to be more accurate since it allowed for 6 monthly assessments while the Greulich and Pyle atlas in this age range was made up of annual assessments for girls while the 6 month age increments for boys were incomplete. Based on this study, Dimeglio et al. added 3 time points moving from 27 to 30 and produced recalibrated graphs for girls and boys [386].

An interesting part of the study was the use of each method to see what correlations existed between skeletal age and chronologic age. The two were considered to be the same if differences were not >6 months. The ages were the same for only 33 % boys/35 % girls with the Sauvegrain method and for 30 % boys/28 % girls with the Greulich and Pyle method. This finding clearly supports the value of using skeletal age as part of the timing decision process.

The other problem appears referable to the nature of the predominant disorders being studied in any particular series. Very few studies take into account the differing developmental patterns of the lower extremity length discrepancies that have been described. In those series where type I patterns predominate, there is relatively little problem with utilizing the more straightforward projections of the Green-Anderson, Moseley, Menelaus, or multiplier methods. Where, however, there are types II, III, IV, and V discrepancies, the failure to recognize these patterns can further worsen the accuracy of timing. Studies reporting on timing in epiphyseal arrest procedures should be read with these considerations in mind.

(c) *Tanner-Whitehouse Methods*: The Tanner-Whitehouse method for determining bone age was originally based on a cross-sectional study of 3000 healthy British children assessing radiographs of the left wrist and hand.

(i) *Tanner-Whitehouse 2 method*: In what is commonly referred to as the TW2 method of assessing skeletal maturity, 20 bones were assessed at increasing ages and given a grading letter correlated with a specific weighted score. The bones included the distal radius and ulna, 7 carpal bones (excluding only the pisiform), first, third, and fifth metacarpals and their associated phalanges (2, 3, and 3 respectively) [388]

(ii) *Tanner-Whitehouse 3 method*: Modifications to the scoring system were made in 2001 with the revision referred to as TW3 [389]. The carpal bones were no longer included with scores including the distal radius and ulna along with the three metacarpals (first, third, fifth) and their respective phalanges (2, 3, and 3). This system is sometimes referred to as the TW3RUS system (R = radius, U = Ulna, and S = Short bones being the metacarpals and their phalanges). In the TW system, the grading (for the RUS components) assesses the epiphyses and adjacent metaphyses.

Owing to concerns about differing rates of skeletal maturation in differing racial groups, the TW method has been applied in several countries to provide reference points for specific groups of children. These include studies from North America (Houston, Texas) [390], North India [391], Tokyo, Japan [392], Korea [393], Beijing, China [394], China (5 cities) [395], and Italy [396].

(d) *Digital Skeletal Age (DSA) skeletal maturity scoring system*: *Sanders et al*. Sanders and colleagues have further simplified the Tanner-Whitehouse approach using a digital skeletal maturity scoring system based on just the metacarpals and phalanges [397]. Defined in a previous article [398] with skeletal age studies based on left posteroanterior hand and wrist radiographs, immature girls with idiopathic scoliosis were followed through their growth spurt. The various bones underwent changes in an orderly sequence. Eight stages were defined using all five digits. The study essentially assesses the relationship of the epiphyses (secondary ossification centers) of each bone to its adjacent metaphysis, including, at later ages, physeal fusion (Table 6.3).

(e) *Assessmentsof Results of EpiphysealArrests*: A study by Blair et al. reviewed retrospectively 67 distal femoral and proximal tibial epiphyseal arrests performed over a 14 year period [399]. Only 22 patients had a final discrepancy of <1 cm. Setting aside 10 of 45 failures due to inadequate surgical technique, the remaining 35 failures were secondary to errors in timing. This report utilized the Green-Anderson growth tables. Porat et al. on the other hand, reported good results in 90 % of their patients, although the series was small involving only 20 children [400]. In five children with anisomelia whose expected discrepancy was 4.5 cm results at maturity show an average discrepancy of 0.7 cm. In 10 girls with lower extremity length discrepancy caused by ischemic necrosis with congenital dislocation of the hip, the average discrepancy at maturity was 0.6 cm with the expected nontreated value 4.0 cm. In five children with discrepancy caused by infection, the average discrepancy was 3.8 cm at time of epiphyseal arrest, whereas at maturity it had diminished to 0.5 cm. This group utilized the Moseley straight line graph, CT scanograms for length

Table 6.3 .

Stage	Key features	Tanner-whitehouse-III stage	Greulich and reference	Related maturity signs
1. Juvenile slow	Digital epiphyses are not covered	Some digits are at stage E or less	Female 8 year + 10 mo, male 12 year + 6 mo (note fifth middle phalanx)	Tanner stage 1
2. Preadolescent slow	All digital epiphyses are covered	All digits are at stage F	Female 10 year, male 13 year	Tanner stage 2, starting growth spurt
3. Adolescent rapid—early	The preponderance of digits is capped. The second through fifth metacarpal epiphyses are wider than their metaphyses	All digits are at stage G	Female 11 and 12 year, male 13 year + 6 mo and 14 year	Peak height velocity, Risser stage 0, open pelvic triradiate cartilage
4. Adolescent rapid—late	Any of distal phalangeal physes are clearly beginning to close (see detailed description in the text)	Any distal phalanges are at stage H	Female 13 year (digits 2, 3, and 4), male 15 year (digits 4 and 5)	Girls typically in Tanner stage 3, Risser stage 0, open triradiate cartilage
5. Adolescent steady—early	All distal phalangeal physes are closed. Others are open	All distal phalanges and thumb metacarpal are at stage 1. Others remain at stage G	Female 13 year + 6 mo, male 15 year + 6 mo	Risser stage 0, triradiate cartilage closed, menarche only occasionally starts earlier than this
6. Adolescent steady—late	Middle or proximal phalangeal physes are closing	Middle or proximal phalanges are at stages H and 1	Female 14 year male 16 year (late)	Risser sign positive (stage 1 or more)
7. Early mature	Only distal radial physis is open. Metacarpal physeal scars may be present	All digits are at stage I. The distal radial physis is at stage G or H	Female 15 year, male 17 year	Risser stage 4
8. Mature	Distal radial physis is completely closed	All digits are at stage I	Female 17 year, male 19 year	Risser stage 5

determination and the percutaneous epiphyseal arrest procedure. Lampe et al. performed a prospective study in 30 children who underwent 33 epiphyseal arrest procedures using the Moseley straight line graph method [401]. The mean predicted length discrepancy was 5.2 cm and the mean discrepancy at the end of growth was 1.4 cm with a range from 0 to 4.3 cm. In nine patients out of the 30 (30 %) the final length discrepancy exceeded 1.5 cm. They felt that the altered skeletal maturation was most problematic in those cases where the projection was inaccurate. Variation in radiographic determination of skeletal age was also a source of error as noted by Cundy et al. [402]. Little et al. reviewed 71 epiphyseal arrest procedures in efforts to compare the Green-Anderson, Moseley, and Menelaus methods of projection [403]. They felt that each of the different methods did not have a meaningful superiority in projecting the end result and that all had somewhat limited accuracy. They advocated the Menelaus method owing to its simplicity. The mean preoperative discrepancy in their series was 3.12 cm (range 1.4–7.4 cm) and the mean discrepancy at follow-up was 1.05 cm (range −2 to 4.4 cm). They determined that 34 % of the patients (24) had discrepancies >1.5 cm at skeletal maturity and 27 % (19 patients) had discrepancies >2.0 cm. This study was quite detailed in that 8 different methods were assessed involving 4 variations of the Anderson and Green technique, and two each of the Menelaus and Moseley techniques. They concluded that it was the inherent variability of the individuals requiring epiphyseal arrest that prevented the methods from predicting the outcome more satisfactorily. It was the inability to project the date of skeletal maturity that played the major role in the imperfect results. CT documentation of the length discrepancies provided the most accurate determination. There should be relatively little difference between the Green-Anderson, Moseley and Paley et al. methods, and even that of Menelaus, since each of these approaches uses the same source of growth data, this being the Anderson et al. femoral and tibial length charts and growth remaining charts. Westh and Menelaus assessed 94 patients with a mean length discrepancy of 4 cm and a mean final discrepancy of <2 cm [339]. Dewaele and Fabry compared the accuracy of the Green-Anderson and Moseley methods

[404]. In 83 patients, the mean length discrepancy was 3.37 cm and the mean final discrepancy 1.69 cm. They felt that the Moseley method was more accurate.

6.9.2.3 Partial Therapeutic Growth Plate Arrest

There are two treatment situations which can lead to a recommendation for performance of an asymmetric or partial growth plate arrest.

(a) *To complete an already existing focal arrest to prevent further angular deformity*: Partial arrest of an affected epiphysis can be performed to terminate all growth in a growth plate which has suffered a focal or partial arrest which is considered to be too extensive for bone bridge resection. By completing the arrest across the entire width of the growth plate, development or worsening of angular deformity is prevented. Projection should also be made of the amount of growth remaining in the opposite physis. If the patient is near skeletal maturation, no additional measures are needed. If further growth is in the 2–5 cm range, contralateral epiphyseal arrest is warranted to prevent an invariable discrepancy from developing. If growth remaining is >5 cm, the need for ipsilateral lengthening should be discussed.

(b) *To treat angular deformity without need for osteotomy*: The second reason for performance of an asymmetric or partial growth plate arrest relates to treatment of angular deformity rather than to treatment of shortening. It has been recognized for several decades that creation of an asymmetric growth plate arrest would still allow the remaining physis to continue to function and correct angular deformity without need for osteotomy.

(i) *Staples*: The earliest proponents of widespread use of this treatment were Blount and colleagues who utilized stapling on one side of an epiphysis to correct angular deformity. The technique has its major application at the distal femur or proximal tibia for angular deformities centered at the knee. Blount and colleagues reported on 82 knees treated with epiphyseal stapling over a 20 year period and followed to skeletal maturity [405]. The deformities were allowed to overcorrect before the staples were removed and an effective rebound phenomenon occurred in 22 patients with 35 deformities. In older children, the staples were removed when the legs looked straight. Blount felt that exaggerated physiological deformities may correct spontaneously and should not be stapled before the skeletal age of 11 years in girls and 12 years in boys. Deformities secondary to specific disease processes could be corrected earlier although rarely below 8 years of age. They concluded that results were satisfactory or improved in 87 % of the deformities treated. Two staples were used in most patients. There were 64 valgus deformities and 18 varus deformities. The two largest groups of patients were idiopathic-physiologic or secondary to poliomyelitis with other scattered disorders involving hemihypertrophy, rickets, and occasional skeletal dysplasias. Two biologic phenomena were associated with removal of the staples with growth still active. (i) The group generally allowed for some overcorrection counting on the rebound growth phenomenon to occur in which the stapled side of the bone elongated more rapidly than the other for a few months after staple removal. (ii) Following that the rate of growth tended to remain equal and then the physis closed 4–6 months prematurely on the stapled side. It is evident that a considerable amount of personal experience and judgment went into the timing of such procedures using staples

Bowen et al. developed a chart in an effort to project the appropriate time for correction of any angular deformity (Fig. 6.20a) [406]. Rather than relying on stapling with removal of the staple after a certain degree of overcorrection they performed a bony epiphysiodesis asymmetrically based on a timing chart. Their operation was performed for idiopathic or physiologic genu valgum or varum in the adolescent patient. With an asymmetric stapling, for example on the medial side of the distal femur, continued growth from the lateral physis would be expected. The growth however would not be linear but would represent an arc of a circle with the radius equal to the width the bone measured at the physis. The arc of continued growth relates to the angle of deformity as the circumference of the circle relates to the total number of degrees in the circle. With use of a specific formula a chart was constructed to relate the amount of growth remaining to the angular change for varying physeal distances. This information was then combined with the Green-Anderson growth remaining chart which allowed the angular deformity to be related to the linear growth remaining for the patient's skeletal age. An early study of 13 extremities treated surgically indicated that as a general rule following partial tibial epiphyseal arrest 5° of angular correction could be expected for each year of remaining growth and following partial distal femoral epiphyseal arrest 7° of correction could be expected for each year of remaining growth. The mean ages at surgery were quite similar to those recommended by Blount and his group. In the 7 patients having procedures on 13 extremities the average chronologic age was 12 years 8 months with the girls averaging approximately 12½ years of age and the boys slightly more than 13 years. The average preoperative deformity was 11.6° of femoral–tibial valgus and the average deformity at

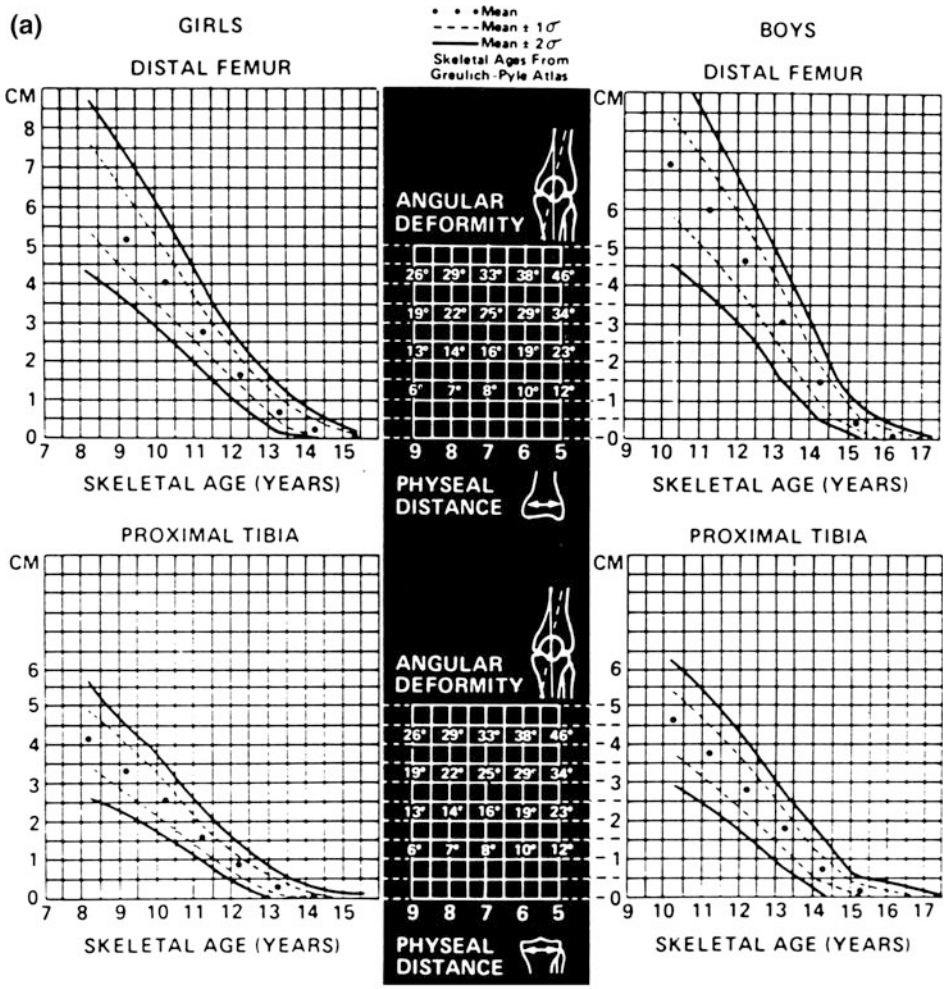


Fig. 6.20 (continued)

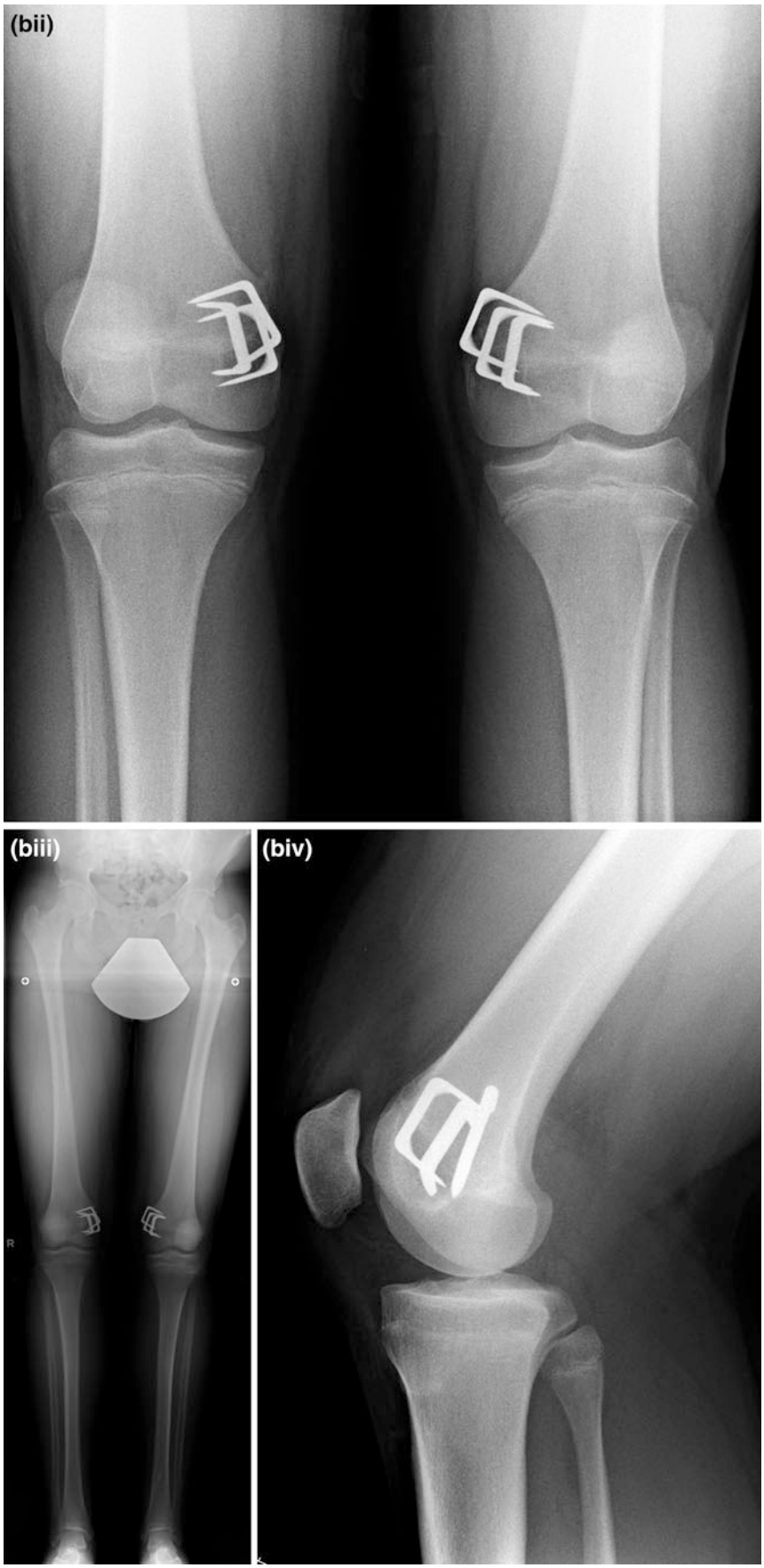


Fig. 6.20 (continued)

follow-up was 6.6°. An example of using hemiepiphysiodesis with staples close to the time of skeletal maturity to correct angular deformity without osteotomy is illustrated in Fig. 6.20bi–iv.

(ii) *Transphyseal screws*: Hemiepiphysiodesis using transphyseal screws has also proven to be effective. Metaizeau et al. used single screw transphyseal placement for 9 cases of angular correction, 6 for genu valgum, and 3 genu varum [373] The average femoral–tibial angle was 7.66° preoperative and 0.86° at skeletal maturity. Noulth and Kuo also treated 9 cases of angular deformity (knee) with hemiphyseodesis using a single transphyseal screw [374]. The mean angular deformity prior to surgery was 18° (range 8–35°) with decrease to 5.5°(1–25°). Khoury et al. corrected deformities at the knee [375]. All were knee deformities involving 30 patients with 66 bones operated. Screws were placed across physes at distal medial or lateral femur or proximal medial or lateral tibia. Distal femoral correction was 6.91° (SD ± 3.75°) a rate of 0.75°/month. In the tibia, the average correction was 3.88°, a rate of 0.37°/month. In 13 cases where the screw was removed with considerable growth remaining, there was no premature growth cessation and minimal rebound deformity.

(iii) 8-*plate for guided growth*: Stevens has used the principle of hemiepiphysiodesis to correct angular long bone deformities in children as young as 18 months of age [374]. He developed a two-hole plate (with two nonlocking extraperiosteal screws) placed across the physis with one screw in epiphyseal bone and one in metaphyseal bone. The plate with diverging screws is considered to act across the physis as a tension band rather than by physeal compression as with staples. Stevens reported in 2007 on its use in 34 consecutive patients with 65 deformities of femur and tibia. Once correction has occurred the plate is removed. It is essential to place the plate extraperiosteally and to not pass the screws into the physis if postplate removal growth is to be maintained. The rate of correction was described as 30 % more rapid than noted with stapling and there had been no permanent growth arrests. Plate breakage has been minimized with development of 12 and 16 mm plates and solid screws of 24 and 32 mm lengths. Depending on its position of placement, the screws can correct in sagittal, coronal, or oblique planes. Recurrence of deformity once the plate is removed is referred to as rebound deformity, which reflects the fact that the underlying disorder causing initial deformity has not been cured but rather inhibited by the plate. The value of the procedure involves correction without osteotomy and its attendant complexities and problems.

With renewed interest in the procedure and introduction of a new device (the 8-plate), current assessments of the approach are appearing. Wiemann et al. report similar results comparing the traditional staples with the non-locking plate hemiepiphysiodesis [407]. The rate of angular correction was about 10° per year with comparable complications. Shin et al. found that staples and transphyseal screws at the knee had similar effectiveness correcting angular deformity and similar rebound phenomena after fixation removal with an overall 21 % rate (12/56 cases) [408]. Complications such as eight-plate screw breakage have been reported especially in obese patients with Blount disease [409]. Dual plates, solid screws, and stronger implants are suggested solutions. Treatment with the eight-plate is more problematic when used in specific growth plate pathologic disorders such as Blount disease [410] and multiple epiphyseal dysplasia [411]. Stevens and Klatt, however, used the eight-plate to good effect in four patients with rickets although only as part of a series of operative treatments ultimately needed [412]. Since the nonrestrained part of the physis does not have normal growth it may not respond in hoped for fashion leading to imperfect correction. The restrained part of the physis also not normal, may not resume growth with device removal. Good correction of flexion contracture with anterior distal femoral plate placement has been noted in anthrogrypotic patients with knee flexion contractures [413]. Klatt and Stevens used two 8-plates anteriorly at the distal femur to correct knee flexion contractures without osteotomy [414]. Most of the patients had knee flexion deformities in cerebral palsy. In 18 patients with 29 deformities, the mean deformity was 23.4° (range 10–50). Residual deformity was a mean of 8.2° (range 0–30°). At full correction, the plates were removed. The average age at surgery was 10.8 years (range 4–17) but generally the procedure was best done after 8 years of age.

Excellent reviews of hemiepiphysiodesis have been written by Saran and Rathgen [415] and Eastwood and Sanghrajka [416]. Guided growth is used most commonly to treat coronal plane deformity at the knee. Over- and undercorrection must be carefully looked for. For those with more than 2 years of skeletal growth remaining, temporary hemiepiphyseal arrest is attractive, although fixation removal

◀ **Fig. 6.20** Asymmetric stapling is performed to allow for correction of angular deformity without need for osteotomy. **a** A chart developed by Bowen et al. estimates the correct time of asymmetric epiphyseal arrest in relation to the patient's skeletal age and the degree of angular deformity correction sought (Reprinted with permission from Bowen et al. Partial epiphysiodesis at the knee to correct angular deformity. Clin Orthop Rel Res 1985;198:184–190. Copyright 1985 Wolters Kluwer Health). **bi–iv** Clinical example of hemiepiphyseodesis technique for angular correction shows correction of bilateral knee valgus deformities with medial distal femoral stapling

is usually needed, leading to the possibility of partial deformity recurrence.

6.9.2.4 Metaphyseal Shortening Osteotomies

Wagner has pointed out the value of correcting a longer femur or tibia which also has angular or rotational deformity by performing a metaphyseal shortening osteotomy [417]. The most common site is the proximal femoral metaphysis followed by the distal femoral metaphysis. He stressed the maintenance of a medial cortical strut in continuity with the lesser trochanter to allow for stabilization and a greater area of bone repair at the osteotomy site. An AO large fragment blade-plate is used for stabilization. Shortening osteotomies of the distal femoral metaphysis are carried out in a similar fashion. A strut of medial cortical bone in the metaphysis is also left intact. The distal femoral metaphyseal shortening osteotomy is often complicated by a relatively slow rehabilitation owing to periarticular scarring, knee joint stiffness, and disruption of the quadriceps mechanism. That site is chosen therefore only if the angular bone deformity necessitates correction there. Bianco has reviewed shortening and angular correction procedures in the femur [418]. An intact strut can only be used for uni-planar corrections. For bi- or multi-planar corrections (rotational or flexion/extension components) a complete osteotomy is needed.

Metaphyseal shortening osteotomy of the tibia and fibula is recommended only if angular deformity necessitates such a procedure. The tibia should rarely be shortened by more than 4 cm. The advantage of the metaphyseal site for shortening is the rapid bony consolidation. Complications can occur proximally in relation to the peroneal nerve with a relatively marked shift in length and alignment. If possible, diaphyseal procedures are recommended where tibial shortening appears mandatory.

Effects of Opening/Closing High Tibial Osteotomies on Limb Length

Magnussen et al. have done an interesting study assessing changes in limb length that accompany high tibial osteotomy for angular correction [419]. Although the study was done in adults, the size of the wedges and the amount of angular correction are similar to what is accomplished in adolescent patients. The mean medial opening wedge was 9.3 mm. The entire limb length increased by 5.5 ± 4.4 mm with the tibia increasing by 4.3 ± 2.3 mm. The mean lateral closing wedge was 8.0 mm. The entire limb length decreased by 2.7 ± 4.0 mm with the tibia decreasing by 4.1 ± 2.9 mm.

6.9.2.5 Diaphyseal Shortening (Resection)

The diaphysis can be shortened at skeletal maturity to equalize limb lengths. The exact amount of bone required is removed and the bone is stabilized with a metal plate, screws, or intramedullary rod. When done at skeletal maturity, there is no concern about overgrowth following surgery and no need to project the final discrepancy. This approach is recommended primarily for discrepancies between 2.5 and 5 cm that were not detected by or persist at maturity.

Shortening of the bones of the longer leg to achieve length equality is a much older and simpler procedure than elongation of the shorter leg. Blount and Zeier have credited Rizzoli of Italy with the earliest descriptions of this procedure [360]. White [420] and Wilson and Thompson [121] reported early attempts from the late nineteenth and early twentieth century which generally involved fracturing of the shaft of the femur or open oblique osteotomy, allowing the fragments to overlap the necessary amount, and then treating the limb until healing occurred. The first formal shortening of the tibia and fibula was reported by Brooke in 1927 in which segments of bone, 1 and 2 in. long, respectively, were removed and then applied as grafts to enhance healing [421]. The femur could also be shortened by a step-cut method followed by internal fixation. The first large series of cases was reported by Camera who resected a portion of the femoral shaft and then used the resected bone as an intramedullary graft [422]. He reported on 32 cases with the average period of external fixation of 50 days. Moore reported on 13 femoral shortenings with bone resection with the average amount of shortening obtained 2.5 in. and the average period for complete union 2.5 months [423]. White reported on 45 cases of femoral shortening with a transverse osteotomy of the shaft, overlapping of the 2 fragments the necessary amount and fixation by long metal pins which were then incorporated into a hip spica cast [420]. Treatment then followed with casting and eventual bracing. Many patients were under age 14 years; in younger children he shortened 0.5 in. more than necessary to compensate for the subsequent overgrowth phenomenon. The quadriceps muscle always maintained its ability to fully extend the knee with no loss of strength detected. The average amount of shortening obtained was 2.5 in. with a range between 2 and 3 1/8 in. Wilson and Thompson reported 5 femoral shortening operations using the White technique with the average shortening of 2 1/8 in. obtained [121]. They reviewed the major series of lower extremity shortening procedures. In the works reported above plus their own, there were 98 femoral and 2 tibial shortening procedures for the 100 cases. The only 2 tibial procedures were those reported by Brooke. The average shortening obtained was 2 in. and the complications reported were relatively small involving separation of fragments necessitating reoperation in 2 cases, infections in 7, delayed union in 2, and no instances of nonunion or angular deformity. In comparison to the results reported during that era for limb lengthening, the relative simplicity of the procedure was clearly shown.

Fig. 6.21 Radiographs of 2 cases of diaphyseal shortening are shown, one of a femur stabilized by an intramedullary rod (**a**–**e**) and one of a tibia and fibula with the tibia stabilized with an AO plate (**f**–**m**). 5 cm were removed from the longer femur at skeletal maturity at open operation. 5.5 cm were removed from the longer tibia and fibula in a 15-year-old girl at skeletal maturity. **a** An anteroposterior film of the proximal 2/3rds of the femur approximately 10 weeks postsurgery shows the healing osteotomy site. There are 2 trans fixation screws proximally and 2 distally to serve as controls preventing rotation or lengthening at the osteotomy site. **b** A lateral radiograph at the same time shows maintained position of the IM rod and healing progressing well. **c** and **d** Anteroposterior (**c**) and lateral (**d**) radiographs show the fixation device distally. **e** Anteroposterior radiograph of entire femur at healing is shown. **f** Anteroposterior radiograph of tibia and fibula 1 week postsurgery. Tibia is stabilized with AO plate and patient is in a short leg cast for comfort. **g** Anteroposterior radiograph at 6 weeks postsurgery. **h** Lateral radiograph at 6 weeks postsurgery. **i** Anteroposterior radiograph at 4 months postsurgery. **j** Lateral radiograph at 4 months postsurgery. **k** Anteroposterior radiograph at 9 months postsurgery. **l** Oblique radiograph at 9 months postsurgery. **m** Lateral radiograph at 9 months postsurgery

The large majority of lower extremity diaphyseal shortening procedures are still performed in the mid-diaphyseal or proximal subtrochanteric region of the femur where negative postoperative sequelae are less marked. There have been reports of the inadvisability of performing shortening of the tibia and fibula owing to increased problems with nerve or vessel kinking or muscle control at the foot and ankle region afterward. The muscle compartments are much tighter than those of the thigh and they have more structures passing through them in a smaller area. As a result, the lag effect and the compressive effect of vascular disruption are greater in the leg. Many reports of leg shortening with good results are described below, however.

An effective approach is to shorten the femoral diaphysis by resection following which an intramedullary rod is placed to allow for rigid stabilization and immediate weight bearing (Fig. 6.21a–e). Our preference is to do open shortening of the diaphysis to remove the diaphyseal segment of the bone. There are also reports of closed shortening in which the osteotomy site is not opened so as to limit the incidence of infection and perhaps hasten the rate of healing by leaving the bone removed beside the shortened diaphysis. The operative success rate is improved with the use of an AO universal intramedullary nail locked statically at both proximal and distal sites [424]. Excellent results can be achieved if the complications of malrotation and distraction at the osteotomy

site are prevented. As with any femoral fracture or osteotomy in the non-childhood years, fat embolism can be encountered.

Shortening of up to 2 in. or 5 cm can be performed readily in the femur in one stage. There is concern about performing more shortening than this owing to the lag effect of the shortening on the quadriceps muscle. In the large majority of studies performed, any quadriceps lag can be overcome usually within a year of surgery with intensive physical therapy. It is, however, difficult to guarantee this effect if more than 5 cm of bone is removed. Two complications of the shortening technique which must be guarded carefully against are stabilization of the femoral fragments with inappropriate rotation or subsequent loss of close apposition of the fragments which not only increases the likelihood of delayed or nonunion but also leads to a failure to gain a complete correction of the discrepancy. Both the rotational and distraction possibilities with intramedullary rodding can be minimized with application of a small four-holed AO side plate with a unicortical grip or with use of a universal AO nail with static locking proximal and distal screws. Liedberg and Persson reported on 11 midshaft femoral shortening procedures where stability was provided with a reamed Kuntscher intramedullary rod and a step osteotomy for rotational control [425]. D'Aubigne and Dubousset described excellent results with a step-cut or Z shortening followed by intramedullary stabilization and fixation with screws to control rotation [426]. Femoral shortening can also be done with correction of proximal and distal angular deformity by removing appropriately shaped trapezoidal wedges.

Wagner has commented on some of the important principles underlying diaphyseal femoral and tibial shortening osteotomies [417]. Wherever possible he has recommended the use of an intramedullary nail as distinct from a side plate and cortical screws since the intramedullary nail allows for early weight bearing. With femoral shortening he recommends removing no more than 6 cm of bone to avoid muscular insufficiency and he supports the use of open osteotomy to remove the bony segment from the diaphysis. Attention to rotation is important. Even with a tibial and fibular shortening osteotomy an intramedullary tibial nail is favored. Reaming of the medullary cavity is essential to insure a tight fit and minimize the likelihood of rotational abnormalities. The tibia is resected in its narrowest portion at the middle third. The stable mechanical fit by an intramedullary rod makes the diaphyseal site for shortening preferable to metaphyseal except for those disorders where axial correction is needed.

In a review of 46 limb shortening operations, 37 in the femur and 9 in the tibia, Kenwright and Albinana felt that shortening as much as 7.5 cm could be done in the femur and 5 cm in the tibia in adults of normal height without any loss of function [427]. Major problems with the technique were technical in nature and involved inadequate stabilization at the osteotomy site. Attention to detail, however, should minimize or eliminate these problems. The optimal site for femoral shortening was at the subtrochanteric region using an open approach and stabilization with an intramedullary rod with proximal locking. Extreme importance was attached to preventing separation at the osteotomy site postoperatively and in achieving appropriate rotation. After tibial shortening one problem, cosmetic in nature, was complaint by the patient of localized increase in the bulk of the leg. For that reason, they recommended that tibial shortenings be limited to 4 cm or less.

Closed nailing had been shown to be reliable by Winquist [428] and by Blair et al. who also expressed concern about controlling rotation, possible instrumentation breakage, and the mass of bone which persisted and was occasionally troublesome [399]. They also felt that healing in the tibial shortening procedure would be most enhanced with excision at the level of the flare in the lower diaphysis. They used either a standard AO intramedullary nail or an AO plate but felt that with intramedullary nailing locking mechanisms should be incorporated. Sasso et al. also demonstrated results after closed femoral shortening [429]. Shortening averaged 4.4 cm with a range from 3 to 5 cm in 18 cases. Complications included 1 episode of fat embolism and 3 cases of loss of fixation. They limited the shortening to 5 cm because of concern about quadriceps lag and in no instance at this amount of resection were any negative sequelae noted with a full knee range of motion and excellent strength regained.

One possible but rare complication of closed intramedullary nailing of the femur in association with shortening is avascular necrosis (AVN) of the femoral head. Mileski et al. have reported such a problem in an adolescent female who at age 11 years underwent a closed intramedullary femoral shortening [430]. The rod was subsequently removed after healing. AVN was not diagnosed after rod placement but was noted 15 months after rod removal. The authors felt that the vascular insult may have been caused by using a rod entry point that was slightly medially placed although it was also possible that the rod removal had contributed to the vascular insult. This represents the first report of this complication with femoral shortening although Herzog et al. [431] reported 4 cases of femoral head necrosis following intramedullary Kuntscher nailing of femoral fractures in 26 children and O'Malley et al. [432] reported AVN in a 13-year-old boy with a closed intramedullary nailing of a femoral diaphyseal fracture. This problem of AVN with femoral intramedullary rodding has also occurred with rigid rod nailing for femoral diaphyseal fractures. Use of a trochanteric rather than piriformis fossa entry point for the rod has greatly minimized this complication.

Broughton et al. reported on 12 patients who underwent tibial and fibular shortening by diaphyseal resection to correct limb length discrepancy over a 25 year period [433]. Each of the 12 patients did well with no major

complications. A step-cut technique or Z-type shortening was employed for the tibia accompanied by a mid-fibular resection of the required amount. The tibial fragments were then stabilized by two screws. All operations except in two were performed either at or just beyond skeletal maturity. The shortening achieved ranged from 2.5 to 5.1 cm. Normal function and appearance were documented in all following uneventful healing. A healing of tibial and fibular shortening at skeletal maturity using AO plate stabilization of the tibia is illustrated in Fig. 6.21f–m.

6.9.3 Procedures to Lengthen the Shorter Limb

6.9.3.1 Stimulation of Epiphyseal Growth Plate of the Shorter Limb

The earliest approaches to the treatment of lower extremity length discrepancy beginning in the late nineteenth century and continuing into the first half of the twentieth century involved efforts to stimulate growth of the shorter side prior to skeletal maturity. There was early recognition of the fact that periosteal irritation frequently led to long bone overgrowth and the therapeutic method which evolved from this observation was an attempt to stimulate and irritate the periosteum to allow for increased growth of the adjacent physis. Ollier was the first to develop this technique [159]. He performed periosteal elevation in the rabbit tibia causing overgrowth of 2–5 mm within 3 months. Over the subsequent decades many methods were used to stimulate the periosteum including: cutting the periosteum, circumferential stripping or elevation of the diaphyseal periosteum, and placing objects underneath the periosteum to allow for chronic irritation (these objects including ivory pegs).

Several differing techniques were used subsequently both experimentally and clinically to enhance physeal growth.

(a) *Sympathectomy*: In 1930 Harris reported on lumbar sympathectomy performed on the short side of a patient with poliomyelitis to take advantage of the observation that those having sympathectomy for vascular disease frequently developed vascular dilatation and increased warmth of the affected side [434]. It was postulated that this increased vascular response would enhance physeal growth. In many instances, overgrowth was indeed caused by the sympathectomies but its occurrence was unpredictable and rarely exceeded one cm. These techniques are not used today.

Harris and McDonald in 1936 reported on the response to 46 lumbar ganglionectomies [435]. Use of the procedure was based on the observation that in certain pathological conditions in growing children characterized by prolonged hyperemia in the neighborhood of the epiphyseal growth plates there was overgrowth of the involved extremity. They attempted to reproduce the earlier clinical finding by performing lumbar sympathectomy in experimental animals but in no instance were they able to reproduce growth stimulation on the ipsilateral side. They performed 70 lumbar sympathectomies in patients with poliomyelitis and assessed the clinical response. Forty six were available for review. They showed many instances where lumbar sympathectomy enhanced the growth of the extremity. In 21 of 46 patients (46 %) the shortness had become less in amounts varying from 1/8 of an inch to 1 in. The average age at time of surgery in this favorable group was 8½ years. In 8 cases (17 %) the amount of shortness present at operation remained unchanged which still represented a positive response since the progressive shortening had ceased. Beneficial results were demonstrated in 63 % of the cases. In 17 cases (37 %), the shortness progressed in spite of operation. In many of this latter group, the authors felt that effective sympathectomy had either not been obtained or maintained. When they subdivided their assessment to include only those with very clear sympathectomy 20 of 29 cases showed diminution of shortness, 4 showed no increase in shortness and in only 5 did the shortness increase. Beneficial affects on growth were thus increased to 82 %.

Barr et al. assessed the results in 1950 of 23 unilateral lumbar ganglionectomy procedures in patients with poliomyelitis [436]. Ipsilateral lumbar ganglionectomy had in some instances a stimulating effect upon the growth of the shorter extremity. The most favorable interpretation of their results showed that the patients had an average decrease in discrepancy of 1.5 cm, based upon projections of the expected discrepancy. In the control group of 23 cases, 21 increased and 2 decreased with the average increase of 1.8 cm; in the ganglionectomy group of 23 cases, 13 increased, 9 decreased, and 1 was unchanged with an overall average increase in discrepancy of 0.3 cm. It was calculated that the average decrease in discrepancy with ganglionectomy was 1.5 cm.

(b) *Surgically induced arteriovenous fistula*: Observations made in the late 1800s and early 1900s reported overgrowth of childhood limbs in patients who had sustained an arteriovenous (AV) fistula. Horton reported 23 cases of congenital arteriovenous fistula with overgrowth of the involved extremity almost always seen [273]. In mid-century, efforts were made to incorporate this observation into clinical practice by surgically inducing arteriovenous fistulas in the mid-thigh region on the short side to treat developing limb length discrepancies. Janes and Musgrove showed the growth stimulation effect of an

experimentally created arteriovenous fistula [437]. Janes et al. created the first AV fistula in a child with a short limb due to polio and 10 years later reported results [438]. Mears et al. induced 55 fistulas and studied their results in detail [439]. The fistula was placed between the superficial femoral artery and vein. There were no major cardio-pulmonary complications. Thirty-nine patients were available for long-term review. All patients but 3 had a short limb due to polio. In 28 there was either a decrease or at least no increase in the amount of discrepancy. In 11 the limb length inequality continued to increase after the fistula was established. Thus 72 % of the group had a discrepancy which was diminished or stabilized by the fistula. Lengthening of the shorter leg after establishment of the AV fistula was 0–0.5 cm in 11, 0.5–2.5 cm in 13, and 2.5–5 cm in 4. When continued shortening occurred after the AV fistula, the amounts were still much less than would have been anticipated with 5 patients having 0–0.5 cm of additional shortening and 6 from 0.5 to 2.5 cm of additional shortening. The growth pattern following establishment of the fistula was unpredictable and the response quite variable in terms of extent.

Petty et al. assessed their results following surgical creation of a femoral arteriovenous fistula to treat limb length discrepancy in 28 patients [440]. Of the fistulae made 21 of 28 were done when the patient was felt to be the optimal 8 or 9 years of age. The fistula was created between the femoral artery and vein in the mid-thigh region. There were considerable complications secondary to fistula creation although none was limb threatening. Closure of the fistula was eventually performed in all by 16 years of age. Of the 28 patients operated, 17 subsequently had an epiphyseal arrest on the opposite side. The average length discrepancy in this group was 4.6 cm at time of fistula creation and the average increased to 5.9 cm at the time of epiphyseal arrest. Eleven patients did not have an epiphyseal arrest and in this group at fistula creation the average discrepancy was 4.1 cm and at fistula closure it had decreased to 2.4 cm. Only 9 of 28 patients (32 %) showed a decrease in length discrepancy of more than 1 cm as a result of an AV fistula alone. Twenty-one of 28 patients (75 %) showed no further increase in discrepancy however. The authors concluded that "artificially created arteriovenous fistulae can accelerate growth in the lower extremity, but the results vary greatly and are unpredictable". By the early 1970s, both Janes and Sweeting [441] and Petty et al. [440] no longer performed or recommended the procedure for treatment of length inequality.

(c) *Elevation and stripping of the metaphyseal and diaphyseal periosteum*: Increased growth in length had long been noted after stripping of the periosteum of the metaphysis and diaphysis in several experimental animal procedures. An experimental study of stimulation of longitudinal growth of long bones by periosteal stripping in dogs and monkeys was reported by Sola et al. [442]. They assessed not only an initial periosteal stripping, but the effects following a second stripping 1 or 2 months after the first procedure. Once again there was a tendency to show increased growth although it was not particularly marked nor was it invariably seen. In operation on the dog involving a single stripping of the femur and tibia, the mean increase in length was only 0.16 cm with 63 % showing increase of growth on the operated side. When two stripping procedures were done, the mean increase was greater at 0.35 cm but still only 69 % of the animals showed increase on the operated side. When two procedures were done on the monkey, the increase was only 0.17 cm although 87.5 % showed an increase. The stripping procedure was extensive going from growth plate to growth plate in both femur and tibia.

A detailed study of the effects of stripping of the periosteum in rabbits was performed by Wu and Miltner [443]. Periosteal stripping was performed in variable parts of the right tibia and right femur. In all instances, there was overgrowth on the operated side. Twenty-two rabbits were used. The right tibia alone was operated on in 18 animals and both the right femur and tibia were operated on in 4. Definite longitudinal overgrowth of the operated bone was observed in all instances except 3. The amount was small and limited primarily to the first 3 months postsurgery with the overgrowth varying from 0.5 to 6 mm.

Chan and Hodgson applied this procedure to 45 patients suffering from poliomyelitis with the operations done between 1961 and 1968 [444]. The age at surgery ranged from 5 to 13 years and all patients had a short limb at the time of surgery averaging 3.4 cm (1.1 to 9.5 cm). The periosteum was completely stripped with an elevator in both the femur and tibia. A definite overgrowth >4 mm was noted in 31 patients (69 %); there was no significant increase or loss of growth over the normal side in 9 (20 %); and there was a continuing shortness in 5 (11 %). In the favorable group, the average overgrowth was 1.3 cm during the mean time period of 9 months with a range from 0.6 to 4.4 cm. In many patients the overgrowth affect was noted to persist as long as 1, 2, and even 4 years postsurgery. The average period of stimulation, however, could not be determined accurately. The authors concluded that it was best to do the

stimulation operation when the child was 8 years of age. No meaningful or long-term complications were seen.

Jenkins et al. studied 13 of these patients at a later time from 3 to 5 years postsurgery [445]. They continued to note some degree of stimulation but again a variable response. In 28 femurs assessed 3–5 years following periosteal stripping, there was an increase in growth of a mean 0.5 cm in 17, a decrease in growth of 0.81 cm in 8, and no change in 3. In the 26 tibias, 18 had an increase of 0.75 cm, 5 a decrease of 0.5 cm, and 3 were the same.

(d) *Short-wave diathermy*: Doyle and Smart reported that short wave diathermy enhanced epiphyseal growth in rats [446]. Preliminary experiments indicated that a temperature of 40 °C would be effective to induce increased growth without tissue damage. The right lower extremity was maintained at this temperature throughout the treatment. Twenty female rabbits were used in which insulated copper plates, 2 by 8 in., permitted the administration of diathermy to 4–6 animals via a short wave medical diathermy apparatus. Treatment was directed to the epiphyses of the right knee. The animals were treated for 0.5–1 h each day or on alternating days from the 21st to the 70th day of life. The average total duration of diathermy was 25 h. Of those animals appropriate for assessment, the treated right hind limb was longer than the untreated left in all instances. The increase in the combined length of the treated tibias and femurs varied from 0.4 to 2.8 mm averaging 1.4 mm. The advantage of the procedure was that it would increase the temperature in tissues at deeper levels without causing bodily damage. Diathermy acted by producing deep tissue heating and increased blood flow. Granberry and Janes repeated the experiment on the dog, without showing beneficial effects [447]. They used microwave diathermy to increase the temperatures 3–5° centigrade in the tibia. In their experiment, one knee each of 7 young dogs was heated by microwave diathermy at 100 watts for a total of 100 h but they noted no significant growth alteration.

(e) *Efforts to stimulate epiphyseal growth by insertion of multiple implants and creation of bone damage in the metaphyseal regions*: Wilson and Thompson noted that the many attempts to stimulate epiphyseal growth had not been successful enough to warrant clinical use, a feeling still prevalent after additional attempts since then [121].

Compere and Adams addressed the effects of trauma to the diaphysis on subsequent longitudinal growth, performing 2 series of experiments in rabbits with limited trauma [448]. Three drill holes were placed through both lateral and medial cortices near the upper and lower metaphysis and in the mid third of the shaft. This served to disrupt the medullary blood supply. When animals without fracture during the postoperative phase were assessed there were no differences in length of either the tibia or femur. This led to the conclusion that trauma sufficient to interrupt the medullary blood supply but not great enough to cause regional hyperaemia did not consistently cause growth stimulation. Fractures were then made in the femur and tibia between metal markers to assess the overgrowth phenomenon. They demonstrated in agreement with Bisgard that overgrowth of a long bone may occur following fracture even without shortening and that the longitudinal overgrowth occurred entirely from stimulation of the epiphyseal growth cartilage. They then assessed patients in relation to growth of tibias from which bone grafts had been taken. Growth arrest lines were used for the assessment. Small amounts of increased growth ranging from 0.1 to 0.8 cm occurred following tibial bone grafts. The growth stimulus lasted only as long as healing of the defect site was occurring. They concluded that minimal trauma to the shaft or to the metaphysis of the long bone with or without interruption of the medullary blood supply did not produce any definite increase of longitudinal bone growth. Gross trauma such as caused by a fracture or a removal of a large segment of bone for grafting both of which necessitated extensive bone repair did reproduce epiphyseal stimulation and increased longitudinal overgrowth. The increased rate of growth continued during the period of healing but not much beyond. The growth stimulation appeared secondary to the hyperaemia which included the epiphyseal region.

Wu and Miltner reviewed clinical situations where overgrowth occurred [443]. Metaphyseal and diaphyseal fractures were known to cause overgrowth in long bones in children. Infection could clearly damage growth if it involved the physeal cartilage but in instances where the physeal cartilage persisted the increased hyperaemia lead to overgrowth. They performed several experiments on rabbits aged 5–8 weeks to assess growth phenomena. **Group 1**. Insertion of foreign material into a drill hole placed immediately distal to the proximal epiphyseal cartilage of the tibia. The foreign materials included cotton, gauze, paper, wood, brass and iron shot. There was no difference in length of the bones operated. **Group 2**. Indirect interference of circulation of bone. The epiphyseal circulation was left intact but the nutrient arteries and periosteal vessels were damaged extensively. There was no appreciable change in longitudinal growth of the bone after the experiments. Destruction of the nutrient artery and the extraperiosteal blood supply in particular caused no changes in the longitudinal growth of the bone agreeing with the extensive studies of Ollier and Haas. **Group 3**. Curretage of bone marrow. The tibial bone marrow was curreted through a metaphyseal drill hole. There was no significant change in the length of the operated

bones. **Group 4**. Stripping of the periosteum. Many variable patterns were used and in virtually all instances definite longitudinal overgrowth of the operated bone was seen from 0.5 to 6.0 mm.

Chapchal and Zaldenrust assessed the effect of various metals, metal alloys, and ivory placed in the metaphysis and also in the epiphyses of the bones comprising the knee joints of several animals [449]. They concluded that some lengthening of the bones was obtained but that the amount was minimal and uncertain. Pease attempted to assess overgrowth using foreign bodies in the metaphyseal regions [450]. His work also involved clinical investigation of the phenomenon. He placed transverse screws across the entire metaphyseal diameter of distal femur and/or proximal tibia using vitallium, stainless steel, vanadium, and ivory screws. Two screws per region were used. In all cases, stimulation of growth followed operation to a variable degree and there were no deformities indicative of asymmetric stimulation. The screws were placed parallel to each other and to the adjacent growth plate and extended to or slightly through the opposite cortex. Seven patients were operated with two screws placed in tibia and femur in most with one patient having the procedure only in the femur. The operation was repeated occasionally. Seventeen segments were stimulated. In two instances, there was no overgrowth while in the others the overgrowth stimulation varied from 0.1 to 2.2 cm. The mean length increase for 17 cases with growth stimulation was 0.7 cm.

Carpenter and Dalton repeated the clinical work in 30 cases in which epiphyseal stimulation was attempted by the use of intramedullary implants in a distal femur and proximal tibia [451]. Periosteum was elevated and a cortical window made to the metaphyseal side of the distal femoral and proximal tibial growth plates. The medullary canal was curetted and the cavity then tightly packed with small chips of ivory. Each patient was followed for a minimum of 2 years with radiographic and clinical measurements made at 3 month intervals. Some increase in growth was obtained in 26 of the 30 patients. The gain was 1/8 of an inch in 10, 1/4 of inch in 11, 0.5 of an inch in 3, 3/4 of an inch in 1 and 1 in. in 1. In 70 % of the cases, the maximum gain was only 1/8–1/4 of an inch and it was concluded that the degree of stimulation was neither great enough or predictable enough to warrant clinical use.

Tupman reported a detailed study to stimulate bone growth by inserting beef bone pegs into the epiphyseal and metaphyseal region in children [452]. The first clinical attempt to stimulate growth in dogs by introducing ivory pegs into the femur and tibia was in 1869 by von Langenbeck who claimed 1 cm overgrowth in 3.5 months. Tupman reviewed 28 patients who had a total of 51 operative procedures. Insertions of material were in the distal femoral and proximal tibial metaphyses. Three tunnels were made with a drill in the metaphysis close to but not involving the physis. Into each of these tunnels in the femur and tibia, a beef bone peg was inserted across the bone diameter. In some, ivory pegs were inserted for comparison. In one part of the series performed at a hospital, no leg subjected to a single operation showed any evidence of acceleration of growth. It was felt, however, that documentation might have been somewhat inadequate. In a second series at another hospital, there were groups in which effective stimulation took place, some in which the operation had no effect on progression and some where the operation was fully ineffective. Only limited conclusions could be made. The operation appeared more effective in younger children than in those close to puberty. The best that could be said was that the growth was stimulated somewhat in 12 of 28 patients with best results seen when operation was done between 6 and 12 years of age. Once again some stimulation was noted but it tended to be of a small amount and unpredictable.

6.9.3.2 Lengthening of the Diaphysis

(a) *Clinical Approaches 1900–1960s*: Much interest in, and occasional efforts at, lengthening lower extremity long bones were reported in the nineteenth century. No acceptable techniques evolved but valuable biological and mechanical principles gradually became evident with continued work over the next several decades.

Codivilla: Well-documented attempts at long bone lengthening date from accounts by Codivilla of Bologna, Italy in 1903 and 1905 [453]. He began one of his articles with the following still relevant sentence: "The difficulties to be encountered in lengthening a shortened limb are found in operation to be greater as regards the fleshy parts than as regards the bones." Following osteotomy or fracture of the bone, skin traction had been applied characteristically with limited effect due to pressure necrosis of the skin, pain, and the fact that much of the force applied "did not reach the skeleton". Codivilla went on to describe the evolution of his technique which eventually involved osteotomy of the bone, application of a hip spica cast, removal of the foot portion of the cast, application of a force directly to the skeleton with transverse placement of a calcaneal wire of 5–6 mm diameter, incorporation of the transverse pin and two side bars into the plaster cast, cutting of the cast at the level of the osteotomy and application of counter-balanced traction to gain length immediately followed by completion of the cast at the desired length until healing. He reported on 26 patients who gained between 3 and 8 cm. Freiberg supported the validity of the approach using it following a femoral fracture in a 9-year-old boy to reduce a 2 1/4 in. shortening to 0.5 in. 5 weeks after injury [454]. A double skeletal transfixator method, after the length had been achieved, then evolved.

Ombredanne: Ombredanne began utilizing principles subsequently incorporated in more formal apparatuses at later times [455]. In 1913, he described an oblique osteotomy and lengthening of the femur slowly and gradually with an apparatus fitted to the side of the thigh and working against one pin inserted above the osteotomy site and one below. He achieved up to 4.0 cm lengthening but no detailed follow-up of the procedure was performed.

Putti: The next technical advance in limb lengthening was described by Putti also of Bologna, in 1921 [456]. He described a need for lengthening of the femur when the discrepancy was >2 in. and questioned early on whether lengthening of such a magnitude was "possible without damaging the muscles, nerves and vessels." His own work and that of Magnusson then showed the possibility of lengthening safely by 2–3 in. Putti defined the need for continuous traction. He developed a unilateral distraction apparatus for lengthening the femur which used two large transcortical metal pins on either side of the osteotomy held apart by a telescoping tube which contained a strong spring press moved by a screw. The apparatus was designed to be sufficiently strong to overcome resistance, to stabilize the osteotomy site and the alignment, and to provide traction. Gradual traction was applied to separate the bone fragments but the time taken for lengthening was not reported.

Putti elaborated on operative lengthening of the femur in 1934, with an altered technique [457]. He stressed that operative bone lengthening was particularly valuable during the period of "childhood when the reparative power of the long bones is most vigorous thereby minimizing the danger of non-union." Skeletal traction mandated the use of skeletal countertraction. The Z-osteotomy was replaced with an oblique osteotomy. The patient was then put in bed with traction placed on the upper wire. Increasing traction was applied to the lower Kirschner wire until the desired length usually from 2.5 to 4 in. was attained. This gradual skeletal traction usually required 18–21 days. A hip spica cast was then applied with the transfixion wires included at which time the traction was discontinued. Results were reported in 11 patients. Putti added that "in the eleven cases I have treated by this method no complications whatever arose other than a single case of temporary 'toe drop' caused by overstretching of the external popliteal nerve presumably due to faulty position of the knee. The paralysis promptly cleared up with rest." The concept of gradual traction was introduced and Putti indicated that the time required to obtain the desired lengthening was approximately 20 days. The period of immobilization in the corrected position was 4 months in a plaster cast with an additional period of limited support for several months in which physical therapy continued. No indication was made of the amount of lengthening achieved.

Magnuson described femoral lengthening of 2.5–4 in. in 14 patients using double transfixion wires and plaster with lengthening at one sitting by skeletal traction over 20–30 min [458]. The osteotomy was a Z-type to allow for bone contact to enhance healing. The apparatus was left on for 30 days following which a cast was applied. In 10 cases of femoral shortening which were operated the lengthening varied from 3 to 4 in.

Abbott: Abbott directed his attention to lengthening the tibia and fibula in patients with poliomyelitis and reported a method of lengthening in 1927 that gained wide acceptance [459]. He used Putti's concepts of skeletal traction and countertraction but developed a lengthening apparatus which was the true precursor of apparatuses used even now. His method employed a preliminary Z-lengthening of the tendo Achilles, oblique osteotomy of the distal third of the fibula, insertion of single proximal and distal 3/16 " wide traction pins which passed completely through the limb to enable fixation to a biplanar distraction apparatus to control angulation, circumferential division of the periosteum at the osteotomy site, a Z-type tibial osteotomy, and a delay in lengthening from 7 to 10 days postsurgery. The two distraction devices consisted of telescoping brass tubes and a strong coil spring with lengthening performed by turning of a thumb screw. The limb was immobilized on a Thomas splint to which were also attached two metal stabilizers to prevent anterior angulation. Lengthening was done once daily and ranged from 1/16th to 1/8th of an inch. In his initial report, the maximum amount of length which Abbott felt could be achieved safely was 2 in. (5 cm). The entire time in traction was between 3 and 4 weeks. Overall the apparatus remained in place for 8–10 weeks at which time the limb was immobilized in a cast. The external apparatus and the wires were removed from 4 to 5 months after surgery when there was sufficient callus to permit the patient to walk with a splint. Abbott indicated that "in every case treated by this method callus filled in this space lying between the fragments in a comparatively short time." The operation was performed in those cases with 1.5 in. or more of shortening. Abbott warned of the extreme care needed in the postoperative phase and suggested "the surgeon who has not the time to give for daily adjustment of the apparatus should leave it entirely alone." Abbott then provided a very detailed account of his first six patients of whom one was regarded as a failure. In the other five, the gains in length varied from 1 3/4 to 1 7/8 in. with all these increased lengths secured from 21 to 28 days. Union of the fragments sufficient to allow for weight bearing in a splint was present in all cases from 4 to 5 months after surgery and in all the completed cases consolidation of the callus had taken place in 6 months. The amount of lengthening was initially kept relatively small because of concerns of negative sequelae with larger

lengthenings. The recommendation and determination of the initial paper, however, allowed for increasing lengthening to 2 in.

The next year Abbott and Crego reported on a similar procedure for operative lengthening of the femur [460]. Eight cases were reported with the gain in length ranging between 1.5 and 3.5 in. The authors felt that with experience in an average case a gain of 2.5 in. could be secured without producing injury to the blood vessels or nerves. The principles again involved osteotomy of the bone, direct bone traction which was gradual and continuous, maintenance of alignment and contact of the fragments obtained by transverse wires entirely through the limb above and below the osteotomy and attached to the screw extension pieces. The osteotomy was accompanied by sectioning of deep fascial structures, the iliotibial band, and the biceps tendon to diminish the resistance of the soft parts. The authors emphasized that "by far the most important and difficult part of the entire procedure is the postoperative care of the patient during the lengthening process." The lengthening began approximately 5–6 days after operation. Lengthening was performed once daily with the average daily gain of 1/8 of an inch and the entire time of traction extending over a period 4–5 weeks. The apparatus was removed and a cast applied in 10–12 weeks, protected weight bearing was allowed at 5 months, and full weight bearing in 7–8 months.

Abbott next presented a review of 48 tibial and fibular lengthenings in which he again stressed his three principles: (1) to lengthen a bone traction and countertraction must be taken directly on that bone; (2) to overcome the elastic resistance of the soft parts the traction must be slow and continuous; and (3) after osteotomy and the application of traction complete control of the fragments including their appropriate alignment must be maintained during the lengthening process [461, 462]. The apparatus evolved to the use of two pins above and two below the osteotomy site. The lengthening began only when all swelling had disappeared which was usually at 7–10 days. In the 48 patients, the gain in length ranged from 1.5 to 3 1/4 in. The average time of union to permit weight bearing with a splint was 4–5 months and consolidation of callus generally occurred in 6–7 months with restoration of the medullary canal in 10–12 months. The complications listed by Abbott were surprisingly infrequent involving 2 fractures, one worsening of paralysis of the dorsiflexor of the foot, and one infection which involved an osteomyelitis of the bone, and occasional over-lengthening of the tibia allowed for valgus deformation at the ankle.

In a later paper, Abbott reviewed his results in 73 procedures of which 48 were in the tibia and fibula and 25 in the femur [462]. In the femur, the maximum gain was 3.5 in. and the minimum 1 in. This paper describes the technique of the apparatus and the intraoperative and postoperative approaches in great detail. Abbott noted that the tibia and fibula provided much more dependable results than the femoral lengthenings which had more complications [462]. There were only two incomplete fractures following the tibial lengthenings but 7 fractures occurred through femoral callus during the early weightbearing phase. There were three cases of nerve paralysis. One involved paralysis of the sciatic nerve associated with subluxation of the knee. Infection of the pin sites was commonly seen but only one deep osteomyelitis occurred.

Other Reviews of Abbott Technique: Following Abbott's development and subsequent refinement of his technique limb lengthening enjoyed a surge of popularity. Three major reviews of relatively large series of the Abbott procedure appeared in the 1930s. These series served to define both the benefits and negative aspects of these interventions although the detailed descriptions of the complications considerably diminished enthusiasm for lengthenings. Haboush and Finkelstein reported on 17 tibial-fibular lengthenings, 16 of which were done for poliomyelitis [463]. They used Abbott's technique although they did modify his apparatus somewhat. Their major problems involved (1) anterior-medial angulation during the bone lengthening process; (2) more tibial elongation than fibular; (3) valgus of the foot; (4) equinus of the foot; (5) osteomyelitis both at the site of the tibial osteotomy and at the site of pin insertions; (6) delayed union leading in some instances to nonunion. The modifications of their apparatus were designed to address these problems. One of their major conclusions was that the fascia in particular yielded poorly to lengthening which led to both the angular problems and the severe pain which they described as being "a rather constant feature in this series of cases". One of the major changes in their operative technique was a more thorough division of the fascia in the limb along with the interosseous membrane and complete circumferential division of the periosteum of both tibia and fibula.

A more positive review was published in 1935 by Brockway who provided a clinical resume of 46 leg lengthening operations using the Abbott technique and apparatus [464]. He provided average values for the key criteria in his long range assessment although ranges of numbers and case by case details were not given. The average age of the patient was 14 years. His report is most instructive to note in comparison with current approaches using the distraction osteogenesis principles. The number of days following surgery before the lengthening process was started averaged 7.5. The average length obtained was 1 and 9–10 in. The number of days required to obtain this length was 35 making the average daily increase in length 1.3 mm. The average time before the pins were removed (at which time the long leg cast was applied) was 11.4 weeks. The average time that plaster was worn following the removal of

the pins was 13 weeks and the average time before full weight bearing was allowed postsurgery was 9.5 months. Brockway did note complications with the procedure but his overall impression was positive and he indicated that "on the whole, very gratifying results have been obtained by this operation and it is now a routine procedure." Poor results involved fracture of the tibia, some cases of skin slough, delayed bone healing, and anterior bowing of the tibia.

The most critical of the early reviews was published in 1936 by Compere [465]. The large list of complications which he referred to led him to the belief that shortening was by far the more preferable approach to limb equalization. The paper describes five patients in detail each of whom had a large number of complications. There is no indication as to how many patients were operated. The discussion focuses on the negative aspects of the procedure but neglects any positive indications either in his own work or the work of others. Compere listed 14 complications which, in the absence of any indication that he had any good results at all, clearly led to a major dampening of enthusiasm for this intervention in particular in North America. The complications he listed follow: (1) stretch paralysis of the sciatic or the external popliteal nerve; (2) increased weakness of lengthened muscles in old cases of poliomyelitis; (3) fracture of the osteotomy; (4) malunion; (5) delayed union or non-union; (6) osteomyelitis from wound infection; (7) traumatic arthritis and limitation of motion in the knee; (8) late fracture; (9) pressure or stretch necrosis of the skin in the zone of lengthening; (10) necrosis of bone due to excessive subperiosteal stripping which also might increase the likelihood of infection; (11) malposition of the foot due to rotation following lengthening; (12) circulatory disturbance with prolonged oedema in the lengthened limb; (13) displacement of the head or of the distal end of the fibula when this bone is not lengthened as much as the tibia; and (14) protrusion of the osteotomy fragment of the tibia through the skin. Complications have characterized lengthening procedures from the beginning. Table 6.4 lists the large group of possible disorders. Many of these are seemingly inherent with the procedures, but awareness should help minimize them.

The major English language orthopedic journals did not publish any subsequent large limb lengthening review for 12 years until the report of Allan [466]. He used a tibial distraction apparatus which incorporated the principles of Abbott and some modifications of Haboush and Finkelstein as well as his own. An oblique osteotomy of the bone was performed to enhance repair after lengthening. To minimize angulation, Allan applied a plaster of Paris long leg cast and incorporated it into the distraction apparatus with the cast cut at the osteotomy site. The periosteum was left intact and a careful technique sought to minimize damage to the soft tissues. Distraction began immediately and proceeded at a rate of 1/16 of an inch per day. Allan reported that "little pain should be experienced." When sufficient callus had formed as indicated on X-rays but prior to firm union the plaster cast and wires were removed, any malalignment was adjusted, and the limb was stabilized in plaster until union was complete. Femoral lengthening produced greater difficulty than tibial. In 47 cases of tibial-fibular lengthening, the average time before weight bearing was 6.5 months and the average lengthening obtained was 2 and 1/3 in. In 40 femoral lengthenings, the average time for weight bearing was 5 months and the average lengthening obtained was 1 and 5/8 in. The technique was evolving during the course of the series. Allan felt that bone was laid down in parallel lines between the fragments with the osteogenic material strung out across the gap and that most of the repair came from periosteum. He noted that all bones returned to normal radiographic appearances within a year or so of consolidation. Union eventually occurred in every case but there was a marked delay in 12 cases, union taking from 9 to 16 months. Although Allan recognized that the most resistant structures to stretching were the periosteum, the interosseous membrane, and the deep fascia, he specifically mentioned that these were to be left intact as much as possible. The blood vessel response distal to the lengthening site was benign. He felt that the external popliteal nerve and the compartment part of the great sciatic nerve could be stretched to 2 in. in the thigh without losing function and that it could be stretched to 3 in. with only temporary impairment. He attributed vascular complications experienced by other surgeons to subperiosteal bone exposure and to dividing the periosteum and fascial structures transversely.

Anderson: The next technical advance in limb lengthening came from adoption of the technique described by WV Anderson of Edinburgh, Scotland in the mid-1960s [467]. This technique evolved from an operation in 1954 but he did not report the technique in detail until 1967. He described the evolution of his technique from that of Abbott which was practiced with some modifications in his institution for approximately 20 years prior to 1954 with "satisfactory results obtained, with increases of length up to 3½ in. in the tibia, with no complications of any severity." We quote two paragraphs from Anderson's paper which eloquently review the subsequent reactions to the Abbott procedure after its seemingly excellent early results. "Unfortunately, this procedure appeared to be so simple and satisfactory that its rapid and deserving popularity almost brought about its eclipse. It was performed widely by many surgeons who failed to realize the fundamental importance of suiting the operation to the patient; by this failure they were directly responsible for the numerous and terrifying complications which followed this tragic misuse. These ranged from gross sepsis to amputation, following vascular failure. The procedure was condemned loudly and bitterly because it produced too much pain and was technically difficult and

Table 6.4 Possible complications in limb lengthening procedures

Bone	Premature union
	• incomplete osteotomy
	• long latency period prior to beginning lengthening
	• interruption of lengthening due to other causes
	Malunion
	• angular deformity/axial deviation
	• unstable apparatus
	• imperfect pin placement or initial malalignment postosteotomy
	• altered muscle pull with increased extent of lengthening
	– proximal femur—varus
	– distal femur—valgus
	– proximal tibia—valgus
	– distal tibia—varus
	• tibial lengthening greater than fibular → valgus ankle
	• angular deformation post fixator removal (softened bone at distraction site)
	Scanty union
	Delayed union
	Nonunion
	Osteomyelitis
	• lengthening site
	• pin-tract site
	Osteoporosis
	Late fracture
	• shortening
	• angular deformity
	Pin/wire pull-out
Skin	Pin-site irritation/infection
	Skin slough 2° malaligned fragment pressure
	Fragment protrusion
Muscle	Fibrosis
	Contracture
	Weakness
	• myopathic
	• neurogenic
	Pin skewers muscle to compromise mobility
Nerve	Intraoperative phase
	• pin skewers nerve
	Distraction phase
	• excessive stretching; sciatic, peroneal, posterior tibial, radial nerve
	• sensory: paresthesia, hyperesthesia, anesthesia, transitory, permanent
	• motor: partial paralysis; paralysis
Vessel	Intraoperative phase
	• pin skewers vessel
	• vessel damaged during osteotomy
	Distraction phase
	• excess vessel stretching
	Compartment syndrome
	Hypertension
	• excessive arterial stretching
	Thrombophlebitis
Joint	Stiffness: ankle equinus, knee extension, hip adduction/flexion contractures
	Cartilage degeneration
	Subluxation
	• knee
	• hip
	Dislocation
	• hip
	Septic arthritis (pin placed into joint cavity)
Physeal cartilage	Increased growth of femur following completion of lengthening*
	Diminished growth of tibia following completion of lengthening*

*in relation to pre-lengthening growth rates

destructive by those who had, in fact, made it so themselves." For many years, it was practically given up in the land where it originated. The alternative methods of equalization were more fully developed in particular of epiphysiodesis and stapling, while shortening the longer side was in much more favor than lengthening.

Eventually, the Edinburgh group where Anderson worked modified the apparatus and the procedure and began distraction on the operating room table. They noted that "contrary to the findings in America, we had none of the complications which ended in the condemnations of the operation. The pain was minimal, even from the day of the operation. There were no vascular or neurologic changes of any importance and no major sepsis occurred. The operation was accepted by operating and nursing staff, and the patient, as a simple routine procedure. One complication which was reported by others and appeared in the Edinburgh series was the slowness of the lengthening of the fibula which led to valgus deformation of the ankle. This was greatly minimized by a distal tibial-fibular synostosis obtained prior to the lengthening procedure. The Anderson technique as subsequently practiced evolved in a patient who suffered a transverse fracture of the mid-tibia as he was waiting for a more formal Abbott type lengthening. This opportunity

presented itself such that the apparatus was applied for stability and lengthening was performed. There was surprisingly good maintenance of alignment and it was noted that the lengthened site healed readily. The advantage of this approach was that a very small linear incision only was required, there was very little disruption of the periosteum and the transverse osteotomy was made following positioning of several transcortical drill holes and manual osteoclasis. There was a 1/8 in. lengthening on the operating room table with subsequent lengthenings starting on the 3rd or 4th day of 1 turn daily equaling 1/16 of an inch. Anderson indicated that "in the average case the length of 2–3 in. may be obtained without difficulty" and "up to 1 and ½ in. can be expected before any tendency to foot deformity (tendo-Achilles tightness) becomes evident." The patient remained in bed with the limb suspended in a traction frame. When new bone was seen radiographically external fixation was removed and the limb was immobilized in plaster. Anderson noted empirically that 1/16 of an inch increase per day remained the most satisfactory rate of lengthening. Anything less may predispose to early bone union with callus formation overcoming the rate of lengthening, thus preventing full length desired being obtained, and a faster rate may cause delay in union, considerable pain and possible nerve and vascular complications. Anderson specifically remarked that "pain is so exceptional (in their lengthening unit) that apart from the immediate postoperative pain (in itself minimal) it is regarded as indicative of something abnormal and subsequently of importance." Following new bone formation deemed sufficient to prevent collapse, the apparatus was removed and the limb was placed in a long leg cast followed by eventual transfer to a walking brace. Femoral lengthening was performed in a similar fashion.

A major review of the Anderson approach was published by Coleman and Noonan from the Salt Lake City Shriners Unit in 1967 [468] and by Coleman and Stevens in 1978 [469]. Thirty-one tibial lengthenings using the Anderson technique with limited surgical exposure were reported. They performed the Anderson technique as he had described it emphasizing "the advantage of osteotomy of the tibia by a limited surgical exposure, in which the hematoma remains localized, periosteal stripping is avoided, there is relatively little soft tissue damage, and the periosteal tube is preserved. A distal tibial-fibular synostosis was performed initially prior to lengthening to prevent valgus deformity at the ankle but eventually stabilization was done using a transfixion screw at the same time as the lengthening procedure. A cast was applied at the same time as the distraction apparatus and osteotomy to help minimize the development of equinus at the ankle. Distraction was at the rate of 1/16 in./day. In the thirty-one patients satisfactory union was obtained in all with an average gain in length of 5.0 cm (range 2.0–6.0). Non-union occurred in 4 patients but satisfactory union was subsequently obtained with bone grafting. The authors modified their technique to do a bone grafting procedure in all patients who at 4 months after surgery "show lack of complete bone bridging". There were no wound infections and only pin tract infection. There was no permanent detectable injury to the neurovascular structures.

Manning reported on a large series of femoral and tibial lengthenings using the Anderson apparatus and technique [470]. The patient remained in bed for the lengthening procedures with the distraction apparatus supported in traction. Distraction took place once daily with a gain of 1/16 of an inch (1.6 mm). Once length had been achieved and early healing was underway the patient was transferred to a cast and ultimately to a brace. Lengthenings were done with 211 procedures performed, 161 on the tibia, and 50 on the femur. The average gain was 3.06 cm with 122 of the tibias lengthened 5.0 cm or more, and 21 femurs 5.0 cm or more. Major complications related to fracture after lengthening had been completed and delayed union or nonunion. Fractures occurred in 30 limbs (14 %). These all subsequently united relatively quickly but shortening occurred in many lessening the advantage of the original lengthening procedure. Bone grafting was resorted to for slow union or nonunion present 6 months after the lengthening had been completed. Such grafts were used in 23 tibia lengthenings (14 %) and 2 femoral lengthenings (4 %). Each then healed uneventfully.

Chacha and Chong reported on overall favorable results with 35 tibial lengthenings (31 Anderson type) with an average gain of 5.2 cm and a range of 2.8–6.5 cm [471]. Malhis and Bowen reported on 12 tibial lengthening using the Anderson method [472]. The mean amount of lengthening achieved was 6 cm (range 3–10 cm) and the mean percent lengthening was 24.5 % (range 13–42 %). Bosworth used the Abbott technique but recommended not beginning lengthenings until 10 days after the osteotomy [473].

One-Stage Lengthening Procedures. Le Coeur: Le Coeur of Paris described a one-stage lengthening procedure with immediate stabilization and applied the technique 169 times between 1952 and 1962 [474]. The amount of length gained varied between 3.0 and 4.7 mm and owing to the immediate fixation used the amount gained was maintained with certainty. The period of immobilization was similar to that used for fracture repair. The tibia was the more favorable site for lengthening but femoral procedures were also performed. The operation was accompanied by multiple transverse muscle and fascial releases which allowed for lengthening of the soft tissues readily in conjunction with the bone elongation. A lengthy oblique incision of the tibia was made following which a bipolar traction apparatus was applied to upper and lower regions of the tibia. Once the soft tissue releases had been performed, the oblique osteotomy made, and the traction apparatus positioned, lengthening began

with the knee in partial flexion. The knee remained in flexion during the lengthening procedure. Once the desired length had been reached and the surrounding muscle and fascial tissues released, osteosynthesis was performed with four or more transverse screws. No cast was used at this stage. The patient remained in bed with the knee flexed for approximately 45 days to allow healing to occur. The patient then began walking with crutches. If a long leg cast was needed it was placed with the knee still flexed. Le Coeur indicated that femoral lengthening could also be done with the same technique although it was more difficult. In 125 cases involving 88 tibial and 37 femoral lengthenings, the amount gained ranged between 3.0 and 4.7 mm. In younger children with open growth plates, there was often an added overgrowth providing an additional 1–2 cm of lengthening. There were no vascular complications. There were 11 neurologic complications in the 125 procedures, the large majority of which resolved fully. There were two full paralyses of the sciatic nerve which lasted for a year, two partial sciatic lesions which cleared in 1 or 2 months, three paralytic lesions, and four partial neuralgias with the tibial lengthenings. Bone repair was uneventful occurring in most in 45 days with no pseudarthroses created. Fractures did complicate the procedure and occurred both during the early repair phase and also following healing anywhere from 3 months to 4 years post procedure. There were 14 fractures reported in the 125 lengthenings (11 %) with 7 in the femur and 7 in the tibia. The vast majority of lengthenings were performed for shortening secondary to poliomyelitis.

Cauchoix, Morel et al..: A one-stage femoral lengthening was also described by Cauchoix, Morel and colleagues [475] with results from the 100 initial patients reported in 1972 [476] and a total of 180 cases reviewed in 1978 [477]. The operation involved a lengthy mid-diaphyseal Z-osteotomy of the femur in the frontal plane with the length of the longitudinal cut 8 cm in the adult and 6 cm in the growing child. Distraction was performed against two transverse 5 mm Steinmann pins placed in the transverse axis through the proximal and distal femoral fragments. The knee remained flexed during the lengthening procedure and care was taken to keep the bone fragments in contact using a bone holder which was alternately opened and closed during the lengthening procedure. Considerable releases of the fascia were done along with decortication of the middle third of the femur and formal exposure of the sciatic nerve to check that it was not excessively stretched during the lengthening procedure. Once lengthening had been achieved, internal fixation was secured by a posteriorly placed vitallium plate. The bone gaps left by the Z lengthening were then filled with iliac crest autogenous cancellous bone graft. The average gain in 180 cases was 3.7 cm with 169 of 175 one-stage, one-time lengthenings ranging between 2.6 and 4.5 cm. In five instances, greater lengthening was achieved by performing the procedure twice. The operation was done with relatively strict limits in terms of the maximum amount of lengthening that could be achieved owing primarily to limitations involving stretching of the sciatic nerve. One hundred and eleven of the 175 cases were concentrated in the lengthening range of 3.1–4.0 cm. The usual limit in the child was 3.5 cm and maximum lengthening to be aimed for in the adult was considered 4.5 cm. The extent of lengthening was in the range of 10–15 % of the length of the femoral shaft. Only one case of nonunion was observed in the children with 11 cases in adolescents and adults (15 %). In the latter group the average time for bony union was over 6 months. During the evolution of the procedure, the subperiosteal approach to the femur was gradually replaced with the musculoperiosteal decortication approach. Knee motion was either not affected or only minimally affected by the one stage lengthenings. Of 180 patients 157 experienced no change in knee motion. There were no vascular complications in the series. Nerve complications were evident; however, there was one case of sciatic nerve palsy with a 4 cm lengthening and two cases of quadriceps palsy, both with femoral nerve involvement with partial improvement. Additional complications involved infection, early breakage of internal fixation, nonunion, and late fractures of the lengthened femur which occurred on eight occasions. The authors stressed that sustained flexion of the knee during the procedure prevented vascular and nervous complications. They felt that the procedure was warranted for moderate discrepancies although strict observance of the maximum lengthening guidelines was essential to minimize complications.

D'Aubigne and Dubousset: D'Aubigne and Dubousset described a one-stage lengthening of the femur using a transverse osteotomy with lengthening performed immediately over an intramedullary rod and the lengthening stabilized by insertion of a cortical bone block [426]. They described 16 patients in whom transient peroneal palsy occurred three times, delayed or nonunion three times, and knee flexion contractures requiring surgical release twice.

Wagner has stressed that one-stage lengthenings should be restricted to the femur and that a maximum of 4 cm increase can be obtained safely [478].

Kawamura. Gradual Lengthening: Kawamura and associates began lengthening immediately after osteotomy feeling that "since operative damage to soft tissues is minimized it is not necessary to delay the start of bone lengthening for a few days" [479]. Further lengthening was accomplished intermittently in three to five sessions under anesthesia.

The periosteum was elevated circumferentially following which osteotomy was performed. When the periosteum was elevated along the line of osteotomy in experimental dog models with 10 % lengthening the periosteum tore almost completely. In the second group, the periosteum was incised

longitudinally and detached for about 5 cm above and below the line of osteotomy. With distraction, the periosteum persisted as a tube localizing the fracture hematoma and rupture did not occur until 20 % lengthening. Histologic study of 130 dog procedures was done. After tibial osteotomy lengthening was performed gradually up to 10 % over 2–4 weeks. At 3 weeks, new bone formation from the inner surface of the periosteum was seen. Preservation of the periosteal tube was helpful in enhancing early bone repair. The repair response was mediated both by periosteal and nutrient vessels. Kawamura also felt that injury to the nutrient artery should if at all possible be prevented. Oblique osteotomy was used to lessen slightly the length in the gap needing repair. The nutrient artery was intact at this time frame also. In the center of the lengthened area hematoma was seen. At 3 weeks, there was excellent vascular supply to the repair callus and at 5–7 weeks there was vigorous proliferation of arterial supply from nutrient branches although a slight avascular zone was still seen centrally. By 8 weeks, most of the avascular zone had disappeared indicating that the lengthened area had reunited. At 12 weeks, there was a well-reconstituted medullary and cortical blood supply. The study showed that after a 10 % gradual lengthening following cortical osteotomy, the bone union progressed similar to that seen after a fracture.

Kawamura also noted the effect of diaphyseal lengthening on the physis in dogs at either end. The effect of tibial lengthening on the longitudinal growth of the bone was assessed in young dogs between 1 and 3 months of age. Osteotomy was performed and lengthening carried out to 0, 10, 15, and 20 % in 4–6 stages over 2 weeks. Subsequent longitudinal bone growth was then studied between 2 and 18 weeks postoperation. In lengthenings of 15 and 20 %, the growth plate showed marked narrowing both by radiographic and histologic study. There was marked growth plate deformity by 3 weeks in bones lengthened between 15 and 20 % with disturbance of endochondral ossification. Early closure of the epiphyseal growth plate was seen in 1/3 of the dogs with 10 % lengthening and in all dogs lengthened 15 and 20 %. In those animals lengthened 15 and 20 %, the ultimate gain compared to those lengthened only 10 % was negated "since the normal bone growth was lost in the larger mechanical lengthenings." They concluded that lengthening should be carried out gradually and limited to about 10 % of the original bone length.

Technique. The distal metaphysis of the fibula was resected subperiosteally for a distance of 2–3 cm and when lengthenings were projected to be more than 11 % it was felt advisable to fix the distal fibular fragment to the tibia with a screw. Four Steinmann pins were then introduced into the tibia 2 above and 2 below the proposed osteotomy site and the leg was placed in the distraction apparatus cradle. A small 1 cm incision was made over the mid tibial region with the periosteum incised longitudinally and elevated from the tibial surface. The periosteum was freed circumferentially. The oblique osteotomy was outlined by several drill holes penetrating the cortices with the osteotome subsequently cutting only the cortex in an effort to spare the nutrient intramedullary vessels. The initial lengthening was carried out to a distance not exceeding 3 % of the tibial length immediately. Kawamura did not find it necessary to divide the deep fascia, interosseous membrane, or intermuscular septum. Lengthening of the tendo-Achilles was performed if it was tight or if tightness was anticipated. Since operative damage to soft tissues was minimal it was not considered necessary to delay the start of lengthening to allow for soft tissue repair. Further lengthening was achieved by a small amount each day or in 3–6 sessions a few days apart with more lengthening done. It was felt that 3–6 weeks might be required to gain the desired length. When the required gain was achieved and consolidation of callus had occurred, the limb was placed in a plaster cast incorporating the pins. A similar procedure was performed for the femoral lengthening.

Over a 17 year period this group performed 252 tibial and 58 femoral lengthenings in children [480]. The tibial technique was standardized and 223 of 252 cases were reported as obtaining "highly satisfactory results." The 58 femoral lengthenings were also considered to be satisfactory. The vast majority of patients had good or excellent results with tibial lengthening up to 15 % with similar findings in the femur with lengthenings up to 11 %. Their observations in young dog experimental lengthenings done before the age of closure of the epiphyseal growth plates showed that gains in length were preserved in lengthenings of 10 % but in lengthenings of more than 15 % subsequent growth was often markedly decreased. Fifty-seven patients were studied in terms of subsequent longitudinal growth following tibial lengthening. Of the total of 57 patients, 35 showed a decrease in expected growth. Kawamura stressed that complications in this regard could be avoided with lengthenings kept to within 10 or 15 % of overall length. The lengthening was to be carried out gradually in 3–6 stages over 3–6 weeks and the initial lengthening done immediately should not be more than 3 % of the bone length.

Complications. Kawamura listed in detail the possible complications with limb lengthening. 1. Complications due to overstretching. These included angular deformity, arthritis, stiff joints, loss of muscle power, stretch paralysis, and neuralgia. 2. Complications due to interference of blood supply. These included delayed union and non-union, bone necrosis, and circulatory disturbances distal to the operative site. 3. Complications due to inadequate fixation of fragments. These involved overlying skin slough, fragment protrusion, anterior bone angulation, late fracture, and pin

site infection which could lead to osteomyelitis. 4. Direct operative complications included fracture of the osteotomized shaft, pin pull out, hypertension, and shock.

(b) *Improved results due to more rigid fixators. Gradual Distraction. Judet Technique*: The Judet technique, developed in France and reported in 1969, provided much more rigid stabilization thus enhancing comfort in association with lengthening [481]. It involved a lengthening by gradual distraction in association with an oblique osteotomy, decortication to hasten bone repair but use of neither graft nor internal metallic stabilization. The external fixator used 5 mm diameter pins with three or four placed in the proximal fragment and an equal number distally. A unilateral distractor was attached. The procedure was designed for use in the tibia. The distal fibula was stabilized by a transfixion screw to the distal tibia to allow for lengthening of both bones simultaneously and maintenance of the orientation of the ankle mortice. The oblique osteotomy of the tibia was made in the frontal plane and was of the greatest length possible with the average amount being 10.5 cm. A plaster splint immobilized the knee in extension and the foot at a right angle at the termination of the operative phase. The limb was maintained in the cast during the period of the lengthening which was performed at a rate of 1.5 mm/day. Each day hip, knee, and ankle range of motion exercises were done. When the lengthening was completed, the lower extremity was placed in a long leg cast which was then replaced at varying times with a lighter plastic brace. At 6 months, the distractor and fibular-tibial pins were removed with the tibia continuing to be protected in brace for an additional 6 months.

Pouliquen et al. reviewed 108 tibial lengthenings performed by the Judet method [482]. Of these, the large majority, 79, were due to poliomyelitis. The average lengthening obtained was 4.37 cm with a range from 2.6 to 6.0 cm. The average gain was in the range of 16 %. Bone union in the most favorable cases was obtained at an average of 4 months and a secondary bone graft was needed in only 5 instances. There were 17 instances of neurologic impairment although only 2 showed persistent anesthesia and 1 permanent paralysis of the extensor hallucis longus muscle. Postlengthening fractures occurred in nine patients, five of which were nondisplaced and treated only with a simple cast with four requiring additional surgical intervention. Overall, 10 secondary bone grafts were required, 5 for a delay in primary healing, and 5 for pseudarthrosis or fractures. The paper also performed detailed comparison with tibial lengthening studies from 7 other series.

Excellent reviews of limb lengthening techniques have been provided by Caton [483] and Paley [484]. Some of the less well-known earlier European techniques have been reviewed by Wiedemann [485].

Wagner Technique: Wagner in 1978 reported his technique which had major improvements from previous approaches and re-stimulated widespread interest in lengthening procedures [478]. His unilateral fixator was structurally very stable and allowed patients to be ambulatory with crutches immediately after the surgery and throughout the lengthening procedure. This alone was a major advance since virtually all previous lengthening procedures required prolonged bed rest, at least during the lengthening and early consolidation phases. Diaphyseal lengthening began immediately with approximately one cm of distraction performed in the operating room at time of instrumentation (described by Wagner as lengthening "until stabilization is achieved by soft tissue tension"). A one-time daily lengthening of 1.6 mm was performed. Once the desired length was reached a second operative procedure was done in all patients involving application of a long side plate, autogenous iliac crest bone grafting, and removal of the external fixator (Fig. 6.22a–h). The advantage of the second operative approach was that rigid internal stabilization was achieved immediately and rehabilitation was enhanced since range of motion exercises could be performed more easily once the bone and soft tissue transfixing pins were removed. The Wagner technique represented a significant advance over the Anderson and previous methods owing to the fact that the patient could remain ambulatory and pain was considerably diminished owing to the increased stability of the external fixator.

By the time Wagner developed his approach, the etiology of limb length discrepancy had changed with fewer children suffering from poliomyelitis. Of the 58 patients in his initial paper, only 10 had poliomyelitis with the largest group involving congenital short femur and the next largest sequelae of epiphyseal fracture. Wagner found that preoperative consideration of the entire limb was of increasingly great importance. Of particular importance prior to lengthening procedures was the correction of joint contractures and surgical intervention to correct acetabular dysplasia and angular bone deformities. He reviewed the advantages and disadvantages of operative limb lengthening and the various shortening procedures.

Carlioz et al. reported on their first 30 cases of the Wagner lengthening involving 15 femoral lengthenings, 7 tibial lengthenings, and 8 cases associated with correction of angular deformities or pseudarthrosis [486]. In the straightforward femoral lengthenings, the gain ranged between 4.0 and 7.0 cm. Among the complications were three subsequent fractures. The percentage of lengthening was in the range of

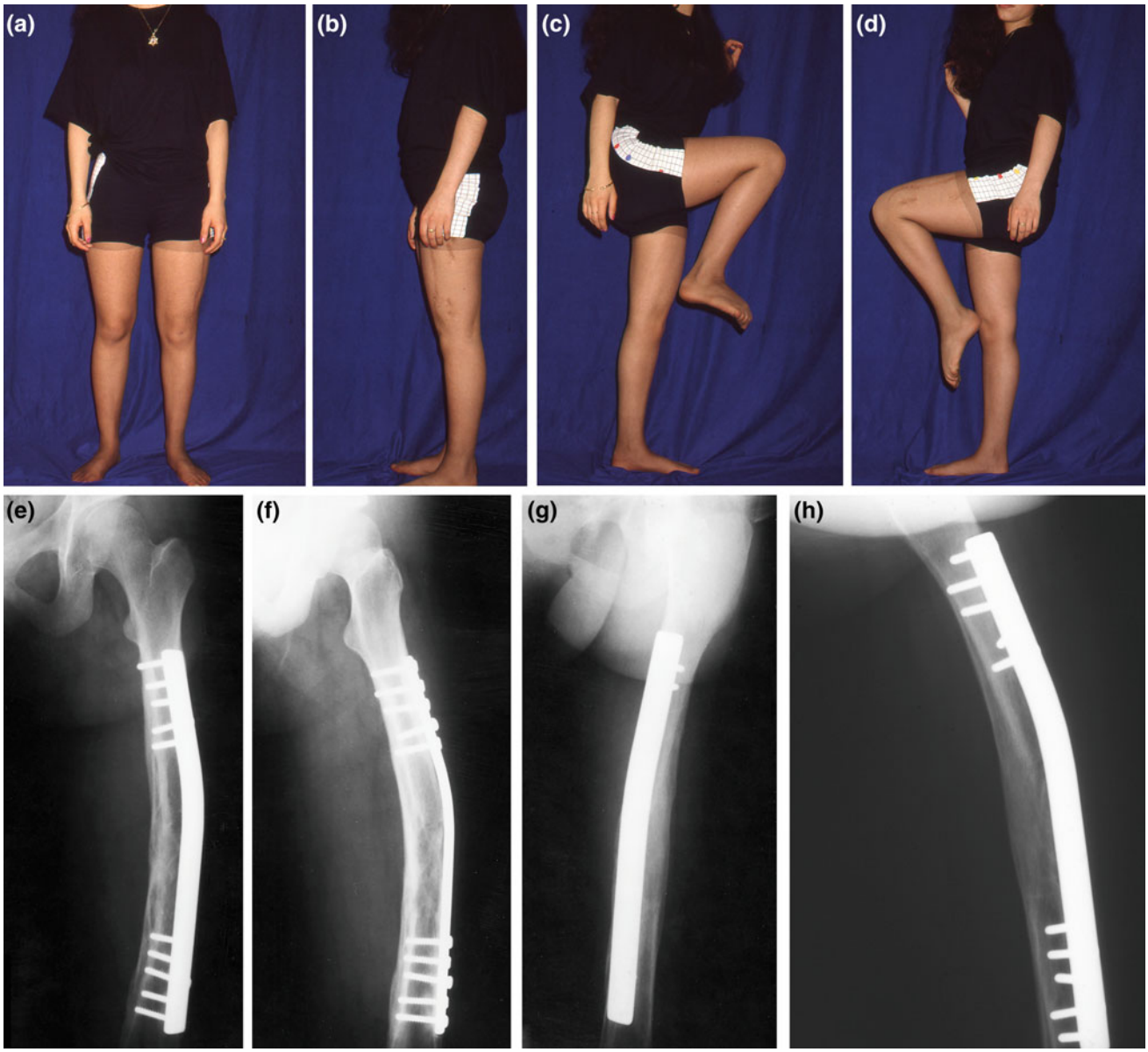


Fig. 6.22 Illustrations of a diaphyseal lengthening technique are shown. End result following lengthening of a femur using the Wagner method is shown in clinical photographs. As with any lengthening technique, the aim is to attain a symmetric appearance of both lower extremities with a full range of motion of adjacent joints. Following attainment of the desired length by distraction, additional operation is performed at which time a Wagner plate and bone graft are applied. The plate designed by Wagner for this procedure has no holes spanning the lengthened gap as these are prone to breakage if a regular AO plate is used. Although additional surgeries were required with this technique there was one major advantage in comparison to previous methods, where the distraction device was left on until full healing, in that rehabilitation in terms of range of motion of the adjacent joints and muscle strengthening were markedly quickened and improved. **a**–**d** Clinical photographs show symmetric appearance of lower extremities posthealing looked at from the front (**a**) and side (**b**) showing the operated limb with full knee extension. Side views of the patient with the knee maximally flexed show comparable hip and knee flexion on non-operated (**c**) and operated (**d**) sides. **e**–**h** Show anteroposterior (**e**), lateral (**f**), and oblique (**g**, **h**) projections at healing

15 % with no cases beyond 20 %. In the straightforward tibial lengthenings, the range of correction was between 4.0 and 5.8 mm with an average percentage increase of 15 % with one case being 26 %. Early experience of this group was quite favorable. A few years later, their group reported on 48 femoral lengthenings using the Wagner technique (Blachier et al.) [487]. The mean lengthening obtained was 5.2 cm with the most extensive 11.2 cm. In terms of percentage gained lengthening values were 15.6 % of initial bone length. On six occasions, the lengthening was >20 % with a maximum of 24 %. Many complications were noted varying from minor to much more serious in importance.

Superficial infection was frequent but easily managed. In 22 of the 48 cases, varus deformation occurred during lengthening but was easily corrected in most at the time of plate application and grafting. In some instances, however, the varus was not corrected even at the time of plate application. Subluxation at hip and knee was seen on occasion as were contractures without subluxation at these two joints. Five patients had neurologic complications; in four there was full and rapid recovery of the anterior foot dorsiflexors but in one paralysis of the peroneal and tibialis posterior nerves was complete and recovering only slowly at time of publication. There were 12 deep infections which on occasion compromised the long-term result. On occasion, fracture or pseudoarthrosis at the site of infection further complicated treatment.

Caton et al. also reported early favorable results with the Wagner technique in 33 lengthenings of which 20 were in the femur and 13 in the tibia [488]. The mean lengthening obtained was 5.35 cm and although many complications were seen 70 % of cases had none. The mean percentage lengthening was in the range of 16.2 % with a mean lengthening of 4.8 cm for the tibias and 5.7 cm for the femurs.

The use of more rigid fixators such as those of Wagner or Judet became popular in the 1970s. Some series are reported in which the fixators were used although differing techniques than initially described by the developers were applied. A study by Rigault et al. assessed 36 femoral lengthenings in which 21 used the Judet distractor and 15 the Wagner [489]. In most instances an oblique femoral osteotomy was used, there was an initial 5–10 mm lengthening at the time of surgery and progressive lengthening was then performed at a rate of 1–2 mm/day. The bone was allowed to heal without application of the graft and side plate as recommended by Wagner. The mean lengthening gained in the 36 cases was 5.2 cm which was an 18.3 % increase in length. The series was complicated by a high rate of fracture (9 of 36 or 25 %). Those having the oblique osteotomy had a mean gain of 5.6 cm while those having more transverse osteotomies had a mean gain of 4.7 cm. Bone graft was performed in 6 of the 36 cases because of delayed healing. Rigault et al. also described 48 tibial lengthenings using either the Judet or Wagner apparatus along with a long oblique osteotomy, decortication, and multiple soft tissue releases to stabilize the knee and minimize equinus deformities at the ankle [490]. In general, the distractor was left in place until radiographic bone consolidation was evident following which a brace or walking cast was applied to protect the limb during the return to full weight bearing. The mean lengthening was 4.2 cm or 17.5 % of preoperative bone length. Fractures were seen in 10 %. In the 10 more complicated cases, the mean lengthening was 5.5 cm or 16.5 %.

Many groups reported their results with the Wagner technique. Wagner reported on 58 femoral lengthenings in patients below the age of 17 years in which the average gain in length was 6.8 cm [478]. Bjerkreim and Hellum [491] reported average lengthening of 5.8 cm in the femur; Aldeghiri et al. [492] 4.9 cm in the femur and 4.0 cm in the tibia; and Paterson et al. 5.8 cm in the femur and 5.2 cm in the tibia [493]. Stephens reported an average femoral lengthening of 5.7 cm in 18 Wagner procedures and average tibial lengthening of 5.6 cm in 7 Wagner procedures [494]. Osterman and Merikanto reported on a mean increase with 26 tibial lengthenings of 4.1 cm and with 9 femoral lengthenings of 4.9 cm [495]. Mahlis and Bowen reported 27 femoral lengthening with a mean increase of 6 cm (range 3–9.5 cm) (mean percentage increase 17.6 %, range 7–36 %) and 11 tibial lengthenings with a mean increase of 6.1 cm (range 4.5–9 cm) (mean percentage increase 20 %, range 10–32 %) [472]. Ahmadi et al. compared results with 50 Anderson, 40 Rezaian, and 51 Wagner lengthenings all done for poliomyelitis [496]. The mean gain was 4.8 cm and complications showed six refractures (4 %) as well as others commonly seen, but in relatively low rates. Results in the three techniques were similar; the Wagner was favored for relative ease of use.

Complications with the Wagner procedure: The study of and literature on the complications of limb lengthening surgery is somewhat unique in relation to the rest of the orthopedic literature, primarily because of the intrinsic nature of the difficulties with this procedure. A characteristic approach is to divide what would generally be considered complications into (i) problems, which are felt to be intrinsic, cannot be avoided, and include such disorders as delayed union and nonunion, pin track infections, and transient restriction and motion of adjacent joints, and (ii) complications which are extrinsic and should be avoided including infection, nerve damage, fractures, and subluxations. Others use the terms minor and major complications.

DeBastiani et al. reported a 26 % complication rate with the Wagner method [497]. Hood and Riseborough [498] noted 37 complications in 40 procedures, while Wagner [498] noted a complication rate of 45 % in 58 patients.

Luke et al. specifically reviewed fractures after the Wagner limb lengthening procedure [499]. In a series of 27 cases, there were 10 fractures following lengthening in 8 patients of which 6 were spontaneous and 4 traumatic. The fracture occurred through the lengthened area after plate and screw removal in 8 patients, through a proximal screw hole and plate in 1 patient, and through an external fixator pin hole with hardware intact in another. Seven fatigue fractures occurred after plate removal in Wagner's series. Hood and Riseborough [498] reported 4 fractures after 40 Wagner lengthenings; Mosca and Mosely [500] reported 63 Wagner lengthenings with 16 subsequent fractures; and Chandler

et al. [501] reported 21 lengthenings with 2 subsequent fractures. The above 4 studies thus reported a total of 182 Wagner lengthenings with 29 subsequent fractures (16 %), while the most recent report of Luke noted a 37 % rate (10 of 27). The amounts lengthened in both tibia and femur were not remarkable in those suffering either spontaneous or traumatic fractures with the tibial percent lengthening at approximately 16 % and the femoral 20 %. Some attempted to minimize the fracture sequelae by a four-stage procedure involving the osteotomy, plating and bone grafting of the lengthened area, and then instead of removing the hardware at one stage, doing a two-stage procedure with removal of alternate screws and partial loosening of the plate followed several months later by removal of all remaining hardware.

Osterman and Merikanto noted that a major complication was late femoral fracture which occurred in 6 of the 26 instances although there were no tibial fractures [495]. There was 1 hip dislocation, 1 talar deformation, 1 peroneal nerve entrapment, and 1 infection which delayed bone union. The authors cautioned about early removal of the stabilizing plates and also indicated the need for bone lengthening to be performed by well-trained teams.

Karger et al. reported primarily on Wagner lengthenings involving 51 femurs and 18 tibias. Complications were more marked when the lengthening exceeded 25 % of initial bone length [502]. They were also much higher in the femur than in the tibia. Some modifications to the Wagner procedure were incorporated; while 44 patients had the entire sequence described by Wagner, 18 had only the stage-one procedure but did not have grafting and plating since the authors felt initially that healing would be appropriate. In 51 femurs lengthened by the Wagner technique, the mean lengthening achieved was 7.57 cm which represented a 25 % increase whereas in 18 tibias, the mean length achieved was 6.07 cm accounting for 23 % increase in length. The complications were divided into groups referred to as problems, obstacles, minor sequelae, and major sequelae. They were commonly seen in the femoral lengthenings but somewhat less frequently in the tibial. Fractures were common occurring in 18 of 51 femoral procedures and 3 of 18 tibial. Angulation was noted in 25 in the femoral group all of which were varus with a mean deformity of 25°. Some had flexion deformities as well. There were 10 of 18 angular deformities in Group 2, all of which were valgus with a mean of 16°. Pin tract infections and deep infections were noted as were joint restrictions of motion including 12 transient knee subluxations.

Salai et al. described three hip subluxations during femoral lengthening with the Wagner technique [503]. Each of the patients had some predisposing hip and acetabular abnormality indicating the importance of assessing the hip prior to and during the course of lengthening and fully correcting malposition surgically prior to the lengthening procedure.

(c) *Distraction Osteogenesis*: Although many good and excellent outcomes were obtained with the Anderson and Wagner techniques, problems and complications still occurred. The Anderson technique frequently required supplementary bone grafting while the Wagner approach required at least three surgical interventions and subsequent fractures after plate removal were a problem. Work continued with different techniques to improve results.

(i) *Clinical Techniques. Distraction Osteogenesis. Ilizarov; Monticelli and Spinelli; DeBastiani; Aldegheri and associates; Canadell and associates*: Techniques developed by Ilizarov [504–508] in Russia; Monticelli and Spinelli in Italy [509]; DeBastiani, Aldegheri, and associates in Italy [497]; and Canadell and associates [510–512] in Spain have allowed for lengthening and bone repair such that bone grafting and plating were infrequently required. These techniques, described collectively under the term distraction osteogenesis or callotasis, are dependent on four principles, the first two of which are truly integral to the effectiveness: (a) delay prior to the initiation of bone lengthening for 7–10 days to allow early repair, or callus formation, to occur, (b) gradual lengthening of 1 mm/day performed at four separate times to minimize damage to newly formed vessels and repair tissue, (c) corticotomy leaving the medullary vasculature intact or at least minimally disturbed, and (d) maintenance of an intact periosteum. There has been somewhat of a polarization between schools performing the distraction osteogenesis technique based on the type of external fixator used. The Ilizarov technique uses circular and hemispheric external fixators stabilized by multiple narrow wires; the Monticelli-Spinelli method uses a single circular fixator to hold epiphyseal wires and two diaphyseal level rings held together by longitudinal rods between which the metaphyseal corticotomy is performed; and the Orthofix and Monotube methods use a unilateral fixator with two upper and two lower 5 mm wide pins (Fig. 6.23a). The early results were promising but even with these techniques problems similar to those reported with earlier methods are encountered. Healing time still remains prolonged and associated with osteopenia, muscle atrophy, and joint stiffness.

Paley summarized the work of Ilizarov and the Kurgan school who worked extensively on distraction osteogenesis [484]. More than 1,000 publications from their institute had

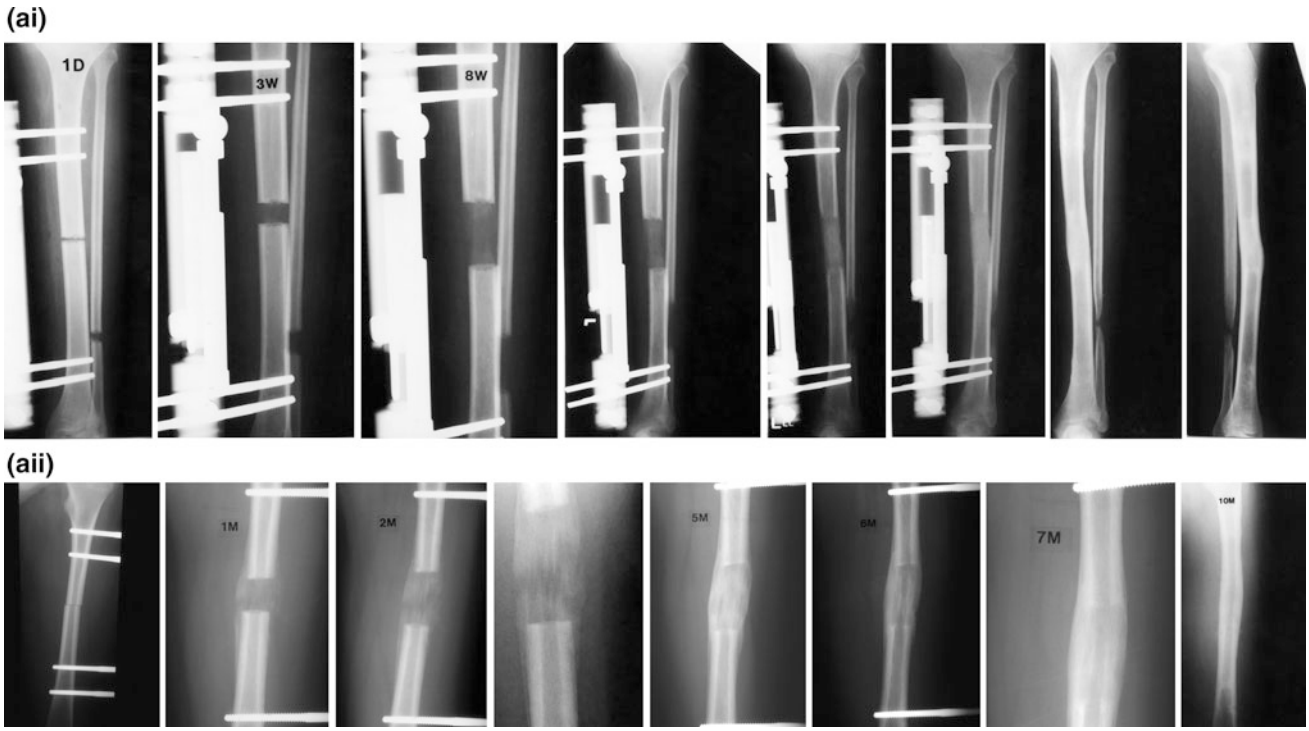
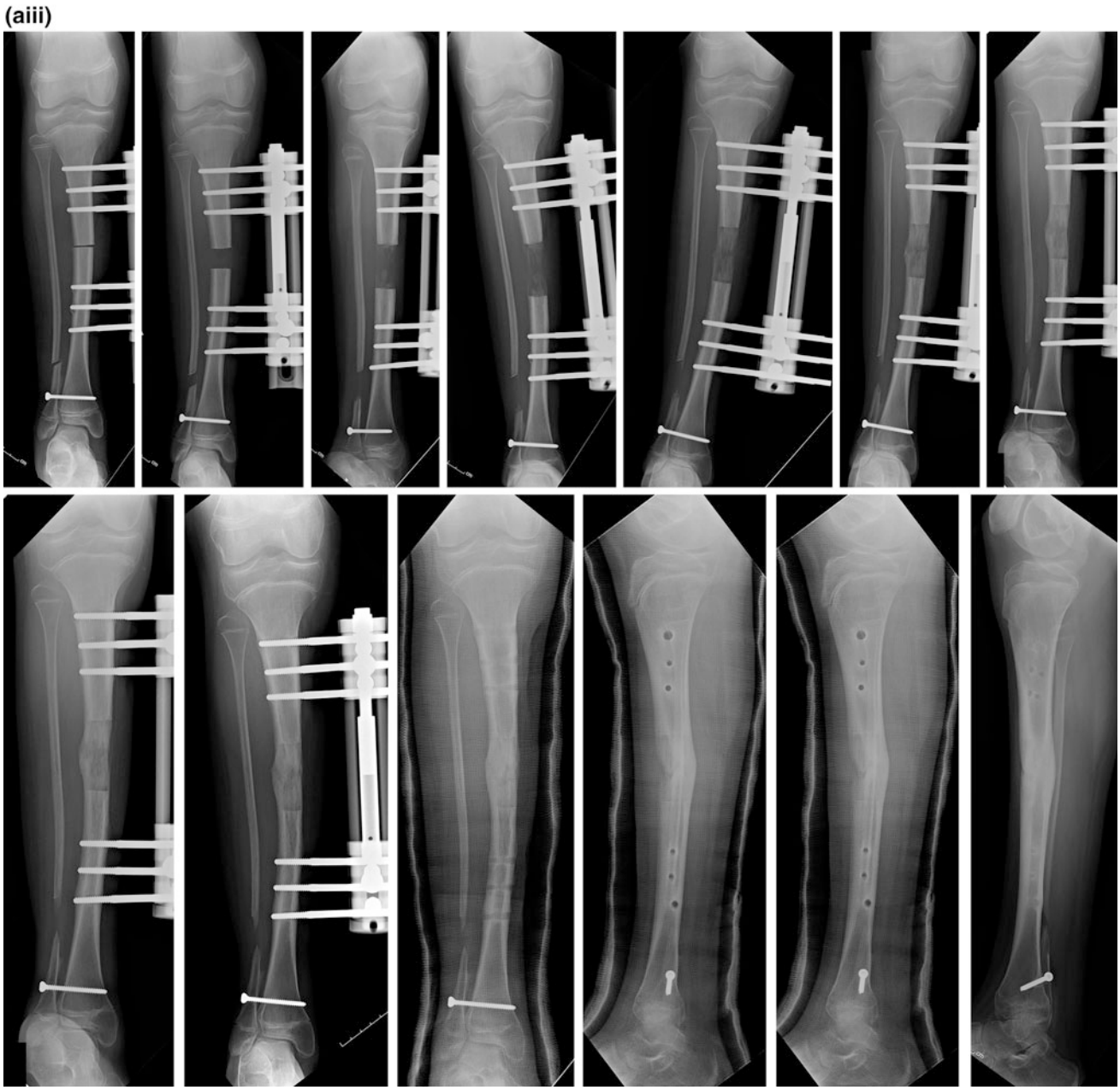


Fig. 6.23 (continued)

described various approaches to the technique, with most published in Russian. Major studies were reported by Ilizarov of 237 femoral lengthenings with an average lengthening of 7.4 cm, (range 3–15 cm) and complications listed in 12 patients (5.6 %). Ilizarov also published results of 217 tibial lengthenings in both children and adults with the mean gain of 7 cm, (range 4–15 cm). Paley [513], Aronson [514], and Birch and Samchukov [515] have reviewed the complications with the technique in detail. The Ilizarov apparatus has three major components: bone fixaton elements (wires, half-pins), external supporting elements (rings, arches), and connecting elements (rods, plates, hinges) to connect the rings and arches and allow for manipulation of the relationship between them.

Stanitski et al. reported the results in 36 femoral lengthenings using the Ilizarov technique with the average lengthening 8.3 cm (range 3.5–12) and a lengthening index, months of treatment/cm lengthening, of 0.74 [516]. Stanitski et al. reported on 62 tibial lengthenings using the Ilizarov technique with the average lengthening of 7.5 cm (range 3.5–12) representing the equivalent of a 32 % average overall increase [517]. Franke et al. reported good results with the Ilizarov technique whether they used distraction epiphysiolysis or metaphyseal corticotomy [518]. In the distraction epiphysiolysis procedure, they lengthened 22 tibias with an average lengthening of 8.25 cm (range of 4–18 cm) and 30 tibias using the metaphyseal-diaphyseal corticotomy with an average of 7.9 cm lengthening (range 4–15 cm). Their report is detailed assessing the average time of distraction, the average time to removal of the apparatus, and the average time to full weight bearing. They subdivided results into the amount of lengthening from 4 to 5 cm in 1 group, 5.5–9.5 cm in another, and 10 cm or greater in the next. Tetsworth and Paley showed excellent lower extremity alignment correction as well as length correction with the Ilizarov method [519].

Monticelli and Spinelli reported 43 cases of metaphyseal lengthening using the distraction osteogenesis technique with their own fixator with a mean gain of 7 cm and a range from 4 to 10 cm [509] DeBastiani and colleagues using open corticotomy and callus distraction with their monolateral fixator (Orthofix) performed limb lengthenings on 100 segments with a lengthening index of 1.2 months for the femur, 1.4 months for the tibia, and 0.8 months for the humerus [497]. The average amount of lengthening obtained in the femur in patients with achondroplasia was 7.8 cm (5.5–12) representing a mean 26 % increase, while in the tibia the average amount of lengthening obtained was 7.8 cm (6–10.5 cm) representing a 36 % increase. In patients with limb length discrepancy from congenital and acquired disorders, the average amount of lengthening in the femur was 4.7 cm (3–9; 11 %), in the tibia 4.7 cm (3–9; 17 %) and in the humerus 7.5 cm (7–8; 34 %). Aldegheri et al. reported on 270 femoral and tibial lengthenings using the Orthofix callotasis method [520]. Ninety-five patients had limb length inequality and 45 had achondroplasia/hypochondroplasia. The average length increase was 6.6 cm or 24.6 % of initial length. The mean healing index was 39 and the complication rate 13.3 %.



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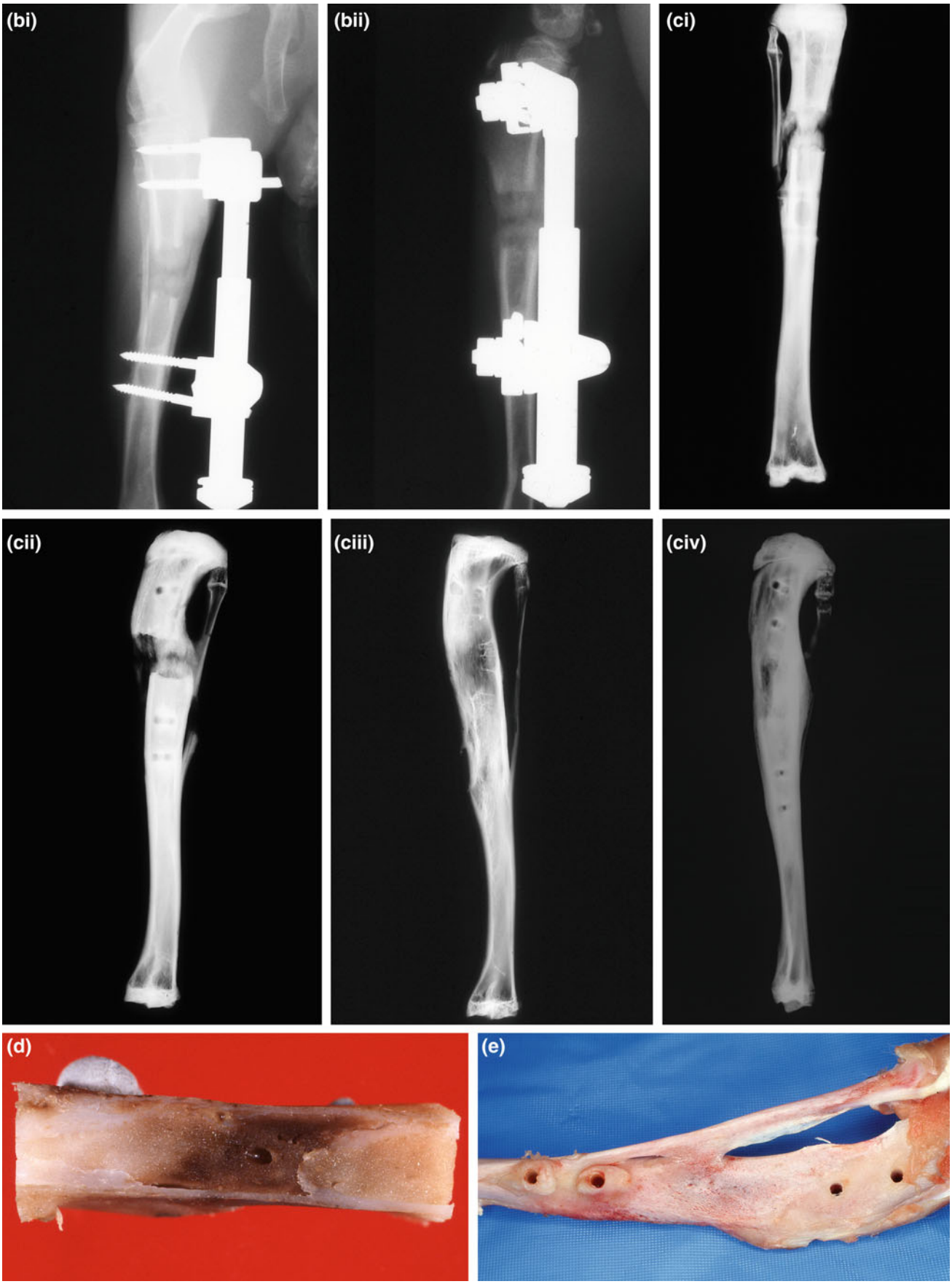
Long-term studies of relatively large numbers of patients with the callotasis technique show findings similar to other lengthening techniques. Glorion et al. reviewed 79 cases of femoral lengthening by the callotasis technique with 9 patients having the Judet apparatus and 70 the Orthofix [521]. They concluded that the incidence of complications did not seem to be less than encountered with previous methods of lengthening. The complications were the same in terms of nature and extent whether callotasis had been performed using the Ilizarov or Orthofix techniques. The averaging lengthening achieved was 5.2 cm (3.5–8.5 cm) which represented a mean increase in femoral length of 17.7 %. In the 79 cases, however, there were 87 complications, a rate of 110 %, although several complications were often encountered during one procedure. They noted that 30 % of the lengthenings were performed without any complication and 62 % with relatively mild complications such that additional surgery was not needed. The healing index was 39.6 days/cm which was comparable to other callotasis studies. Dynamization was considered to be an important adjunct to the healing process.



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Canadell summarized the experience of his group from Pamplona, Spain. Assessment of 93 lengthenings performed over a 3 year period using the principles of distraction osteogenesis and a unilateral fixator was reported along with conclusions realized over a 25 year period involving more than 800 lengthenings [510–512]. The 93 lengthenings involved 27 with unilateral discrepancy owing to pathologic conditions and 34 patients having bilateral lengthenings for symmetrical shortening with skeletal dysplasia disorders. The average lengthening obtained was 8.37 cm with complication rate of 2.1 per lengthening. The repair index was the same for both femur and tibia but humeral lengthenings healed in a much quicker fashion. There was only a slight overall difference in repair between metaphyseal and diaphyseal osteotomies and those involving distraction epiphyseolysis. The diaphyseal and metaphyseal lengthenings provided slightly greater increases in length. The rate of distraction was somewhat slower in the epiphyseal distraction procedures although the rate of healing was somewhat quicker once length had been obtained. Canadell also noted that repeat lengthenings could be performed readily on the same bone generally with an interval of 2 years between each procedure. The number of complications was greater during the course of the first lengthening than with the second. Two femurs had been lengthened 5 times and 2 others had been lengthened 3 times. Lengthening was resorted to for discrepancies of 3 cm or more. It was difficult to prevent traumatic rupture of the medullary cavity and in only 30 % of cases were the contents intact. Protection of the periosteum was considered essential. The ideal rate of distraction was 1 mm/day with 0.25 mm lengthened at four evenly spaced time periods. The ideal age to conduct lengthening was between 8 and 12 years at which time the osteogenic capacity was greatest. In those younger than 8 years of age repair was often so rapid that the desired lengthening could not be achieved. Lengthening was contraindicated after the age of 30 years. Considering all lengthenings done, the index of maturation was 1.16 months/cm. Distraction was begun at different times after percutaneous metaphyseal or diaphyseal osteotomy and application of a monolateral fixator dependent on the age of the patient using a rough guideline of 1 day delay per year of age. Thus a child of 8 years of age had lengthening started 8 days after initial surgery and for someone 15 years of age they waited 15 days. The quickest healing rate was most favorable in those with short stature conditions averaging 0.8 months/cm and it was much longer in those with unilateral length discrepancies being in the range of 1.5 months/cm. The greatest lengthenings were also obtained in those with short stature with an average of 11.2 cm per segment lengthened. In 8 patients with a chondrodysplasia he reported extensive lower extremity lengthenings gaining 23.2 cm, 12.35 in the femur and 10.85 in the tibia. The ideal site for osteotomy was the metaphysis. More sensitive angiographic studies indicated that in 90 % of diaphyseal osteotomies the medullary vessels were damaged which was one of the reasons the metaphyseal site was favored since the vascularity was more diffuse and richer in that region. On both a clinical and experimental basis it was vastly more important to respect the continuity of the periosteum than the medullary circulation. Dynamization was strongly supported for enhancing repair.

◀ **Fig. 6.23** **a** Examples of the distraction osteogenesis technique are shown. **ai1**Çô**8** Anteroposterior films of tibia and fibula lengthening show distraction gap from day 1 until full healing at 1 year. The fibula has never fully united but has not been a clinical problem. Progressive new bone formation is seen resulting in full cortical reconstitution of the tibial diaphysis on anteroposterior (**ai-7**) and lateral projections (**ai-8**) with reformation of the marrow cavity. Lengthening was begun one-week post surgery. Note that early bone regenerate is more dense adjacent to the upper and lower persisting bone with the central part of the gap region showing lesser ossification and radiodensity. A unilateral fixator was used. **aii1–8** Results of a femoral lengthening are shown using distraction osteogenesis principle and the Orthofix apparatus. Anteroposterior films of the femur are shown from time of initial osteotomy and insertion of apparatus to complete healing at 10 months. Note the close apposition of the cortices at time of initial procedure. Lengthening was begun at 1 week. At 12 days, there is just the beginning trace of new bone formation just lateral to the cortical regions. At 1 and 2 months, new bone is clearly forming in the gap and slightly lateral and medial to it along with increasing length noted. A central gap region is seen, at 2 months (**aii-3**) with more bone formed adjacent to the ortices above and below. A higher power view shows this formation pattern more clearly (**aii-4**). Progressive new bone formation is seen at progressive months. Note the marrow cavity reconstitution at 6 months particularly in comparison with the appearance at 5 months where bone across the gap was relatively uniform. Final cortical and marrow reconstitution at 10 months of age is seen. The patient has continued with normal function and increased bone density with a full range of motion at hip and knee. **aiii(1–13)** Results of the tibial lengthening are shown using distraction osteogenesis principle and the Orthofix apparatus. Images showing the leg in cast were during the period following heel cord lengthening. **b** Radiographs of rabbit tibia undergoing distraction at 22 days following surgery (i-*anteroposterior*; ii-*lateral*). Healing pattern is similar to that in the human with central region healing more slowly. **c** Specimen radiographs allow for better demonstration of bone repair at varying times following surgery and distraction. Distraction began at time of surgery. The specimen **c** i and ii (AP and *lateral*) were done 14 days after surgery and initiation of distraction, in (iii) 32 days (*lateral*); and in (iv) 44 days (*lateral*) postsurgery. *Note* the excellent cortical reconstitution and marrow reformation in the final lateral radiographs. **d** Specimen photographs obtained after decalcification and hemisectioning the bone repair gap and the adjacent cortices prior to histologic sectioning. Photograph of rabbit sacrificed at 46 days shows the excellent reconstitution of the cortex as well as marrow continuity. The lengthened region which totaled 9 mm or 9 % of the initial bone length is indicated by the darker staining more vascular marrow centrally. **e** The lengthened tibia is shown at sacrifice after the fixator had been removed and surrounding soft tissues had been dissected. This had been lengthened 11 mm, an amount which corresponded to 10.7 % of its initial length. Lengthening proceeded for 14 days and the fixator was left on for an additional 30 days with sacrifice 44 days postsurgery

Noonan et al. subsequently reviewed femoral and tibial lengthening cases from the clinic of Canadell and colleagues in relation to etiology, age and site of the osteotomy on the outcome, the prevalence of complications, and need for additional procedures [522]. They reviewed distraction osteogenesis of 114 femurs and 147 tibias. The group used monolateral external fixators: Wagner for 96 femurs and 100 tibas, Orthofix for 2 femurs and 3 tibias, and Monotube for 16 femurs and 44 tibias.

The femurs were lengthened an average of 11 cms (range 3.5–17) or 48 % of the original femoral length (range 8–86 %). There were 114 complications leading to 87 additional operations. The femoral lengthenings done for limb length discrepancy had significantly higher complication rates for each amount of length gained than those performed for achondroplasia or other skeletal dysplasias. The rate of complication for femoral lengthenings in those 14 years old or older was significantly higher than those under 14 years of age. Femoral lengthenings through the metaphysis had significantly higher rates of complication than those through the diaphysis. In the femurs, 52 or 114 (46 %) had no additional operative procedures. Complications/additional operations included: interval fixation and bone grafting for non-union, femoral osteoclasis (to improve position), pin removal, internal fixation for fracture through callus, osteotomy, closed manipulation under anesthesia and cast application, repositioning or exchange of fixator, hip region tenotomy for contracture or subluxation (rectus femoris, iliotibial band and/or adductors.)

The tibias were lengthened an average of 9 cms (range 3–15.6) or 41 % (range 9–100) of original length. There were 196 complications leading to 219 additional operations. The Achilles tendon was lengthened during or after 73 (50 %) of the lengthenings. The rate of complications and additional operations in those 14 years of age or older was significantly greater than in those <14 years of age. The site of tibial osteotomy did not affect the rate of problems or need for associated operations. In the tibias, 42 of 147 (29 %) had no complications. Complications/additional procedures included: equinus contracture needing tendoAchilles lengthening (73), valgus angulation before fixator removed (19), knee contracture or subluxation (3), and premature healing of fibula (4). Operative procedures included the tendoAchilles lengthening, removal of pins, osteotomy for malalignment, removal or manipulation of fixator, interval fixation with bone grafting for non-union, knee manipulation, fibular osteoclasis, and peroneal nerve repair.

Fractures continue to be seen fairly often even after distraction osteogenesis lengthenings. Danziger et al. reported 9 femoral fractures after 18 Ilizarov femoral lengthenings but no tibial fractures with 8 tibial lengthenings [523]. Glorion et al. using primarily the Orthofix technique in 61 lengthenings had fractures in 6 instances [524]. Their technique involved percutaneous osteotomy referred to as compactotomy when at the level of the metaphysis or corticotomy when done within diaphyseal bone. The cortex alone was cut with a small 5-mm osteotome with care taken not to enter the medullary cavity in an effort to spare the nutrient artery and medullary circulation. The periosteum remained intact. The remainder of the cortex was then broken either by rotating the osteotome to distract the bone ends or by rotating the fixator pins. Distraction did not begin until 7 days post surgery at a rate of 0.25 mm elongation 4 times daily. The average time to healing is still extensive and the lengthening index (months healing/1 cm lengthening) has most studies showing an index around 1 (if 5 cm are lengthened the time to healing is 5 months).

Suzuki et al. studied 26 femoral lengthenings using the Orthofix callotasis technique from the viewpoint of dislocation and subluxation of the femoral head during the lengthening procedure [525]. Lengthening began 1 week postsurgery with the rate of distraction 0.25 mm every 6 h. The mean amount of lengthening obtained was 5.0 cm with a range from 2.0 to 7.5 cm. One group of 14 hips with a CE angle of >20° at the start of lengthening showed no deterioration in position with the lengthening while the other group of 12 hips with an angle of 20° or less showed deterioration of femoral head position in 5 of the 12 hips. One developed a complete dislocation and the other four subluxed, showing a decrease in the CE angle. Four of the 5 had history of congenital dislocation of the hip and the other had multiple epiphyseal dysplasia. The authors recommended that in cases in which the CE angle was 20° or less preoperatively bone procedures such as innominate osteotomy should precede the femoral lengthening.

Detailed presentations of distraction osteogenesis are illustrated in Fig. 6.23ai 1–8, aii 1–8, aiii 1–13. Limb lengthenings were performed increasingly with the callotasis technique for those with symmetrical limb shortening due to skeletal dysplasias [526–528]; these are discussed in greater detail in Chap. 3.

(ii) *Comparison of Techniques Within The Same Centers*: Many studies from centers where large numbers of lengthening procedures are done have presented data comparing differing techniques. Pouliquen et al. compared femoral lengthenings in 82 cases divided between 6 techniques of which 5 were used relatively frequently [529]. These involved the one stage lengthening, 14 cases; Judet technique, 20; Wagner, 13; a tranverse osteotomy and graft technique, 11; and callotasis, 20. The authors concluded that the callotasis technique was the best since there were no serious complications in 20 cases. The amounts lengthened, however, were similar with the several techniques with the exception of the one

stage lengthening which was reserved for relatively smaller discrepancies. In that group, the average lengthening was 3.6 cm or 7.8 % of bone length. The other four techniques had lengthenings on average ranging from 4.6 to 5.5 cm or 12.7 to 15.5 %. In the one-stage lengthening, a Judet distractor was applied followed by oblique osteotomy, application of temporary cerclage wires, lengthening by the distraction technique intraoperatively with the knee flexed and osteosynthesis with a side plate once the desired amount of lengthening had been achieved. The Judet technique involved a unilateral distractor similar to the Wagner but with 4 heavy pins below and 4 above the osteotomy site. The lengthening was at a rate of 1.5 mm/day. Once lengthening had been achieved the distractor was left in place while healing was allowed to occur. Walking began again with protection of a brace which incorporated both the pelvis and the external fixator and was generally maintained until 12 months post initial surgery. The complication rate in the callotasis technique was extremely low at 5 % while it ranged from 27 to 35 % in the 4 other major approaches. The study also reviewed the literature from the 1970s and 1980s in relation to each of the major approaches then used involving the one stage lengthening, the Judet lengthening, the transverse osteotomy plus graft lengthening, Wagner lengthening, Ilizarov lengthening, and callotasis lengthening. The one-stage lengthenings assessed involved 229 cases with lengthening achieved ranging between 3.2 and 3.7 cm and a complication rate between 10.5 and 35 %. Two series of Judet lengthenings with an oblique osteotomy were reviewed involving 56 cases with a mean lengthening of 5.2 cm and a complication rate between 25 and 41 %. There were 11 cases of the transverse osteotomy plus bone graft group also with a 5.5 cm mean lengthening and a 27 % complication rate; 120 cases of the Wagner lengthening with a range of 5.2–6.8 cm increase and a complication rate of 12.5–31 %; Ilizarov lengthenings in 21 cases with a mean lengthening of 5.0–6.1 cm and a complication rate of 6–25 % and; the most favorable group the callotasis technique involving 78 cases with a mean lengthening of 4.7 cm and a 6 % complication rate only.

Faber et al. reviewed several limb lengthening procedures divided between the Wagner approach, the Monticelli-Spinelli metaphyseal corticotomy and distraction, and the Monticelli-Spinelli distraction physiolysis [530]. Complications with each of the three procedures were reviewed in detail and were frequent. The Wagner diaphyseal osteotomy involved more cases of delayed union, late fracture, and axial deviation. The list of complications in 17 femoral lengthenings included 3 with delayed union, 8 axial deviation, 3 late fracture, 2 loss of length, and 1 premature consolidation. As far as the joints were concerned, there was restriction of motion at the hip in 2, knee in 14, and ankle in 2 with 1 hip subluxation, 2 proximal tibial subluxations, and 1 patellar subluxation. There was 1 deep wound infection and 10 pin track infections. One patient had loss of muscle power, and complications leading to discontinuation of the lengthening procedure occurred in 1 with serious restriction of hip motion and in another with hip dislocation. Only 6 tibial procedures were performed with complications involving 1 non-union, 3 axial deviations, 4 late fractures, and 2 premature consolidations. As far as the joints were concerned, there was restriction of the motion at the knee in 1 and at the ankle in 3 and also 1 pin tract infection.

A review of 100 lower limb lengthenings from Brazil assessed 25 tibial lengthenings by the Anderson technique, 45 femoral lengthenings by the Wagner technique, and 16 femoral and 14 tibial lengthenings by the Ilizarov technique [531]. The amount of lengthening achieved and the average healing time showed very little difference between the techniques. The complications seen widely in limb lengthening were present in each although certain types of complication tended to occur with certain types of lengthenings. Good results could be achieved with each method and considerations such as comfort and relative ease of the procedure for both patient and surgical team would play a primary role in choice. In the Anderson group the average lengthening achieved was 4.2 cm, range 3–6 cm, and the average healing time was 197 days with a lengthening index of 1.72 months. In the Wagner group, the femoral lengthenings had an average of 4.6 cm, range 1–12.5 cm, with an average healing time of 185 days with a lengthening index of 1.32 months in a subsection having percutaneous osteotomy and a healing time of 166 days with a lengthening index of 1.23 months in a subgroup having corticotomy. In the Ilizarov group, the average femoral lengthening was 4.7 cm, range 1–7.5 cm, with a healing time at a mean of 186 days and a lengthening index of 1.31 months and for the Ilizarov tibia lengthenings the average was 4.5 cm, range 1–7.5 cm with a healing time of 184 days and a lengthening index of 1.35 months. With the Anderson method, the most common complication was delayed union; with the Wagner technique the most common complications related to bone healing and subsequent fracture; and with the Ilizarov method the most common complication was incomplete corticotomy.

(iii) *Effect of Lengthening on Muscle Strength, Articular Cartilage Structure and Nerve Function*: The effects of lower extremity lengthening on muscle strength,

articular cartilage structure, and nerve function have been assessed clinically and by more sensitive investigational methods.

Muscle strength before and after femoral and tibial lengthening: Maffulli and Fixsen studied quadriceps strength in those with congenital short femur before and at the termination of femoral lengthening [532]. The Orthofix technique was used. Seven patients had an average lengthening of 7.1 cm, a 23.5 % lengthening of the congenital short femur. The normal side was stronger initially than the shortened side. The differences in strength, however, between the 2 sides did not meaningfully change with a difference of 15.7 % at the beginning of the procedure and 13.1 % at the end of the study. When the relationship of the knee extensor strength to the muscle and bone area of the mid-thigh was calculated there was no change post operatively in the normal side but a slight increase in the extensor strength in the operated side. That report is similar to the clinical impression that once a lengthening has been completed effectively and range of joint motion regained the muscle strength is maintained.

Barker et al. prospectively studied the effect of limb lengthening on muscle function and noted a decrease in muscle strength in patients undergoing lower limb lengthening 6 months after fixator removal but a full return to preoperative status by 2 years with the procedure having no adverse effect on function [533].

Lee et al. studied changes in the gastrocnemius muscle in relation to the percentage of lengthening in the rabbit tibia using the callotasis technique [534]. Lengthenings were done of 10, 20, and 30 % assessing 75 rabbits, 25 in each group. The study was based on histopathologic and morphometric assessments of the muscle. Biopsies were obtained from the medial gastrocnemius of both hind legs immediately prior to sacrifice at termination of the lengthening procedure. As compared with the control side the lengthened side had substantial differences with fiber size variation noted in all 3 lengthening groups. Significant differences, however, in internalization of muscle nuclei and endomysial fibrosis, which represent more definitive changes, were observed only after 20 and 30 % lengthenings. There were no differences in degeneration or regeneration among any of the lengthening groups. The fiber size variation was thought to be due to an increased number of atrophic fibers rather than the presence of hypertrophied fibers. As the lengthening percentage increased the histopathologic scores of each parameter of the lengthened side showed a linear increasing trend reflecting an increasing severity of the histopathologic changes. Since the rabbits were sacrificed at the termination of lengthening no information was available as to whether or not some of these changes might have regressed.

Kawamura et al. also noted no significant histochemical or electromyographic changes in those lengthened up to 10 % of their initial bone length [479]. Carroll et al. using a relatively rapid distraction model in sheep, noted that tibial lengthening >11 % of initial length consistently produced irreversible changes in the gastrocnemius and flexor digitorum profundus muscles, including loss of myofibrils, central migration of nuclei, and irregular shapes and sizes of myofibrils [535]. Other observers have reported that up until approximately 20 % lengthening the muscle actually lengthens throughout its entire extent after which lengthening appears to be localized at the osteotomy site and is more associated with fibrosis which itself would tend to weaken the muscle. Lee et al. showed, therefore, that lengthenings up to 10 % have little histopathologic change in muscle and that progressively greater lengthening to 20 % and then 30 % led to more conspicuous changes [534]. They also felt that once lengthening extended beyond 20 % irreversible changes were more likely to occur in the muscle itself. Carroll et al. felt that the changes in the muscle were primary rather than being secondary to nerve stretch phenomena [535]. They concluded that lengthening of the tibia by more than 11 % consistently produced muscle changes in the leg and cartilage damage in the ankle joint.

Effects of lengthening on articular cartilage of adjacent joints: Stanitski et al. documented the effect of femoral lengthening on the articular cartilage [536]. They felt that 30 % femoral lengthening causes reproducible knee cartilage injury evident by actual loss of cartilage substance and fibrillation. Application of a modified Ilizarov apparatus to the femur and tibia with coaxial hinges at the knee followed by 30 % lengthening resulted in less severe damage than when the femur was lengthened independently suggesting that there was a protective effect of the femoral–tibial apparatus on joint compression.

Carroll et al. noted histologic changes in the articular cartilage of the tibiotarsal joint at both gross and histologic levels with tibial lengthenings >11 % including fibrillation, empty lacunae, and matrix degeneration. The tibia had been rendered short initially by a proximal tibial epiphyseal arrest using the Phemister technique, after which a lengthening was performed in 16 [535].

Nakamura et al. studied knee articular cartilage changes in association with limb lengthening by the callotasis technique in 18 rabbits with a distraction rate of 1 mm/day [537]. Distraction began the day after operation. On the right side the frequency was 0.5 mm increments every 12 h while on the left it was controlled automatically leading to 120 smaller incremental increases which averaged 0.0083 mm every 12 min. Histologic changes were much less in the multi step auto-distractor technique side than in the side undergoing twice daily 0.5 mm increments. This study was

also divided into assessments with length increases of 10, 20, and 30 %. The incidence of cartilage degeneration on the 2-step side was 2/5, 5/6, and 6/7 at the 10, 20, and 30 % length increases while on the 120-step side it was much less at 0/5, 1/5, and 1/7 at the corresponding length increases. The numbers 5, 6, and 7 refer to the numbers of animals in each group.

Nerve changes due to the lengthening procedure: Although nerve stretching in association with limb lengthening can lead to sensory and motor nerve deficits, in most patients even with significant lengthening motor and sensory function is maintained. More sensitive neurologic testing is beginning to show that the margin between maintained function and diminished function is narrow. In those patients who develop weakness in association with significant lengthening, there has also been the question as to whether it is myopathic or neuropathic in nature. Young et al. studied six consecutive patients completing tibial lengthening by the Ilizarov method using nerve conduction studies and electromyography (EMG) [538]. At the termination of lengthening there were no complaints of sensory or motor abnormalities in the group and all patients were normal to clinical examination. All six subjects, however, demonstrated significant sensory and motor nerve response abnormalities. Electrodiagnostic testing showed abnormalities in 6 of 6 deep peroneal nerves and 5 of the 6 demonstrated abnormalities in superficial peroneal sensory responses. Two of 6 demonstrated abnormalities related to the posterior tibial nerve. Five of 6 patients demonstrated needle EMG abnormalities. Although the study was limited there was clear evidence for an axonal neuropathy based on the nerve conduction and EMG results. A purely muscle etiology would not be expected to demonstrate sensory nerve abnormalities. The authors did additional studies in an effort to implicate slightly increased compartment pressure as part or all of the causation of the neuropathic findings. The mean lengthening was 5.6 cm with a range from 4.0 to 7.0 cm; the lengthenings, therefore, were well within the normal range in terms of extent.

Galardi assessed peripheral nerve damage during limb lengthening [539]. Electrophysiologic studies on limbs having 5 bilateral tibial lengthenings showed reduced motor conduction velocity in 2 tibial and 3 common peroneal nerves after a mean lengthening of 27 %.

Makarov et al. reviewed the literature concerning neurologic problems in relation to limb lengthening and published the data in chart form in terms of intraoperative and total neurologic complications [540]. A study of 8 reports encompassing 946 cases reported 51 intraoperative nerve injuries (5.4 %) while total neurologic complications from 12 reports described 215 complications in 1214 patients (17.7 %). A study of the Ilizarov technique, originally published in Russian, accounted for 703 of the patients and results from this large series were parallel to the overall reports with 5 % intraoperative complications and 17 % total complications. Makarov et al. used intraoperative somatosensory evoked potentials (SSEP) to detect acute peripheral nerve injury during external fixation application [540]. There were 42 Ilizarov surgical procedures of the lower extremities reported in 40 children. Significant deterioration or total loss of SSEP response during surgery occurred in 4. They proposed the use of monitoring to detect early abnormalities and possibly minimize or eliminate their long-term effects by changes in surgery pattern.

In a report continuing their studies, Makarov et al. continued using somatosensory evoked potential (SSEP) monitoring to detect nerve compromise for their limb lengthening and deformity correction procedures with external fixators [541]. In 306 procedures in 233 patients (mean age 12 years (range 1–21), significant SSEP changes were seen in 58 procedures (19 %). In 32 (10.5 %) the changes were transient, resolving with time/steps to reverse surgical cause. The remaining 26 (8.5 %) were assessed based on whether or not corrective action was taken [16 cases, no action, showed 13 (81.2, 4.2 % overall) with postoperative neurologic defect of which 6 were permanent and 7 resolved slowly over 5–18 months; 10 cases, corrective action taken, showed 4 (40, 1.3 % overall) with a temporary deficit resolving in 1–8 months but none with permanent deficits.]

Noguiera et al. retrospectively studied 814 limb lengthening procedures to assess associated nerve lesions [542]. Existence of a nerve problem was based on clinical signs and symptoms of motor impairment, sensory alterations, referred pain, and/or positive results of quantitative sensory testing. A nerve lesion was detected in 76 of the limbs (9.3 %) with 16 % detected immediately after surgery and 84 % during gradual distraction. Patients with double level tibial lenghtenings and those with skeletal dysplasia were at higher risk for nerve lesions. Nerve decompression was performed in 53 cases (73 %) but slowing the rate of lengthening was sometimes sufficient. Early recognition and response led to better resolution of the problem. Testing with a pressure specified sensory device was the most sensitive way to detect developing nerve problems. Once dealt with, continued lengthening was done. Complete clinical recovery occurred 74 of 76 cases.

Rozbruch et al. report the value of high-resolution ultrasonography in detecting the precise site of nerve involvement [543]. While EMG and nerve conduction studies identify problems they do not locate the site of the problem. MRI and CT are difficult to use because of the extensive metallic instrumentation.

(iv) *Distraction Osteogenesis Research*: The distraction osteogenesis/callostasis technique has a considerable

body of animal research data associated with it. The extensive work of Ilizarov and associates has been presented in English by Paley [484] and in translation by Ilizarov [504, 505, 507, 508]. Ilizarov showed that the proper biomechanical environment was extremely important for bone regeneration which involved not only the interfragment stability but also the timing of the beginning of lengthening and the rate of lengthening. His early work demonstrated that preservation of the intramedullary circulation, in particular the nutrient artery, was important but subsequent assessments have shown that even when cut the nutrient artery will repair quickly over a period of a couple of weeks as long as stability is present. Ilizarov also showed that the rate of osteogenesis was closely related to the distraction rate and that the optimal rate was 1 mm/day with quicker rates of 1.5 and 2 mm a day slowing osteogenesis and a slower rate of 0.5 mm leading to premature consolidation. Repair was improved with 4 separate lengthenings of 0.25 mm each 6 h apart distinct from 1 lengthening per day for the entire distance. The smaller, more frequent lengthenings minimize damage to the repair microvasculature and to the early repair cells and matrices. He showed that bone formed during the course of distraction osteogenesis is well organized and longitudinally oriented in the direction of the distraction forces. New bone forms initially in the medullary canal adjacent to the cut cortices and then passes progressively toward the center of the distraction gap. The central region between either cut cortical zone is referred to as the interzone and is the region where bone forms latest and distraction occurs longest. The region tends to be filled with immature fibroblastic cells which transform relatively late into osteoblasts. In most instances, bone formation is via the intramembranous route with no cartilage forming in the gap region. The new bone is oriented along the longitudinal microvasculature and quickly forms a lamellar orientation. The interzone region ossifies quickly after distraction has stopped. New bone formation is seen as early as the second or third week after beginning distraction and the interzone region is then usually seen as a central transverse radiolucency. During the several months of the remodeling phase the cortex thickens and eventually the medullary cavity is reformed. The original work of DeBastiani and associates is almost totally clinical in nature, although use of the apparatus in experiments distracting the epiphyseal plate has been reported. Specific reports on distraction osteogenesis in the rabbit have been published by White and Kenwright who noted that delayed distraction in the skeletally mature rabbit tibia led to more vigorous osteogenesis compared with immediate distraction [544]. Histologic studies outlined the differences in response to timing. The authors pointed out that delay between initial surgery and onset of start of distraction characterized studies published in the 1930s by Bosworth [473] and Abbott and Saunders [545], the latter specifically noting excellent callus formation when they waited 10 days before distraction. Kojimoto and associates also performed callus distraction in the rabbit and demonstrated excellent bone healing even following medullary vessel destruction as long as the periosteum was carefully preserved [546]. Experimental studies in the dog have been reported by Aronson and associates [547] quantifying mineralization by CT methods and by Delloye and associates [548] documenting regenerate bone formation using microradiography and histology.

Aronson et al. studied the histology of distraction osteogenesis using Ilizarov and Wagner external fixators for tibial lengthenings with 8 dogs in each group [549]. The distraction osteogenesis procedure was performed after a 7 day latency period and distraction at 0.25 mm every 6 h until an osteotomy gap of 2.8 cm (about 15 % of initial tibia length) was achieved. Correlative histologic and radiographic studies were then made at varying time periods. Both groups healed equally well. Radiodense columns of bone appeared regularly between days 21 and 28 of the distraction osteogenesis procedure. These took origin from either bone end with the most central part of the gap persisting as a radiolucent band. Areas of bone repair were aligned in linear fashion parallel to the long axis of the gap and of the entire bone. The next phase of healing encompassed continuous bone tissue traversing the gap from end to end. The radiolucent band corresponded histologically to parallel bundles of collagen intermixed with cells also oriented in the direction of the distraction force. The vascular channels were also noted to be longitudinally oriented and there was no mention of cartilage formation, and at higher power magnification there was direct transformation of fibrous matrix into bone strikingly similar to the intramembranous ossification characteristic of the embryonic phase. In a subsequent histologic analysis of the repair gap in tibial distraction osteogenesis by the Ilizarov method in dogs, it was shown again that intramembranous ossification proceeded from each cortical end toward the central fibrous interzone. There was good correlation between histologic repair and mineralization as shown by CT scanning [547]. Aronson has summarized well the histologic, biochemical, radiographic, vascular, and biomechanical studies on distraction osteogenesis [514].

Delloye et al. studied bone repair during distraction lengthening on the forearms of mature dogs using the

Ilizarov system [548]. With distraction both periosteal and medullary callus on either side of the gap gave rise to new bone trabeculae. These were oriented along the direction of distraction and progressively approached one another. The characteristic central transverse region of gap radiolucency was also reproduced. Bone in longitudinal alignment traversed the entire gap region linking proximal and distal bone fragments 4 weeks after the end of the lengthening period. Most of the new bone formed by intramembranous ossification with some foci of cartilage seen. Specific delineation of the cortex began to be noted at 3 months but was still not fully achieved at 5 months. Procedures were performed on 13 adult female dogs, some unilateral and some bilateral, totaling 20 operative procedures. Slight variations of technique were used to assess their influence on repair. In general, initiation of periosteal and endosteal callus at the bone ends became apparent at 3 weeks and with progressive distraction bone repair along the long axis of the gap and adjacent to either cut end was noted. Bone regeneration occurred equally at proximal and distal ends with the central radiolucent region seen. Bone bridging of the gap was usually achieved in a month after the end of distraction but full cortical definition was not noted circumferentially even at 20 weeks. Microangiography revealed that the integrity of the medullary artery could be preserved after careful corticotomy. Callus was vascularized by both periosteal and medullary systems. The microradiographic study showed the first signs of osteogenesis at both ends of the distracted bone segments from both intramedullary and subperiosteal sources at 2–3 weeks. Longitudinally oriented callus was noted at 4–6 weeks. No evident difference was observed between lengthening after corticotomy or full transverse osteotomy with respect to the amount of callus. Histologic evidence of bone repair was slightly in advance of radiologic manifestations. Medullary and periosteal osteogenesis were particularly active at 2 weeks. Woven bone was synthesized initially and there was abundant vascularity associated with this. With progressive distraction and time the longitudinal orientation of the new bone trabeculae was seen. Bone formed from a membranous ossification sequence with the advancing fronts of osteogenesis approaching each other from either side and fusing approximately 4 weeks after distraction was ended. The healing sequence was the same regardless of whether the bone had been broken by corticotomy or transverse osteotomy. Some areas of highly cellular cartilage and fiber cartilage were noticed during the first 2 months but these were invaded soon by vessels followed by endochondral ossification. Bone marrow appeared to be the larger contributor to the amount of interfragmentary callus but periosteal callus also constantly supplied the peripheral part of the regenerating bone.

Similar findings were reported by Lascombes et al. [550] and Saleh [551] in studies of bone biopsies in human lengthenings. Lascombes et al. were able to harvest 11 biopsies of repair bone during bone lengthening following the Ilizarov technique [550]. The mean age of the patients was 13.5 years and time after the initial procedure ranged from 23 to 502 days. Bone was noted histologically along a long axis of the gap as early as the 3rd week. There was a distinct linear alignment to the bone trabeculae along the long axis of the bone. New bone formation was of the intramembranous type without evidence of a cartilage stage. Osteoblastic and osteoclastic activities were prominent and remodeling was continuing even one year after initial intervention. Mature lamellar bone was noted however by the fourth month postsurgery. Saleh et al. analyzed bone from 8 patients undergoing distraction osteogenesis using the Orthofix technique [551]. The specimens were obtained from 102 days to 4 years post surgery. The earliest bone synthesized was woven with high cellular activity. This was soon covered by lamellar bone which with time developed a characteristic Haversian architecture.

The results of each of several experimental reports on the histology of repair in distraction osteogenesis have been similar. Many have been correlated with clinical studies primarily radiologic but on occasion utilizing biopsy material. Among the characteristic features are the orientation of newly synthesized collagen and then bone trabeculae along the long axis of the repair gap parallel to the distraction forces. In the vast majority of instances, there is direct intramembranous bone formation present initially adjacent to either cut end with the central region or interzone healing last. There is a contribution also from the inner layer of the reconstituting periosteum which also tends to be along the longitudinal axis and to represent new bone formation. On occasion, cartilage can be seen within the distraction gap and this subsequently turns to bone by the endochondral mechanism. The presence of cartilage, however, is best interpreted as a sign of less than optimal stability and does not represent true endochondral growth but rather the formation of cartilage on the basis of increased interfragmentary movement and then conversion of that cartilage to bone once better stabilization occurs. Callotasis means stretching of the bony callus.

Not all instances of bone lengthening heal with a uniform distribution of bone surrounding a central interzone region. Hamanishi et al. classified the radiologic pattern of callus formation seen with the Orthofix procedure in 35 limbs (Fig. 6.23b) Table 6.5 [552]. One of the continuing problems with bone lengthening procedures is this variable state and pattern of bone formation even where the surgeons involved appear comfortable that a relatively uniform technique is being used. The categorization defined by Hamanishi et al. involved (i) the external pattern with lateral bulging of the bone, (ii) a straight pattern in which the gap filled uniformly, (iii) an attenuated pattern in which the diameter of bone

Table 6.5 Classification of distraction callus based on radiographic appearances

External Callus forms between the fragments but also extends beyond the cortices in symmetric widened fashion
Straight Callus forms between the fragments across the entire width of the gap in full alignment with the cortices
Attenuated Callus is narrower than the original bone and forms in hourglass fashion being narrowest midway between the two distracted fragments
Asymmetric Callus formation is asymmetric with more forming on one side of the gap than the other (generally on the concavity when the two fragments become angulated)
Pillar A narrow central linear column of callus is the only bone forming between the two fragments
Agenetic Only scattered discontinuous fragments of callus form in the distraction gap

Based on the classification of Hamanishi et al. Acta Orthop Scand 1992;63:430–433

formed centrally was less than at either end, and opposite pattern where, usually with angular deformity, more bone was formed on the concave than on the convex side, (iv) the pillar category where a thin linear bone collection formed centrally, and (v) the agenetic form where there were only isolated spicules of bone within the gap. The healing index correlated nicely with the pattern as would be expected. The index (correlating the number of months per 1 cm of lengthening) was in the respective types 1.1, 1.3, 1.5, 2.1, 3.7, 4 with an overall mean of 1.7 since most patients were in the external or straight healing pattern category.

One of the main principles articulated by Ilizarov [507, 508] and deBastiani et al. [497] was the need for delay in beginning the lengthening to allow for early revascularization and early bone formation which would subsequently enhance the repair process. Aside from the excellent clinical evidence, experimental studies also confirmed the value of delay in distraction. Gil-Albarova et al. used the Orthofix fixator to compare results in femoral diaphyseal osteotomy on 24 3-month-old lambs beginning distraction in half on the first postoperative day and delaying until the tenth post operative day in the other half [553]. The femur was lengthened by 2 cm at a rate of 1 mm/day. Both radiographic and densitometric studies of the lengthened callus at 1, 2, and 3 months showed that delayed distraction when compared with immediate distraction improved the quality of the callus with quicker, denser and more homogeneous bone formation. The value of delay prior to distraction was also shown clinically by Lokietek et al. comparing clinical results with the Wagner technique with immediate intraoperative lengthening of 1 cm and postoperative distraction of 1 mm/day and the Ilizarov technique which did not begin lengthening until 5–7 days after osteotomy [554]. They concluded that autogenous new bone formation in limb lengthening related primarily to the management protocol and was distinct from the external device used or even the location of the osteotomy. Their best results were reached when the surgical technique involved circumferential decortication, partial corticotomy with osteoclasis or cracking of the posterior element, a postoperative period of fixation without lengthening of 5–7 days, and an eventual distraction rate of 1 mm/day.

(v) *Cell and matrix deposition patterns in distraction osteogenesis*: **Rabbit model**. Studies have been performed in our laboratory on the histologic responses of tibial bone lengthening procedures using 4–5 month old rabbits [555]. The Synthes Mini Lengthening apparatus (Synthes, USA, Inc., Paoli, PA) was easily placed and well tolerated by the animals. Figure 6.23bi, ii shows radiographs of the mini-lengthening apparatus attached to the rabbit tibia at 22 days. The initial work with this apparatus involved the use of skeletally immature 4–5 month old rabbits with distraction begun on the first day postsurgery. Tibial lengthenings were then performed on 20 skeletally immature rabbits using the Synthes apparatus. A complete 360° turn of the spindle knob gives 0.7 mm distraction. This represents the amount of daily lengthening and was performed in 2 stages, one in the morning and the other in the late afternoon. Subsequent studies assessing variable age and distraction parameters increased the total number of procedures to 60. Animals were sacrificed at varying intervals from 6 to 46 days postsurgery. Nine animals were allowed to heal for additional periods after lengthening was completed. The lengthening achieved in those lengthened to the time of consolidation of the regenerate bone, which was generally 21 days, ranged from 11.8 to 13.9 % of total preoperative tibial length. Periodic X-rays of the leg were obtained at one to 2 weekly intervals. At sacrifice the entire tibia was removed and specimen X-rays were obtained in two planes (Fig. 6.23ci–v). The specimens were then processed for light microscopic histologic study.

Tissue preparation involved removal of the distracted segment and adjacent bone with a saw, decalcification, sectioning in sagittal or coronal planes, and slide preparation using the JB4 plastic embedding technique. This allowed excellent visualization of the histologic detail which was then correlated with the radiographic appearances. Specimen photographs were also taken after decalcification and

halving of the specimen (Fig. 6.23d). The specimen X-rays of the entire bone were taken using a standard technique with a magnification factor <0.01. This allowed accurate measurements to be made of the length of the entire bone and of the distraction gap. A lengthened tibia at sacrifice postfixator removal is shown in Fig. 6.23e.

Histologic sections were processed from all animals. At 6 days following lengthening the gap was filled with blood clot and fibrinous tissue with no geometric pattern of organization noted. Mesenchymal cells were accumulating adjacent to each of the bone ends with early intramembranous bone formation seen. The histologic studies from intervening time periods demonstrated the pattern of new bone formation. Animals which had undergone lengthening 16 and 20 days showed the entire spectrum of repair cells and matrices within the gap. The repair was not uniform across the lengthening gap. Immediately adjacent to the cut cortical bone ends the repair bone was being transformed to a lamellar configuration although evidence of initial woven bone persisted. Closer toward the center of the distraction gap the bone repair matrix was aligned longitudinally as were the accompanying blood vessels. Further toward the center of the distraction gap the repair tissue was increasingly more woven in configuration with progressively less lamellar bone deposited. In the center of the distraction gap, mesenchymal cells persisted and in some sections areas of organizing clot persisted. This histologic picture correlated extremely well with the specimen photographs, specimen x-rays and the clinical finding of an inability to further distract the bone after 3 weeks. The model reproduces the clinical and radiographic findings being described in human distraction osteogenesis. Examples of repair sequences shown by histologic processing are illustrated in Figs. 6.24a–f.

(d) *Lengthening along an intramedullary rod*: Lengthening along an intramedullary rod has attractive features. The rod helps maintain alignment during lengthening eliminating translational and angular deformation, allows external fixation to be removed earlier lessening the likelihood of infection and improving joint range of motion, and protects against fracture and deformation after healing while allowing earlier full weight bearing.

(i) *Intramedullary rod with simultaneous external fixator distraction*: For several decades, some surgeons have performed lengthening along an intramedullary rod which serves to enhance stability and help maintain alignment at the lengthening site. The earliest formal paper with this approach was by Bertrand who used one or 2 narrow intramedullary rods during distraction of the femur [556]. Bost and Larsen used an intramedullary rod to assist femoral lengthening in 23 procedures [557]. The intramedullary rod, generally a long Rush rod, needed to be narrow enough to allow distraction to occur and wide enough to allow for stabilization. Each of oblique, step-cut, and transverse osteotomies were used but ultimately they favored the transverse procedure since it was simpler, led to better control of angulation and showed no difference in healing time than the other two patterns. Traction and countertraction were provided through Steinmann pins into the proximal and distal femoral fragments followed either by the application of traction upon the limb suspended in a Thomas splint or the use of a traction-counter traction apparatus which had an upper femoral ring and a frame on both the inner and outer aspects of the thigh and leg. Traction was started immediately after the operation and continued at a low rate until the desired length was obtained or no further length was obtainable. The patient remained in bed during the lengthening procedure. The amount of lengthening of the femur varied from 3/8 of an inch to 4 1/4 in. In the entire series of 23 lengthening operations, the average gain was 2.18 in., or slightly <2 1/4 in. or 5.5 cm. In 20 of the straightforward patients the average time required for the lengthening was about 11 weeks. In 13 of the 23 procedures, union of the bone occurred in an average of 32 weeks and did not vary between the various types of osteotomy. After 10 of the osteotomies one or more bone grafting procedures were necessary to obtain bony union. All of the bone grafting procedures were performed as secondary interventions because of delayed union and no primary bone grafts at the time of lengthening were used. The authors as well as Abbott and Saunders [545] in 1939 specifically noted that lengthening of the callus was occurring. They indicated that "during its growth the bone callus may be stretched out in length." There was one late disturbance in circulation during the process of lengthening but this resolved with reduction of the traction weight. A palsy of the peroneal nerve occurred in 7 patients but in 5 it was transient. There were 5 patients with a posterior subluxation of the tibia on the femur but after management no major problems resulted. Fractures of the lengthened femurs occurred in 4 of the 23 cases. The primary aim of the procedure however, the control of alignment during lengthening, was successfully obtained thus eliminating many of the difficulties associated with lengthening procedures. Transverse osteotomy led to healing as quick and as sound as the step cut or oblique osteotomies. Once reasonable healing had occurred the patients were protected with either cast or brace during the transition phase to full unprotected weight bearing.

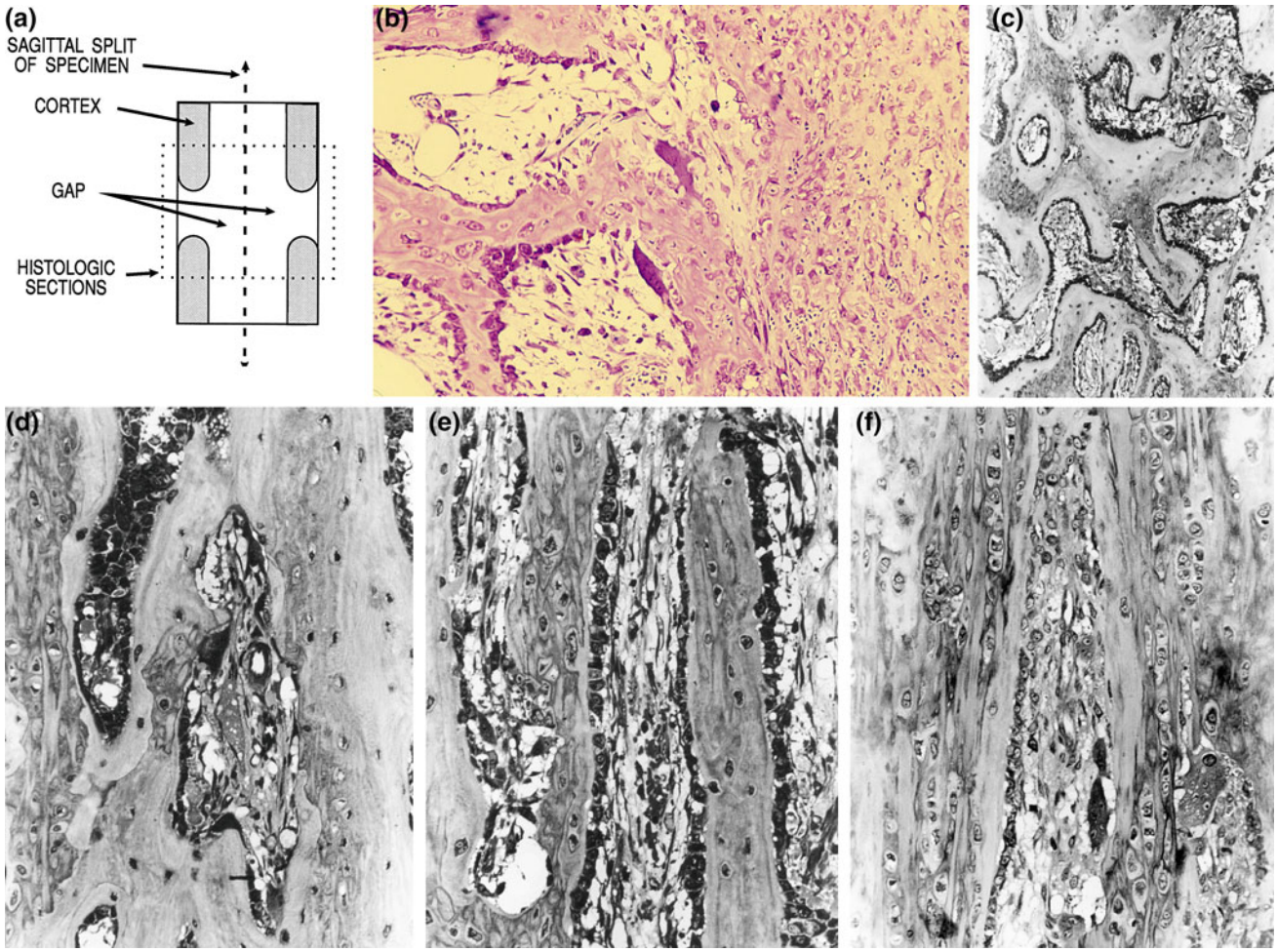

Fig. 6.24 Histologic study of the gap region correlates well with the radiographic studies showing advancing fronts of repair adjacent to each sectioned end rather than a uniform repair process throughout the entire gap simultaneously. **a** The varying regions from which the histologic studies in this figure were taken. **b** Early new bone formation adjacent to cortex is seen at left. At right is undifferentiated mesenchymal tissue at center of gap. **c** Histologic section near the persisting cortex at 10 days following surgery and initiation of distraction. The initial bone synthesized is woven which is more darkly staining here. Shortly thereafter better-oriented lamellar bone is synthesized on the woven scaffold. Osteoblasts line up nicely on the lamellar surfaces. **d** A higher power view in another rabbit in this same general region 2 weeks following surgery now shows a predominance of lamellar bone with only small remnants of woven bone persisting. Note the orderly array of osteoblasts on the lamellar trabecular surfaces. **e** A region closer toward the center of the gap at 3 weeks. Note the predominantly longitudinal orientation of the new bone formation. This is related primarily to the associated longitudinal orientation of the vasculature. At the right a primarily lamellar trabeculum of bone is seen lined with osteoblasts. At the far left some initially deposited woven bone persists. **f** Tissue from the center of the gap region at 2 weeks. This is the most radiolucent appearing region on the radiographs as it is the newest site of bone formation. The mesenchymal cells have formed a primarily woven bone matrix. *Note* however the longitudinal orientation, the early formation of lamellar bone, the lining up of osteoblasts on these lamellar surfaces and in particular the marked osteoclastic resorption occurring even as synthesis proceeds

Wasserstein used an unreamed flexible intramedullary rod in association with distraction through an external fixator of the Ilizarov type followed by a cortical allograft of the distraction gap using a tubular bone segment once the lengthening had been achieved [558]. Wasserstein transplanted cylindrical allografts into the distraction gap both to decrease the treatment time as well as to increase the stability of the fixation and insure proper alignment of the limb. The technique was used in patients between 5 and 25 years old although in selected cases those up to 35 years of age were operated. The technique was best for discrepancies >6 cm since lengthenings under 6 cm appeared to heal adequately with distraction osteogenesis techniques alone. The technique was used in 300 patients over a 15 year period for both femoral and tibial lengthenings (Fig. 6.24).

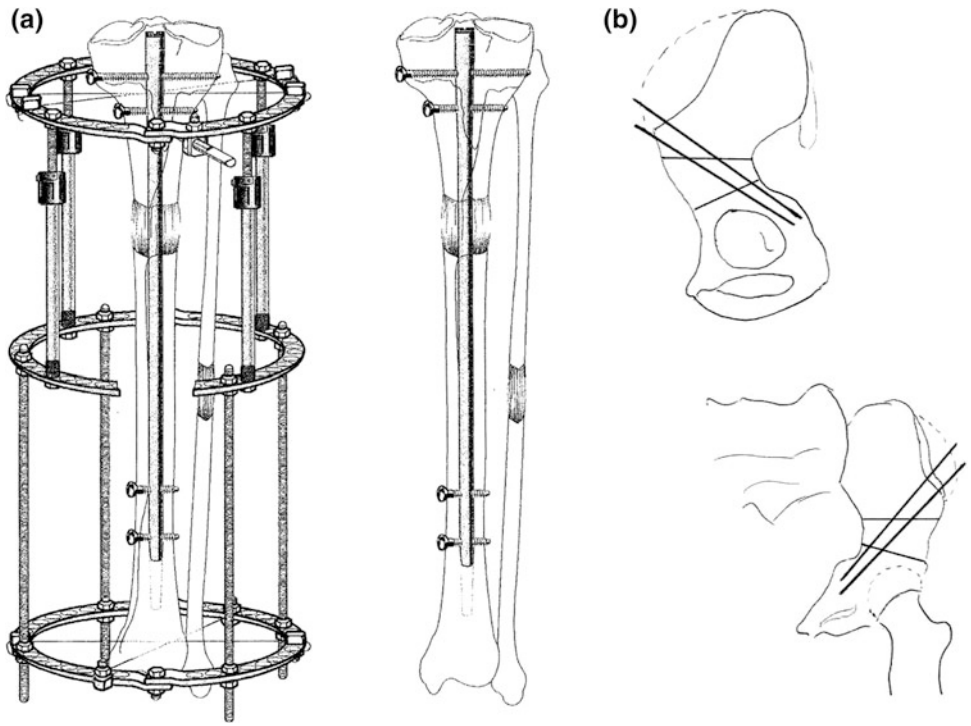

Fig. 6.25 **a** Tibial lengthening around an intramedullary rod is shown (Reprinted with permission from Herzenberg and Paley, Tibial lengthening over nails (LON). Tech Orthop 1997;12:250–259. Copyright 1997 Wolters Kluwer Health). **b** Adaption of the innominate osteotomy by using a rectangular rather than a triangular insert was proposed by Hall and Mills to add length as well as acetabular re-orientation at the pelvic level

Paley et al. have performed femoral lengthening with the Ilizarov or Orthofix distractors over an intramedullary nail and compared it with a matched group of patients having lengthening with the standard Ilizarov technique (Fig. 6.25a) [559]. The Ilizarov external fixator was used in 11 lengthenings and the Orthofix fixator in 21 with a 10 mm intramedullary femoral rod. The mean amount of lengthening in 32 procedures was 5.8 cm (range 2–13 cm) and the mean age of the patients was 26 years (10–53 years). Results in several categories were compared with the standard Ilizarov femoral lengthening that had been performed in 32 matched patients. The authors noted that lengthening over an intramedullary nail reduced the average time of external fixation by almost one half. The range of motion of the knee returned to normal a mean of 2.2 times faster in the group that had lengthening over the intramedullary nail. There were six refractures of the distracted bone in the standard Ilizarov group but none in those protected with the intramedullary nail. They concluded that the advantages of lengthening over an intramedullary nail included a decrease in the duration of external fixation, protection against refracture, and earlier rehabilitation.

Song et al. reported lengthening in 22 femurs over an unreamed femoral intramedullary nail [560]. The mean age was 22 years (13–35 years) and the mean lengthening 5 cm (2.7–8.1 cm). The external fixator was removed after 20 (8–30) weeks. The mean external fixation index was 24 days/cm (11–35) and the mean consolidation index was 43 days/cm (26–55) of lengthening. The authors felt that the approach reduced the duration of external fixation. Other than three patients who required rod removal for osteotomy, all 19 others had no malunion or delayed healing. They cautioned that use of simultaneous external/internal fixation could lead to infection and knee stiffness problems but each of the three who developed deep osteomyelitis had a previous history of osteomyelitis before the index procedure and knee subluxation problems occurred in those with >20 % lengthening.

Popkov et al. reported favorable results in lengthening for Ollier's disease using circular external fixators combined with intramedullary nailing using 2 elastic stabilizing nails [302, 561]. They compared 7 patients with the intramedullary nails to 37 having limb lengthening using only the external fixators and found markedly improved removal times for external fixation. In the ESIN (intramedullary nailing) group the mean healing index (to time of external fixation removal) was 23.2 days/cm for the femur, 22.4 days/cm for the tibia, and 11.6 days/cm for polysegmental (femoral–tibial) cases compared to 31.6 days/cm (femur), 35.7 days/cm (tibia), and 19.9 days/cm (polysegmental) for the external fixators alone. They noted a substantially reduced period of external fixation with limited postoperative complications with the use of intramedullary nails with external fixator limb lengthening.

Guo et al. also noted that tibial lengthening with the Ilizarov method over an intramedullary rod (51 limbs) provided advantages over the Ilizarov method alone (23 limbs) including a shorter time for external fixation (129 vs. 282 days) and lower complication rates (0.47/tibia vs. 1.0) [562]. Kim et al. have reviewed their experience lengthening

tibial segments over an intramedullary nail. In 80 segments (40 patients undergoing bilateral lengthening to increase height) the average lengthening was 7.73 cm (23.5 % of initial length) [563]. In spite of the rod, there was still valgus angulation in 20 limbs (25 %). The same group also reported on 118 tibial segments lengthened over a rod, specifically assessing deep intramedullary infection [564]. Both superficial (13) and deep (6) infections occurred (16 % overall, 11 % superficial, 5 % deep). The deep infections required either early (4) or delayed (2) rod removed and all had delayed healing.

(ii) *Intramedullary rod placement at completion of external fixator distraction*: Rozbruch et al. report a favorable experience completing the lengthening with the external fixator alone and then placing an intramedullary rod to allow for much earlier external fixator removal [565]. They call the procedure "lengthening and then nailing" (LATN). The nail supports the bone during the consolidation phase, protecting it from deformation and re-fracture. The procedures were done primarily in young adults after skeletal maturity. The classic versus LATN groups both has 27 patients at mean ages of 30 (11–57) and 35 (22–55) years. The time of fixator removal was reduced from a mean of 29 weeks to a mean of 12 weeks without evidence of negative problems with the nailing intervention.

Insertion of locked plate at completion of external fixator distraction: In an additional effort to decrease the time that external fixators were on, studies compared healing in 27 extremities lengthened with the Taylor Spatial Frame and then insertion of a locked plate (LAP) and the classic technique in 27 extremities where the external fixator remained in place until full healing [566]. Fixation was on less in the plating (LAP) group (4.5 vs. 6.2 months), pin-tract infection was less in the plating group (2 vs. 12), malalignment was similar (6 vs. 7), but significant varus occurred in the plating group in 2 cases of plate breakage. Possible suggested solution was "stronger plates." In the Wagner technique, which this approach returns to, the plate used was specifically constructed with no screw holes in the segment overlying the lengthened healing gap.

(iii) *Intramedullary telescoping rod for lengthening without need for external fixators*: A more recent innovation in limb lengthening has been the development of an intramedullary rod which contains an internal telescoping mechanism such that the lengthening can be performed in the complete absence of any external fixators. Following osteotomy and fixation of the upper and lower portions of the intramedullary rod to the bone distraction is performed by use of a rotation maneuver of the limb which serves to distract the two segments of the rod at the internal telescoping mechanism using a ratchet effect. The approach has come to be described as intramedullary skeletal kinetic distraction (ISKD). It is primarily used in young to middle-aged adults after skeletal maturity but some centers are using it in late adolescence either at or just before full skeletal maturity.

An early precursor of this technique had been described by Gotz and Schellmann [567] in which a hydraulic distractor was placed in a modified interlocking intramedullary nail to provide for continuous distraction. Guichet and colleagues in France developed a model for this form of lengthening [568]. Baumgart et al. developed the first motorized lengthening device with a subcutaneous receiver [569]. The system developed by Guichet and collaborators has the two telescoping fragments relating to each other internally such that with external rotation of the limb a clicking and locking mechanism allows for elongation with no movement possible in the reverse direction. Fifteen external rotation maneuvers of the lower extremity, which serve to rotate the distal femoral fragment to which the intramedullary rod is attached, allows for a lengthening of 1 mm/day. The device was developed for femoral lengthening [570]. An osteotomy is performed such as would be done for a closed femoral shortening procedure. The principles of distraction osteogenesis are used with lengthening beginning on the eighth postoperative day. The 1 mm/day lengthening is achieved in four separate time periods 6 h apart much as is used in the Orthofix and Ilizarov approaches. Once the appropriate length has been achieved rotation is no longer performed and the rod serves as a regular intramedullary rod until healing occurs. Guichet et al. projected that the mechanical intramedullary system, commonly referred to as the Albizzia nail, would be used as an internal dynamic fixator for the progressive lengthening of segments of the lower extremity. The apparatus also has a dynamization capability built in once the desired lengthening has been reached. The rod is fixed to the femur both proximally and distally allowing for stabilization at the same time that lengthening is occurring. The external rotation movement allowing for the lengthening to occur is one of 20° following which the limb then returns to its normal position. Each rotation corresponds to a lengthening of 1/15 of a mm such that 15 movements correspond to 1 mm of lengthening. Each movement provides an audible clicking sensation. Some patients experience considerable pain with the relatively large degree of rotation necessary to activate the distraction. Other devices are the fully implanted motorized intramedullary nail system (FITBONE) based on the

principles introduced by Baumgart et al. [569] and the ISKD (Intramedullary Skeletal Kinetic Distractor) a mechanically activated implant which distracts by milder rotations of 3°–9° [571]. The rotation oscillations are part of the physiological gait pattern. A distraction of 1 mm is achieved by 160 rotations of 3°. The actual amount of distraction is controlled by an external handheld monitor which measures the orientation of a magnet on the distal part of the internal rod. Patients can measure the daily distraction; if length is insufficient the leg is rotated under the control of the monitor until the desired daily distraction is reached. Krieg et al. reviewed 8 adolescent patients average 15.7 years (range 13–18 years) who had femoral or tibal lengthenings with the FITBONE motorized intramedullary lengthening device [572]. The average lengthening was 3.8 cm (range 2.9–4.7 cm). They felt that the difficulties commonly associated with external fixators were reduced with this method.

Lenze et al. also reported excellent functional results in late adolescent/young adult patients with complications reduced from those expected with external fixators [573]. Nine of 11 patients were under 20 years of age (14–34 years of age) with a mean age of 18.5 years.

The ISKD method is well illustrated in an article by Leidinger et al. [574]. They treated 25 patients at an average age of 25 years (range 16–45 years) with better results in the femur. Hankmeier et al. describe the ISKD technique and principle well [575]. Burghardt et al. presented 242 lower limb lengthenings with a device mechanical failure rate of 6.2 % [576]. Schiedel et al. studied 69 of their unilateral lengthenings with the Intramedullary Skeletal Kinetic Distractor and found eventual better results in the femur (52 of 58, 90 %) than in the tibia (5 of 11, 45 %) [577]. However, there were many problems with only 24 of 69 having problem-free courses while there were 116 difficulties in the other 45 patients. Premature removal of the device was needed in 7 cases, 4 due to breakage.

Betz et al. recently reviewed and compared each of three commonly used techniques: Albizzia, Fitbone, and ISKD [578]. These devices have been used much more often in Europe then in North America so far. The primary patient group is the young to middle-aged adult, postskeletal maturity, with length sequelae of uncorrected childhood disorders or severe limb trauma.

Caton et al. have presented a brief report with the elongating intramedullary nail based on a series of experiments in sheep [483]. They inserted the nail in the femurs of four sheep bilaterally. Each rotation applied to the limb allowed 0.1 mm lengthening with elongation of 1.25 mm/day. In the first group of animals, the mean lengthening obtained was 3.2 cm over 24 days with a percentage elongation of 14.2 %. Regenerated bone was noted radiographically at 15 days and consolidation took place at 5 months. In a second series, the internal device was compared with lengthening using external fixation and mean lengthening up to 90 days was 3.9 cm which was actually somewhat more than with the external fixator. Bone regeneration in the intramedullary group was completely satisfactory. Advantages are attractive in the sense that there is no external apparatus and the skin is virtually intact. There are no structures to impede the muscles such that joint motion should be more readily obtained. Stability is maintained and angulation either prevented or markedly minimized.

(e) *Predictability of Complications with Bone Lengthening in Children*: An overview of the previous sections relating to lower extremity lengthening shows that relatively few problems occur with lengthening a long bone by 10 % but that increasing problems occur as lengthening progresses beyond 20 % of pre-procedure bone length. Antoci et al. studied all aspects of 116 procedures (62 tibial, 54 femoral) from one institution [579]. The focus was on the relationship between complications and amount lengthened. Almost all segments were lengthened by the Ilizarov (108/116) method. The mean patient age at time of surgery was 13.5 years (range 4–20) and the lengthening percentage was 21 ± 16.5 (range 2–94). There was a positive linear relationship for all complications with increasing extent of lengthening. Neurological complications started at a 5 % increase in bone length; with a 15 % increase in length the complication rate was 20 %; with a 25 % increase −35 % rate; and with a 40 % increase −60 % rate. Residual axial deformities began to occur with a 5 % increase; a 15 % increase −20 % rate; a 25 % increase −30 % rate; and a 40 % increase −50 % rate. External fixation pins began to break or become problematic with 10 % length increase with further worsening at a 40 % increase in length leading to a −50 % problem rate. Joint contractures developed with approximately a 15 % increase with further worsening at a 40 % increase in length leading to a −60 % problem rate. They showed that lengthening a bone by 25 % or greater led to appreciably greater complications. Dahl et al. [580] noted increasing frequency of complications at an increase of 15 % of original bone length, Maffulli et al. [581] at 18 % or greater, and Karger et al. [502] at 25 % or greater.

(f) *Longitudinal growth after diaphyseal lengthening done prior to skeletal maturity. Clinical studies*: While an increased rate of femoral growth has been reported after one-stage procedures for lengthening of the femur and a variable rate of growth has been noted after Judet-type procedures for lengthening of the femur and tibia, there have been few detailed radiographically

documented studies of growth of bone after lengthening of the diaphysis. Authors of earlier papers that have included the results of lengthening of the diaphysis have commented on somewhat variable but generally good growth after the procedure. However, these studies were not directed toward the specific assessment of growth after lengthening, nor did they report data from radiographic measurements; thus, the exact rate of growth after lengthening cannot be determined from them.

We noted from the data on growth in patients at the Children's Hospital Boston, that when lengthening was performed on a bone that had several years of growth remaining the lengthened bone continued to grow at a slightly increased rate in some patients, while in others growth became more inhibited than it was before the operation [582]. Data on growth were assessed from 18 patients who underwent lengthening of the femur or tibia by mid-diaphyseal osteotomy and the gradual distraction techniques of Anderson and of Wagner. The goal was to define the growth responses to these lengthening procedures.

Femoral Lengthening. In each of 7 patients, the rate of postoperative growth of the lengthened femur, in relation to that of the normal bone, was increased compared with the preoperative rate. The average rate of preoperative growth of the short femur was 82 % that of the normal side, whereas the average postoperative rate of growth was 90 % of normal. In one patient, the rate of postoperative growth was 21 % greater than the preoperative rate, but in all of the others the increase was from 5 to 8 %. The amount of surgical lengthening of the femur averaged 18 % of the preoperative length of the bone, with a range of 6–35 %.

Tibial Lengthening. In all 11 patients, the rate of growth diminished from the preoperative levels, ranging from a 46 % diminution to a 3 % diminution. The average preoperative rate of growth of the shortened tibiae was 88 % that of the normal side, whereas the average postoperative rate diminished to 64 % of the normal side. The amount of lengthening of the tibiae averaged 20 % of the preoperative length of the bone, with a range of 14–30 %.

Long bones have differing growth responses after lengthening of their diaphyses. However, when growth is assessed according to the specific bone that was lengthened (that is, according to whether the femur or tibia was operated on), more uniform patterns of response are seen. A slight increase in the rate of growth was noted in each of 7 patients who had lengthening for congenital short femur, and the increased rate was maintained for several years after the procedure. There are insufficient data to determine whether this stimulation of growth is maintained until growth ceases at skeletal maturity. Suva et al. documented an almost invariable tendency for increased growth in the femur after a one-stage lengthening [583]. They noted stimulation of growth in 33 of 36 patients who had poliomyelitis, in 8 of 13 who had a congenital short femur (including some who had proximal femoral focal deficiency), and in 4 of 5 in whom the shortening had another etiology. Overgrowth after fracture of the femoral diaphysis treated by skeletal traction followed by casting has been recognized for several decades. Assessment of 74 patients using serial orthoroentgenograms documented overgrowth as a universal phenomenon in patients who are <13 years old, regardless of whether the fracture healed with anatomical reduction, with shortening, or with distraction. Increased vascularity to the entire bone brought about by the repair process has been thought to stimulate growth at the proximal and distal growth plates. As the repair response that is engendered by lengthening of the diaphysis is much more extensive and prolonged than after fracture of the diaphysis, overgrowth is expected. The primary pathological condition that causes the discrepancy and resistance of soft tissue to distraction, which can exert compressive forces on the growth plates to restrain their growth, can both minimize the effects of stimulation. However, in the series reported above, the patients who had lengthening of the femur all had an increased rate of growth [582].

The decreased rate of growth that was seen in all patients after tibial lengthening in the series does not appear to occur universally. Variable growth responses to Judet-type lengthening have been documented radiographically by Pouliquen and Etienne [584] and by Pouliquen et al. [585]. In the more detailed of the 2 articles, the authors reviewed the results after 39 lengthening procedures; 6 were performed on the femur and 33 on the tibia although the report did not deal with the femoral and tibial procedures separately. Their report and the Children's Hospital Boston series are not strictly comparable since the criteria for inclusion of patients and documentation were much stricter in the latter series. Still, comparisons can be made. In the series of Pouliquen et al. of the patients who had poliomyelitis the growth was normal after lengthening in 18, slowed in 7, and arrested in 2. Of their patients who had congenital agenesis growth was normal in one and slowed in 5. The findings in the later group were similar to those in the patients who had lengthening of a congenital short tibia in the Children's Hospital Boston series. Pouliquen et al. noted almost no retardation of growth after lengthening of 5.0 cm or less and progressively greater slowdown of growth when the lengthening, expressed as a percentage of the preoperative length of the bone, increased beyond 15 %. The crucial determinant appears to be the percentage of lengthening rather than the absolute amount of the lengthening. Of their patients who had lengthening of 10–15 %, only one (11 %) of 9 had a slowing of growth, whereas 9 (45 %) of 20 who

had lengthening of 15–20 % and 8 (80 %) of 10 who had lengthening of 20–25 % had a slowdown or cessation of growth.

Sharma et al. also showed frequent growth slowdown following tibial lengthenings for total fibular hemimelia with lengthening prior to skeletal maturation [586]. The average tibial lengthening in 8 cases was 6.7 cm (range 5.3–10) with an average percentage lengthening of 26 % (range 19–40 %). The average postoperative growth rate compared to pre-operative rate showed 2 with no growth at all, and only 1 growing at the pre-operative rate. In 5 femurs, one increased the rate of growth but 4 also showed slowing. Hope et al. noted no change in growth following 10 femoral and 10 tibial lengthenings using the Wagner technique for congenital shortening of the lower limb [587]. It is unclear why their data differ from the Children's Hospital, Boston and the Pouliquen group data or the experimental data of Lee et al. reported below. The absolute amounts of lengthening were not given by Hope et al. only growth ratios and it is known for the tibia that the greater the amount of lengthening the greater the growth slowdown. No patient in the series who had lengthening of the femur had a slowdown of growth, even though the increases in length were often >15 % of the preoperative length.

Reports made before 1978 on lengthening of the tibia raised the matter of postoperative growth, but none included rigorous radiographic documentation of this specific phenomenon. The absence of detailed data allows for only general, qualitative impressions concerning growth after lengthening. Moore noted that of 19 skeletally immature patients with poliomyelitis who had lengthening of the tibia using the Abbott method, the correction was maintained in 15, growth actually increased beyond the normal side in 3, and only one showed increased retardation [423].

In another report on Abbot-type lengthening, many patients who were operated on before the age of 12 years showed an increased discrepancy between the lengths of the extremities at skeletal maturity compared with the amount of lengthening achieved. In these reports, it is unclear how much of the final discrepancy was due to the condition itself, to postoperative complications, or to postoperative retardation of growth. A review of the results after 31 Anderson procedures for lengthening of the tibia revealed a variable degree of postoperative recurrence of limb length discrepancy in patients who had undergone the procedure between the ages of 8 and 19 years, especially in those who had a congenital short tibia [468]. Gross indicated that in some patients growth was stimulated after the Anderson lengthening of the tibia whereas in others the opposite occurred [588]. The majority of patients referred to in these 4 reports had poliomyelitis. The Children's Hospital Boston series included only one patient who had poliomyelitis [582].

It has been proposed that extensive resistance by soft tissues in the leg is responsible for increased inhibition of growth with lengthening of the tibia. The interosseous membrane and the Achilles tendon appear to be more resistant to stretching than the tissues surrounding the femur. The negative effects of increased pressure on epiphyseal growth have been well outlined. Shortening was noted in this series even after extensive releases of soft tissue, including lengthening of the heel cord. Attempts have been made to document the impression that retardation of the growth plate can be due to increased pressure in the limb generated by the distractive forces during lengthening of the tibia. A pressure gauge was developed by Pennecot et al. to measure the forces generated during distraction, and the measurements were then correlated with the rate of subsequent growth [589]. It was concluded that for the tibia there was good correlation between retardation of growth, lengthening of >15 % of the preoperative length of the bone, and the increased forces that were registered.

In the Children's Hospital Boston series the growth response after lengthening of the tibia was different than that after lengthening of the femur [582]. In each of 11 patients who had lengthening of the tibia, growth was retarded in comparison with the preoperative rate. The patients who had a congenital short tibia and the patients who had Ollier's disease had marked retardation of growth of the tibia, while the one patient who had poliomyelitis had only a 3 % decrease. Greiff and Bergmann demonstrated overgrowth in the tibia after tibial fracture [167]. As the process of repair after lengthening of the tibia is more extensive than that after fracture, it is likely that the factors that cause stimulation after fracture are present after lengthening. In the patients in the present series, however, it appears that the factors limiting growth were more influential than those stimulating it.

Growth responses do not appear to be dependent on the techniques that are employed to lengthen the bones. Femoral growth was stimulated with the use of the Wagner apparatus and in another study it was stimulated with the use of a one-stage lengthening. Growth was maintained in some patients who had poliomyelitis after the use of the Abbott, the Anderson, and the Judet method, while retardation of tibial growth increased in patients who had a congenital short tibia, Ollier's disease, or another non-paralytic condition using the Anderson, the Wagner, and the Judet method.

In the human, variable growth responses are demonstrated after lengthening of the diaphysis in bones that have several years of skeletal growth remaining. In Children's Hospital Boston series, the 7 lengthening procedures that were performed for congenital short femur all led to an increased rate of growth. It is anticipated that lengthening can be performed on femora that have several years of growth remaining with the expectation of a continuation of growth at a slightly increased rate. The tibial lengthening procedures that were done for patients who had a congenital short tibia or Ollier's disease all led to retardation of growth

that was more extensive than the preoperative retardation. Hadlow and Nicol have incorporated this growth information into a formula used to aid in timing for femoral and tibial lengthenings incorporating altered growth expectations as well as projections of the pre-operative growth rate [590]. Lengthening of the tibia should include slight overcorrection to compensate for an expected retardation of growth if it is done on a bone that has several years of growth remaining. Preferably, the tibia should be lengthened at or near skeletal maturity to avoid loss of correction secondary to retardation of growth. The timing of surgical intervention for discrepancies in the lengths of the lower extremities before skeletal maturity need to consider both the developmental patterns and the patterns of growth after lengthening.

Experimental studies: A detailed experiment assessing longitudinal growth of the rabbit tibia after distraction osteogenesis was reported by Lee et al. [591]. They divided 99 5-week-old immature rabbits into 5 groups according to the percentage of lengthening done with group I 10 %; group II 20 %; group III 30 %; group IV 40 %; and group V a sham operation with osteotomy without lengthening. They clearly demonstrated that tibial lengthening did not cause retardation of growth when the bone was lengthened by 10–20 % but in those instances where it was lengthened by 30–40 % growth retardation was evident. These data correlate well with the clinical studies from Children's Hospital Boston and those of Pouliquen reported above. In groups I, II, and V, there were no statistically significant growth differences between the operated and control tibias. There were significant differences in the growth ratio in groups III and IV with relative growth ratios of left to right decreased significantly in group III (average 4.2 %); and in group IV (average 7.0 %). Histomorphometric studies were also performed on the physes in each of the groups. These studies correlated well with the gross measurements of length. In groups I, II, and V, there were no statistically significant differences, but in groups III and IV there were significant decreases in the total thickness of the operated tibial growth plates, both proximally and distally compared with controls. There was thinning of both the proliferative and hypertrophic zones. The overall heights of the growth plate were measured and average decrease in the proximal growth plate was 10.4 % in group III and 23.9 % in group IV. Distally it was 11.9 % in group III and 12.4 % in group IV. Similar ratios were found with diminution of the thickness of both the proliferative and hypertrophic zones studied separately.

(g) *Increased awareness of need for joint stabilization and axial correction as well as limb length equalization in complex abnormalities*: Many lower extremity length discrepancies are complex such that shortness of the limb is often combined with subluxation and dislocation of associated joints and with axial malalignment. Wagner clearly pointed out the need to stabilize the joints and correct any axial malalignment prior to initiation of any lengthening procedure and also the need to carefully observe for joint and alignment changes during the course of any lengthening procedure [478]. Saleh and Goonatillake strongly reiterated the need for adherence to these principles [592]. The disorders they discussed included femoral, tibial and fibular congenital abnormalities in 92 patients with the three commonest groups encompassing 77 patients involving proximal femoral focal deficiency, proximal femoral focal deficiency and fibular hemimelia, and hemihypertrophy. They indicated that joint stabilization was mandatory for good function and was an absolute prerequisite prior to beginning limb lengthening. To prevent or minimize the likelihood of hip subluxation or dislocation, femoral head-acetabular congruity would have to be established and pelvic or shelf osteotomy along with proximal femoral osteotomy would often be needed. The greatest challenge is in cases of proximal femoral focal deficiency where there is often need for the above-mentioned procedures and on occasion in the more severe variants femoral–pelvic fusion or at least definitive placement of the proximal femoral shaft into the acetabulum. Knee instability due to anterior cruciate ligament and/or posterior cruciate ligament deficiency is common in dysplastic limbs. Although no specific treatment is needed for this, development of subluxation of the knee during the lengthening procedure must be carefully observed for and managed. Areas of concern at the ankle involve tendo Achilles tightness leading to an equinus deformity and varus-valgus instability with abnormal relationships of the lateral malleolus to the medial malleolus, or with changes in the rate of distal tibial versus distal fibular lengthening. In some instances, the tendo Achilles lengthening, posterior ankle capsulotomy, and distal tibial-fibular stabilization are performed prior to the lengthening procedure. In other instances, orthotic devices are used along with physical therapy to maintain flexibility and anatomic integrity at the ankle region with surgical intervention occurring only with changes that develop. Abnormalities in femoral or tibial alignment of more than a few degrees should be corrected pre-lengthening with appropriate osteotomies. Soft tissue contractures at hip, knee, and ankle must also be released. The final area of stabilization possibly needed prior to lengthening relates to a pseudoarthrosis either of the proximal region of the femur such as can be seen in a proximal femoral focal deficiency or a formal congenital pseudarthrosis of the tibia. Lengthening of a congenital pseudarthrotic tibia is

rarely done although on occasion it has been attempted in that part of the tibia well away from the pseudarthrosis where the bone structure appears normal.

6.9.3.3 Transphyseal Lengthening. Distraction Epiphyseolysis or Chondrodiatasis

(a) *Early Experimental Findings*: Transphyseal lengthening procedures were conceived initially and performed experimentally by Ring [593]. He achieved lengthening between 11 and 32 mm in 20 puppies between 4 and 6 months of age using an external distraction apparatus which elongated both distal radius and ulna. He recognized that when sufficient traction was applied there was a physical transphyseal separation after which continued distraction opened up a space allowing lengthening to occur with subsequent repair with a cylinder of new bone from the periosteum. The physis continued to function and both it and the metaphysis filled the distraction gap with repair bone centrally. Some animals suffered premature growth plate fusion to limit somewhat the length gain achieved but some continued with growth postlengthening.

Continuous transphyseal traction was applied by Fishbane and Riley across the proximal tibial growth plate in 10 puppies [594]. Histologic examination revealed fracture to have occurred in all cases through the metaphyseal zone of primary trabeculae just distal to the hypertrophic zone of the cartilaginous growth plate. The physis itself appeared undamaged. Growth was felt to continue but complete follow-up to skeletal maturity revealed early fusion preceding the normal limb by several weeks in 5 puppies. Rapid bony healing was noted in the distraction gap. The authors felt that the technique could be applied to the human as an effective and reasonably safe way of obtaining increase in limb length.

Sledge and Noble performed transphyseal lengthening experiments in the distal femur of the rabbit [595]. They also varied the forces across the physis and compared histologic findings in efforts to determine the precise site of lengthening. A Salter Harris type I transverse fracture occurred in 13 of the 16 animals to which 5 kg or more force had been applied. The fractures occurred at the lower part of the hypertrophic zone. At lesser levels of force, however, there were markedly fewer or no fractures and lengthening appeared to have occurred in relation to increased thickness of both the proliferative and hypertrophic zones of the physis. Thirteen of 21 animals to which 2 kg were applied and 18 of 19 animals to whom 1 kg was applied showed only a partial microscopic fracture or no fracture. In 17 of 56 animals distracted, there was no fracture of any type and overall there were 34 rabbits in which gross disruption at the plate did not occur. The response of the physis to transphyseal force therefore was clearly dependent on the amount of force applied. The combined force in excess of 2 kg almost always caused fracturing. There was, however, a consistent increase in length on the involved side whether or not fractures in the plate were produced. In the absence of fracturing, they felt that hyperplasia and hypertrophy of the plate were representative of an increased physeal stimulation which in turn led to the length increase.

Jani also noted fracture in the hypertrophic zone and subsequent healing by endochondral ossification in 42 puppies in whom distraction epiphyseolysis had been performed [596, 597]. Further insight into the effect of chondrodiatasis on the physis itself was provided by Elmer et al. [598]. They performed a study in the rabbit to assess the cell activity in the physeal region and noted that the procedure did not produce any significant change in the percentage of cells labeled with tritiated thymidine, the intensity of radioactive sulfate labeling the matrix, or the blood supply of the physis. They felt that lengthening was not the result of stimulating cell division or increased synthetic function of the plate but rather by mechanical passive stretching of the matrix.

Transphyseal lengthening is referred to as distraction epiphysiolysis where the distraction force is sufficiently great that a physeal fracture-separation occurs or chondrodiatasis where lesser distraction forces leave the physis intact with hyperplasia occurring in the proliferating and hypertrophic zones. In the former repair occurs by an intramembranous bone mechanism while in the latter the endochondral mechanism continues. The distraction device spans the growth plate with pins anchored in the secondary ossification center of the epiphysis and in the metaphysis and the distraction forces lengthen the limb by causing a separation at the plate. DeBastiani et al. slowed the rate of lengthening to 0.25 mm every 12 h and advanced the concept that, in so doing, a transphyseal fracture did not occur but that a stretching of the hypertrophic zone only was the lengthening phenomenon [599]. The term chondrodiatasis was used to refer to this occurrence.

(b) *Clinical Use*: The usual sites of limb lengthening in the human have been within the diaphyseal or metaphyseal regions of bone but work by Zavyalov and Plaksin [600], Ilizarov and Soybelman [601], and Monticelli and Spinelli [602–604] showed that transphyseal lengthening was both clinically feasible and advantageous in some regards. The advantages involved the fact that healing was much quicker than in diaphyseal lengthenings since dense cortical bone did not have to be repaired but only metaphyseal bone much as would

occur in a physeal fracture. Early experiments showed that actual physical separation occurred in the hypertrophic zone of the physis leaving the major growth part of the physis intact, a phenomenon referred to as distraction epiphyseolysis. The transphyseal lengthening then occurs mechanically and subsequent growth continues once the physeal defect within the hypertrophic zone of the metaphysis has been repaired.

Although this experimental technique can lead to superb results both clinically and experimentally, it is not currently widely used if there are a few years of growth remaining. There have been reports of premature growth plate cessation following this procedure. In patients, however, who have virtually no growth remaining, the procedure is attractive. It can be performed using either the circular distraction devices of Monticelli and Spinelli and Ilizarov as well as unilateral lengtheners such as the Orthofix device.

Eydelshtyn et al. reported extensively on the distraction epiphyseolysis in a clinical setting in association with meaningful limb lengthening [605]. They noted epiphyseal separation radiologically within 7–10 days and the ability to obtain length increments of 4–7 cm. They suggested that in most instances there was no negative influence on further growth. The cleavage fractures appeared radiologically to have occurred in the metaphysis in 26 of 33 patients with the remaining 7 occurring at the lowest levels of the growth cartilage but preserving the growth mechanism more proximally.

DeBastiani and associates performed chondrodiatasis using the unilateral Orthofix apparatus in 40 segments of patients with limb length discrepancies gaining a mean of 3.3 cm in length (range 1.5–7.0 cm) and in 60 segments in 25 achondroplastic patients gaining a mean of 7.1 cm (3–10.5 cm) [599]. In 16 distraction epiphyseolysis procedures reported by Monticelli and Spinelli, the tibia was lengthened by an average of 6 cm (range 3–10 cm) [604]. The patients were all between 13 and 16 years of age with little to no growth potential persisting. Aldegheri et al. reported on chondrodiatasis used for elongation of 170 bone segments in 75 children, 41 with limb length discrepancies and 34 with achondroplasia [606, 607]. All were operated on with the growth plate open. The Orthofix apparatus was used to lengthen either the distal femoral or distal tibial epiphyseal plates. Distraction began the day after operation at a maximum rate of 0.5 mm/day. There were 92 femoral and 78 tibial lengthenings. The average age was 12 years. In those treated for limb length inequalities the mean lengthening obtained was 3.4 cm (10.9 % of average initial length). The mean lengthening of the femur was 3.0 cm and of the tibia 3.7 cm. In achondroplastic patients, the mean lengthening obtained was 7.4 cm with virtually equal amounts in femur and tibia. Most of the complications were in achondroplastic patients and most of these were in the tibias primarily because of the abnormal shape of the distal tibial epiphyses. The procedure is generally performed at the distal femur or distal tibia just before skeletal maturity. It does not require the use of plates or grafts, because metaphyseal bone heals readily in the gap produced.

Franke et al. performed distraction epiphyseolysis using the Ilizarov apparatus in 22 lower limb segments with an average lengthening of 8.25 cm (range 4–18 cm) [518]. Some of the patients had achondroplasia and it was these patients in whom some of the larger lengthenings occurred. The healing was considerably quicker in the distraction epiphyseolysis group compared with the partial metaphyseal corticotomy group. In a group of 9 patients lengthened between 6 and 9.5 cm the average time to full weight bearing was 9.5 months with the repair index 43.6 days/cm.

(c) *Growth Consequences Related to Force of Distraction and Mechanism of Lengthening*: Although initial reports indicated that growth can continue following healing there have been reports of premature growth cessation and the procedure is best performed within 1 year of expected growth plate closure or in situations where metaphyseal or diaphyseal lengthening is not possible. Clinical papers reporting early physeal closure after chondrodiatasis are increasingly common. Hamanishi et al. reported femoral chondrodiatasis in 5 patients but in 4 of the 5 the physis closed shortly after lengthening and loss of gained length or further shortening occurred in each [608]. They used the Orthofix apparatus and the lengthening rate was 0.25 mm every 12 h. The 5 femora were lengthened a mean of 32 mm (25–43) after 70 days of distraction. Subsequent growth however was markedly diminished in 4 and moderately diminished in the other. They felt that the 0.5 mm/day distraction caused physeal separation rather than hyperplasia of the growth plate alone. Bjerkreim evaluated 10 consecutive proximal tibial physeal distraction cases with a mean lengthening of 6.7 cm [609]. In 6 cases lengthened at 1 mm/day under 13 years of age, subsequent growth was only 6 mm compared with the normal side of 32 mm.

Growth retardation has been seen in several experimental animals after epiphyseal distraction. Letts and Meadows performed distraction epiphysiolysis of the proximal tibia in 18 rabbits [610]. The average distraction gained was 0.54 cm which was 6 % the length of the tibia at time of intervention. Union invariably occurred. In each of 12 younger rabbits operated once, the distracted area united it was shortly followed by premature fusion of the growth plate. In 6 older rabbits operated close to the time of skeletal maturity no negative growth sequelae occurred. Subsequent histology

showed no normal epiphyseal growth plates after repair of the gap. In the study by Fjeld and Stein, subsequent growth retardation was consistently experienced in all animals with an average reduction in growth ranging from 40 to 70 % [611]. The experimental groups involved 10 distal femoral epiphyseal distractions in the goat, 14 in the proximal tibia of the goat and 18 in the distal femur of the dog. They felt that the reduction in gained length with time after the end of distraction must have been due to a retardation of endochondral growth after the elongation procedure. Jani also reported negative growth sequelae after distraction epiphyseolysis experiments in the rabbit [596, 597]. Alberty performed a vascular study of the growth region following physeal distraction in the rabbit [612]. The microangiography assessments were done in relation to 45 distal femoral transphyseal lengthenings. Most of these were performed at a rate of 1.0 or 1.5 mm once daily increases. Both marked enlargement of the epiphyseal arteries and defective metaphyseal capillary filling were noted after 3 days of distraction, changes which persisted in specimens distracted as long as 21 days. New capillaries were observed in the hyperplastic physes and in separation gaps at 21 days. Of note, however, was the fact that vascular anastomoses were noted across the physes at 6 weeks of follow-up. The latter phenomenon was noted in those distracted from 9 to 21 days who then were assessed after an interval of 6 weeks between discontinuation of the distraction and the microangiography. A premature closure or impaired function of the physis was common in association with the transphyseal vascularity.

In spite of the comments of DeBastiani concerning the absence of transphyseal fracture with slower rates of distraction, DePablos et al. found that in each of three models used production of a fracture between the metaphysis and the epiphysis always occurred but that the lower the distraction rate employed the greater was the viability of the growth cartilage [613, 614]. The optimal rate for distraction was 0.5 mm/day. The Orthofix distractor was used in 45 lambs divided into 3 groups each with the rate of distraction being 2, 1, and 0.5 mm/day. Histologic studies showed that at the slowest rate the growth cartilage remained essentially normal whereas in femurs lengthened at a rate of 1 or 2 mm/day obvious lesions of physeal cartilage were observed in particular in those studied 45 days following the conclusion of lengthening and at 6 months of age.

Spriggins et al. assessed the response of the growth plate to increasing force of distraction [615]. They studied the upper tibia in 24 rabbits close to skeletal maturity with the distraction rate of 0.13, 0.26, and 0.53 mm every 24 h. They noted 2 distinct patterns of response. In the group where forces increased to maximum values of 20–22 newtons and then suddenly decreased on subsequent distraction, fracture of the growth plate had occurred whereas in the other group lower forces of 16–18 newtons produced and continued to the end of the distraction period were associated only with physeal hyperplasia without fracture. These results were consistent with those of Sledge and Noble [595], and DeBasianti et al. [599] that a slowed rate of distraction could allow for lengthening without fracture. It was in the two lower distraction rates that histologic evidence of fracture was not seen.

(d) *Histologic findings in physeal distraction*: The application of physeal distraction leads to 2 modes of lengthening. If distraction pressures are comparatively low there is apparent continuity of the physis with hyperplasia of cells in the lower proliferating and hypertrophic zones. In most instances, however, there is a transphyseal fracture with the break occurring in linear fashion within the hypertrophic zone.

Peltonen: Repair phenomena were studied by Peltonen et al. in the distal radius of 40 growing sheep [616, 617]. The distraction was at a rate of 0.5–1 mm a day. The first signs of ossification in the distraction gap were seen radiographically about 3–4 weeks after distraction began. Collagen fiber bundles were oriented parallel to the long axis of the bone in the gap region and served as the focal point for new bone formation. Abundant osteoid was demonstrated in the calcified sections. Thin trabeculae from both the epiphyseal and metaphyseal sides grew toward the center of the distraction gap. At the periphery there was active bone formation from the inner layer of the periosteum. Clinical and radiologic consolidation of the distraction area occurred within 10 weeks of the surgery. The consolidated bone area was composed of partly woven bone and lamellar trabecular bone with most of the lamelli organized in the direction of distraction. In those instances where the physis remained intact, there was an apparent stretching of the endochondral growth mechanism owing to the distractive force. In many instances, however, there was actual transphyseal rupture through the hypertrophic zone. At 12 weeks postoperatively, the repair bone resembled normal metaphyseal bone. Once the hematoma of the stretch injury had been removed, the gap was filled with a collagenous matrix and collagen bundles could be seen organized in the direction of the distraction. Shortly thereafter, trabecular bone had been formed from the inner layer of the periosteum and from epiphyseal and metaphyseal sides.

Peltonen et al. also studied gradual physeal distraction of the distal radius in 2–5 month old sheep [618, 619]. The bone formation occurred from the inner layer of the periosteum, from the metaphysis and from the epiphyseal side toward the center of the distraction area. Prior to bone formation collagen bundles were organized in the direction of distraction. Bone formation occurred from the epiphyseal and

metaphyseal sides. Under polarized light microscopy, lamellar trabecular bone was seen forming along the collagen bundles. Woven bone was frequently seen. In the distraction area at 11 weeks in the study by Peltonen, both lamellar and woven bone were present within individual trabeculae but it was clear that the lamellar bone predominated.

Alberty and Peltonen showed that all physes in 12 growing rabbits undergoing distal femoral distraction showed widening of the proliferative and hypertrophic zones as well as a fracture separation at the hypertrophic zone or at the junction of the hypertrophic zone and the metaphysis in 11 of 12 [620]. Proliferation of the hypertrophic cells with 5-bromo-2-deoxyuridine (Brd Urd) labeling was noted even though normally not seen. The labeling of the physeal regions above, however, was normal in both control and distracted physes being positive in germinal and proliferating cell zones with no labeling in the hypertrophic zone.

DePablos et al.: In the histologic study of dePablos et al. local fracture was noted in each instance [613, 614]. The physis tended to be poorly organized in some instances and normal in some. The lengthened zone was first wholly occupied by a hematoma which quickly underwent fibrous organization. This was replaced by a rich granulation tissue composed of numerous fibroblasts and collagen fibers which aligned themselves parallel to the long axis and the traction axis of the bone. Ossification of the lengthened zone was first observed on the twentieth day of lengthening. This was referred to as desmal ossification although there was some endochondral ossification taking place in the growth cartilage at its lowest regions. The ossification progressively replaced the fibrous granulation tissue. After 4 months, all of the tissue in the lengthened zone showed complete ossification.

Monticelli and Spinelli: Monticelli and Spinelli showed that the gap invariably healed with bone provided that the surrounding perichondrium and periosteum was not excised [602, 603]. The resumption of endochondral ossification was infrequently seen and incomplete when present. The new bone consistently formed along the fibrils as well as along the under surface of the peripheral periosteum. The bone was noted to be well oriented in most instances. Polarization microscopy showed the fibrils to be parallel to the long axis of the bone and to the axis of the distraction. They carried out proximal tibial lengthening experiments on 41 sheep between 3 and 5 months of age. The duration of the distraction varied from 1 to 16 weeks. The lengthening rate varied between 0.5 and 1.5 mm/day with most either 0.5 or 1.0. Separation of the epiphysis from the metaphysis was felt to occur after 3–5 days and the force needed to induce fracture was approximately 18 ± 4 kg. Separation was always noted within the hypertrophic zone. During the first and second weeks, the region between the epiphysis and the metaphysis referred to as the interzone was transparent on radiographs. At the beginning of the third week when the interzone was 10–20 mm wide, faint irregular shadows became visible suggesting early osteogenesis. New bone formation was seen next to the epiphysis and the metaphysis with the central region showing initially little bone formation. After 1 month of distraction, the interzone was 25–30 mm wide and the new bone formation sites began to link longitudinally. Longitudinal bundles were continuous now between the epiphyseal and the metaphyseal ends. The bone formation from the metaphysis was generally more advanced than that from the epiphysis. After 2 months of distraction, the interzone had increased to 42–60 mm and the radiographic shadows were more clearly striated in a longitudinal direction. Ossification proceeded upward and downward toward the center of the interzone where bone repair was ultimately slowest. Only when distraction ceased did the central region begin to show uniform radiodensity. After lengthening of 30–40 mm it took about 2 months for the bone cortex to reform. In a few animals, premature epiphyseal fusion occurred which led to the recommendation that transphyseal lengthening be performed only when the subject's bone growth was nearly complete.

The repair bone from the sheep was subjected to a more detailed morphologic study at 1–4 weeks and 2, 4, 6, and 12 months [603]. One week: An epiphyseal fracture (epiphyseolysis) occurred in all specimens. The fracture gap was filled with hematoma. There was no calcification or bone at this stage. The fracture line occurred within the growth plate around the level where matrix calcification was beginning to occur in the hypertrophic zone. Two weeks: The hematoma occupied a wider space but persisted. Most of the chondrocytes in the physis were unchanged although cell columns of the upper cartilage segment were sometimes distorted. The cartilage on the metaphyseal side was penetrated by many capillary vessels and looked more irregular than in the normal control. Three weeks: The distance between the upper and lower cartilage cell segments had widened owing to the continuing distraction. Hematoma was becoming organized with fibrous material. No bone was yet formed. Four weeks: The gap was now filled with a compact, translucent, grayish tissue and the lower cartilage segment was less evident than previously. There was now a thin shell of bone under the periosteum surrounding the distraction space. This was also seen radiographically. The hematoma had almost been completely resorbed and replaced with connective tissue consisting mainly of elongated cells surrounded by thin fibrils. Many of these were irregularly oriented but the beginning tendency to longitudinal orientation was seen with fibrils aligned in the same direction of the distraction force. A thin layer of circumferential periosteal bone composed of thin trabeculae of primary bone was seen. Two months. A compact gray tissue zone was evident grossly below the epiphyseal cartilage. Subperiosteal bone formation was seen along with metaphyseal ossification. No

traces of hematoma were recognizable, having been replaced completely by connective tissue consisting of elongated fibroblasts and thick bundles of collagen fibrils both of which were preferentially oriented parallel to the tensile force of the distraction. This was particularly evident in the middle portion of the elongated segment. Some of the collagenous material was calcified and there were small spicules of osteoblasts seen. Four and six months: A thin surrounding shell of cortical bone at the distraction area was seen. There was continuing ossification in the subperiosteal area. New bone was also seen near both the epiphyseal and metaphyseal zones. Long thin bundles of collagen fibrils were present in the elongated area. Most of these bundles were now calcified forming thin parallel oriented trabeculae whose longitudinal orientation was the same as that of the distraction force. Together with these calcified collagen bundles true bone trabeculae were found, part of which developed from the epiphyseal cartilage and part from the dislocated metaphyseal trabeculae and the periosteum. The tips of these trabeculae were surrounded by osteoblasts. The persisting physeal cartilage in some instances retained its normal structure but in others it was irregular. No bone trabeculae were present near the epiphyseal cartilage indicating disruption of the normal endochondral sequence. Twelve months: Ossification had progressed in the elongated segment and the fibrous tissue had almost completely been replaced by bone trabeculae. The subperiosteal bone had a compact appearance. The elongated tibias were almost indistinguishable from the contralateral side.

The process of distraction epiphyseolysis was divided into three stages: 1. Epiphyseolysis with formation of the hematoma; 2. Resorption of the hematoma and the formation of fibrous tissue which increases in length as long as the distraction force is applied; and 3. Ossification of the fibrous tissue and reconstitution of the periosteal bone. As the fibrous tissue develops in the second phase the cartilage on the metaphyseal side is resorbed and replaced by fibro-osseous and osseous tissue which is well vascularized. In the third stage, there is first calcification and then true ossification of fibrous tissue with the formation of longitudinal trabeculae lying almost parallel to each other. Ossification takes place directly from the periosteum and from the cellular elements of the fibrous tissue undergoing osteoblastic differentiation in connection with the displaced metaphyseal segment. Ossification also takes place from the epiphyseal cartilage but is less regular and less impressive than from the other two sites. On occasion, the endochondral ossification sequence of the physis persisted but in others it was damaged. Cessation of endochondral ossification was not of clinical significance if the distraction epiphyseolysis was carried out at an age approaching skeletal maturity. Varying reports in the literature could easily be due to the differing type of distraction apparatuses used and the different degree of stabilization provided.

(e) *Treatment of premature physeal closure by means of physeal distraction*: Transphyseal distraction has been used in both experimental and clinical situations to disrupt focal transphyseal bridges. De Pablos et al. used the procedure in 30 lambs 1.5 months old after partial epiphyseal arrest in the distal femur had been induced [613, 614, 621]. Physeal distraction was then done followed by no subsequent intervention in some animals and interposition of fat in others. They demonstrated the ability to disrupt the focal physeal bridge by the distraction technique but recommended that fat be interposed since the bridge reformed in all instances where distraction alone had been used. They recommended physeal distraction to pull apart the bone bridge and if clinically meaningful amounts of growth were still left there was value in performing fat interposition to prevent bridge reformation. The need to resect the bridge however was bypassed.

Connolly et al. applied transphyseal traction to correct acquired growth deformities in the immature dog [622]. Bone bridges were created across the medial distal femoral physis to produce a varus deformity. They were able to bring about correction by transphyseal lengthening both after removal of the bone bridge directly and also by not intervening on the bone bridge but stretching and breaking it with the traction procedure. Many of the animals, suffered premature growth plate closure. They showed, however, that mechanical epiphyseolysis after a bone bridge had formed offered the possibility of treating large areas of epiphyseal arrest in order to restore length and correct angulation. Correction of alignment was also performed in two patients with shortening and angular deformity due to enchondromas but without bone bridges. Correction and lengthening were obtained but premature fusion limited effectiveness.

Kershaw and Kenwright were able to pull apart bone bridges by transphyseal distraction but rabbits killed 3–6 weeks after the distraction showed complete physeal closure suggesting that distraction epiphysiolysis along with bone bridge disruption would have a high potential for producing premature physeal fusion [623].

Bollini et al. used the Ilizarov device to treat a centrally located bone bridge in the lower tibia of a 10 year old girl caused by an epiphyseal fracture-separation [624]. The epiphyseolysis occurred on the fourth postoperative day following lengthening or distraction of 0.25 mm/day. The bone bridge which remained attached to the metaphysis was surgically removed following distraction and was prevented from recurring following interposition of methyl methacrylate. Follow-up at 2 years showed no recurrence and normal

growth. Canadell and De Pablos presented four clinical examples of breaking bone bridges by physeal distraction thus eliminating the need for the complex open resection of such transphyseal tissue [625]. They used an angulated monolateral fixator which with distraction served both to pull apart the bone bridge and then allow for angular correction with time. The procedures were performed 3 times in the distal femur and once in the distal tibia. The physeal bridge broke in each instance a few days after distraction began. In those patients close to growth maturation there was no effort made to interpose tissue. If patients were treated at a younger age then the possibility of a secondary procedure to insert an interpositional tissue would be strongly considered. They made one important technical point. It was essential to fracture the bone bridge first with lengthening forces across and parallel to the angulated physis. The distraction would have to be symmetrical and only after the bridge had broken would angular correction be performed. If angular corrective forces were applied from the beginning, they would subject the healthy part of the physis to compression pressures which could lead to its permanent damage. Physeal distraction was also applied by Aldegheri et al. to pull apart bone bridges and then allow for angular correction utilizing the principle of epiphyseal distraction referred to as hemichondrodiatasis [607]. The Orthofix articulated dynamic axial fixator was used to provide for the asymmetric pressures. Two cancellous screws were placed in the epiphysis and two cortical screws in the diaphysis. Earlier work by De Bastiani was quoted to show that it was possible to elongate just the lateral portion of the distal growth plate of the femur with histologic assessment showing an increase in thickness only in the lateral part of the physis owing to cellular hyperplasia and hypertrophy. The deviation was achieved without fracture of the growth plate. Aldegheri et al. felt that the best results were achieved in post traumatic deformities when the bone bridge occupied <20–30 % of the epiphyseal plate. They recommended performance of the procedure with little growth remaining since the possibility of post procedure growth arrest still existed.

6.9.3.4 Transiliac Lengthening

Millis and Hall showed that in patients with a discrepancy in lower extremity length associated with acetabular dysplasia, primary intrapelvic asymmetry, or a decompensated scoliosis, 2.5 cm of length can be gained through transiliac lengthening by means of a modified innominate osteotomy (Fig. 6.25b) [626]. This approach both increases lower extremity length and corrects structural pelvic abnormalities associated with the discrepancy. Three possible complications involve delayed union, sciatic nerve palsy, and sacroiliac joint disruption. The procedure is most strongly indicated for primary correction of pelvic deformity in which slight limb lengthening is also desired.

6.10 Direct Operation on Epiphyses to Enhance Growth Potential by Removing Focal Transphyseal Tethers

6.10.1 Bone Bridge Resection

Partial destruction of the function of the growth plate is associated with the formation of localized transphyseal bone bridges [627, 628]. These develop most commonly after certain growth plate fracture-separations [624, 629–636], in severe cases of Blount's disease (infantile tibia vara), and after infection. The bone bridges retard growth in a localized part of the physis and predispose to angular deformity as well as shortening since the remaining physeal tissue continues to function. The possibility of removing focal bone bridges was raised over 100 years ago by Ollier [159]. He was able to demonstrate the formation of transphyseal bone bridges in experimental animals. Experimental work in rabbits by others at this time also demonstrated partial bone bridging of the physis [634]. There was good clinical awareness in the latter stages of the nineteenth century of bone bridge formation following epiphyseal trauma with its subsequent affect on growth. Ollier himself made efforts in removing bone bridges surgically but recurrence was common owing to the failure to use an appropriate interpositional tissue to prevent recurrent bridge formation.

The position of the bone bridge defines not only the type of deformity, but also the surgical approach to its removal and the type of material interposed to prevent reformation (Fig. 6.26a). Central bone bridges lead to shortening without angular deformation whereas peripheral bone bridges lead to angular deformity as well as shortening. Bright classified partial growth arrest lesions into three types: I: peripheral lesion; II: central lesion; and III: combined central-peripheral lesion [637]. The exact position and extent of bone bridges can be shown by CT scanning and magnetic resonance imaging (Fig. 6.26b). Examples of bone bridges are shown in Fig. 6.26a.

Langenskiold refocused attention on focal bone bridge formation and developed bridge resection and the implantation of fat for use as a clinical tool [628, 638, 639]. In laboratory experiments many types of interpositional materials were used but fat was both the easiest and the most effective in preventing reformation of bone bridges and maintaining physeal function. Fat is a minimally vascularized tissue and generally persists as fat when interposed in growth plate defects thus keeping the epiphyseal and metaphyseal circulations separate and allowing the remainder of the physis to continue growth. Another interpositional material used was cartilage which in experimental studies had just as effective a result as the fat [640]. In commentary

Fig. 6.26 **a** Mature transphyseal bone bridges can be seen on plain radiographs. A peripheral proximal medial tibial bone bridge following Blount's disease is seen. Varus formation has developed. **b** Magnetic resonance imaging defines the extent of any bone bridge. At distal tibia central bone bridge is black (no signal) and persisting physis white. MRI is from coronal (*lateral*) plane. **c** A series of radiographs shows operative approach for removal of a central bone bridge (**i**) and (**ii**), filling of the defect by fat followed by reinsertion of bone window [(**iii**) and (**iv**)] and resulting following growth resumption several months later (**v**)

on his first 43 clinical procedures excising local bone bridges and interposing autologous fat grafts, the results in general were good to very good; only 7 showed questionable benefit "mainly because the procedure was carried out too close to the end of the growth period" [628]. The large majority of procedures involved the distal femur, proximal tibia and distal tibia. The etiology of partial closure in 38 growth plates was fracture in 28, osteomyelitis in 8 and tuberculosis and Blount's disease in 1 each. Following interposition of the fat graft, the radiolucent area of the fat transplant usually has a rounded or oval shape whereas following subsequent growth the radiolucent area becomes elongated.

The fate of the fat implants was studied experimentally by making round cavities in the proximal end of the tibial growth plates in pigs and filling them with autologous fat. Studies indicated that the volume of fat tissue implanted in the cavities continuously increased parallel with the growth in length of the bone. It appeared that the fat was augmented by fat cells in the metaphysis. Langenskiold et al. recalled three patients several years after surgery for CT scan assessment of the epiphyseal/metaphyseal region [641]. They concluded that the former resection cavities were filled primarily by fatty tissue and that the portion of implanted fat had grown in size corresponding with the growth in length of the bones in the affected ends. Some strands of fibrous tissue were intermingled with the fat. A layer of dense bone remained interposed at the periphery of the fat graft. Langenskiold concluded that the free fat grafts implanted at time

of resection continued to grow and thus had filled out the elongated cavities. The fat persisted well beyond the period of growth termination and the cavities were not filled with fluid or bone. Examples of central bone bridge resection are shown in Fig. 6.26ci–v. An excellent overview of physeal bridge resection has been written by Khoshal and Kiefer [642].

Many clinical studies have assessed the treatment of partial physeal growth arrest by bridge resection and fat interposition. Vickers reported on 15 patients with good early results [643]. Williamson and Staheli assessed 29 physeal resections, 22 of which were followed for more than 2 years [644]. They interpreted their results in the longer term group as 11 excellent, 5 good, 2 fair and 4 poor. Twenty of the 29 bridges were caused by fracture, 3 by tumors, 3 by tibial traction pins and 1 by infection. Twenty of the bridges were peripheral, 6 were central and 3 were combined. The results correlated inversely with bridge size. They were uniformly excellent for bridges <25 % of the physeal volume; bridges between 25 and 50 % yielded good to excellent results in 9 of 12 cases; and results were generally poor in bridges >50 % with only 1 of 4 yielding a good result. Bright reported briefly on 100 patients followed >2 years with silastic interposition material with 81 % of the patients demonstrating some growth after bridge resection and 70 % good to excellent results [637]. Aufaure et al. studied 18 cases of bone bridge resection in childhood and concluded that there were 9 good results and 9 failures. The best results were obtained in cases where the bridge was peripheral, since it was more easily approached, and following a traumatic injury in young children. The larger the bone bridge the greater the likelihood of failure. Extensive bridges in particular those located centrally therefore had a poor prognosis and all bone bridges due to osteomyelitis were failures [645]. Most of the bone bridges were resected at the distal femoral and distal tibial growth plates.

Hasler and Foster specifically addressed the reasons for poor and fair results after physeal bar resection [646]. They had removed bars <40 % of the physis and a remaining growth period of more than 2 years. They reviewed 24 physeal bar resections followed by fat interpositioning. Of the patients available for follow-up there were 9 good (40 %) 4 fair (17 %) and 10 poor (43 %) results. They did not find a correlation between bar size and outcome. MRI and CT scans were very helpful in assessing reasons for imperfect outcomes. The commonest cause of recurrence was what they referred to as a secondary tether due either to incomplete bar resection or bar recurrence. Associated or other reasons were dislocations of the fat graft or premature physeal closure. They concluded that patients with congenital physeal abnormalities or postosteomyelitis abnormalities had a less favorable outcome with growth plate trauma patients much more likely to have successful resections. MRI was very helpful not only in pre-operative planning but also in following the result postsurgery.

Resection has proven to be clinically feasible in many instances if one quarter or less of the growth plate is involved and there is sufficient growth remaining to warrant removing the focal tether. Interposition of fat, cartilage, silastic, or methyl methacrylate can keep the epiphyseal and metaphyseal circulations separate, thus preventing the formation of further bone bridges and allowing the unaffected growth-plate cartilage to continue to grow normally. Each of these methods has advocates; the interposition of fat is the easiest and most commonly used approach clinically. Examples of a bone bridge resection procedure are shown in Fig. 6.26c.

The extent of the bone bridge must be determined prior to making a decision to resect the bridge. Plain biplanar radiographs are inadequate. Tomography was shown to provide a good percentage estimate of physeal area replaced by the bone bridge but CT or MR imaging with three-dimensional reconstruction are used currently [642, 646–649].

6.10.1.1 Varieties of Interpositional Materials

Several interpositional substances have been used following resection of a transphyseal bone bridge to keep the epiphyseal and metaphyseal circulations and bone apart so as to allow physeal growth to continue. Cady et al. performed fat implants into 14 New Zealand white rabbit physes in an effort to determine whether or not physeal regeneration occurred [650]. They found no instance in which the physis regenerated transversely across the gap in either the fat implanted or the control femurs. The fat remained viable and was gradually replaced with fibrous tissue. Three inert materials have also been used as interpositional substances with good effects described. These have included silastic [637, 651], methyl methacrylate [627], and bone wax [642]. Among biologic substances cartilage itself was shown to be excellent in preventing transphyseal revascularization. Lennox et al. performed a comparative experiment in the 5–6 week old white New Zealand rabbit in which two adjacent 4 mm diameter defects were drilled in the distal lateral femoral epiphysis [652]. In the control group, valgus angulation had a mean of 43° with 2.4 cm shortening compared to the opposite side. The group with fat interposition showed a diminution of the valgus angle although it was still 28° with shortening 1.9 cm. Better results were achieved with interposition of femoral head cartilage using punch biopsy plugs of fresh bovine cartilage in one group and frozen bovine cartilage in another. In both the fresh and frozen groups distal femoral growth continued with difference being only 0.6 cm from the opposite side. The fresh and frozen cartilage also led to the least extent of valgus angulation showing 11°. Eulert also working on the distal femur of the developing rabbit, eliminated or greatly minimized partial premature

distal physeal closure by transplantation of iliac crest growth cartilage [653]. The best results were obtained when the growth cartilage was transplanted alone or with a thin layer of bone. The results were poor when the layer of bone transplanted with the cartilage was too thick. They concluded that iliac crest cartilage could be used as a graft following bone bridge resection. When a region had been resected and no interpositional tissue placed the mean valgus at 24 weeks post surgery was 60°. When the cartilage graft was inserted with a thick lamella of bone attached angular deformity was less but still approximately 45°. The best results were achieved when the cartilage graft had only an extremely thin rim of bone attached which led to angular deformity of only 10°. Bright showed the value of silicone–rubber implants in dogs where they were effective in preventing bone bridge reformation in a distal femoral epiphyseal growth plate model [651]. Wirth et al. tried implanting periosteum to see if it would modulate into a cartilage phase; this did not occur and direct bone formation resulted [654]. Studies have also been performed attempting to define use of fat grafts in relatively large central defects. Osterman removed approximately 65 % of the central part of the plate of the distal femur in a 3-week-old rabbit and interposed autologous fat [640]. This work attempted to show that even large defects involving more than half of the epiphyseal plate can be successfully treated.

6.11 Treatment of Premature Partial Physeal Closure by Means of Growth Plate Transplantation

6.11.1 Free Autogenous Iliac Crest Physeal Grafts—Focal Defects

Efforts have been made experimentally to reestablish growth by the transplantation of a free partial growth plate after resection [655] (Fig. 6.27a–pi, ii). This procedure is designed to keep the epiphyseal and metaphyseal circulations apart; the partial growth plate also contributes actively to growth, rather than serving as a passive spacer such as do fat, Silastic, or methyl methacrylate. This approach takes advantage of the fact that the physeal cartilage itself has no direct blood supply but, rather, a dual supply from epiphyseal vessels on one side and metaphyseal vessels on the other. If the defect in the growth plate is at the periphery, its removal leaves the epiphyseal cartilage and bone, the metaphyseal bone, and therefore the dual blood supply intact. In rabbits, oriented cartilage from the iliac crest, transferred after the outer fibrocartilaginous portion has been carefully removed, has been shown to survive and function, since the transplanted tissue is nourished by the intact blood supply of the host bone.

Focal lesions of the physis continue to cause considerable morbidity in terms of angular deformity and shortening. Osteotomy can correct deformity, although it must be repeated frequently if the growth problem has occurred several years prior to maturity. A variety of procedures has evolved to treat the length discrepancies. In an effort to restore normal growth, well-localized focal bone bridges have been resected and a biological or prosthetic material has been inserted to prevent reformation. Free physeal and epiphyseal transplantation is attractive, but previous experimental and clinical attempts have not been successful consistently. Vascularized epiphyseal transplantation has been used with some promising results in experimental animals.

The cartilaginous physis has a dual epiphyseal and metaphyseal blood supply. From the epiphyseal vessels, nutrients are carried by diffusion through the cartilaginous extracellular matrix to chondrocytes; the metaphyseal vasculature serves as a source of osteoprogenitor cells that lay down bone on the calcified cartilage matrix to complete the endochondral sequence. A basic requirement for the survival and normal function of free physeal transplants is that this dual blood supply be preserved at the graft site, and that the free physeal graft not be covered by tissues that impede the diffusion of nutrients from blood vessels into the extracellular matrix of the physis. Studies have been done on the transplantation of free autogenous iliac-crest physeal grafts into defects in the lateral aspect of the distal femoral physis in rabbits [655]. The graft site in the lateral aspect of the distal end of the femur was carefully fashioned to expose the epiphyseal and metaphyseal bone and its vessels. Fibrocartilaginous and perichondrial tissue was removed from the surfaces of the free physeal graft to facilitate the diffusion of nutrients into the physeal cartilage. The physeal grafts were readily incorporated into the graft site, the morphology of the physis was retained and the physeal transplant prevented bone bridge formation, growth arrest, and valgus deformity.

Focal physeal bone bridges develop most commonly following certain fracture-separations or as medial bridging of the proximal tibial physis in association with severe Blount's disease. In such situations, the epiphyseal and metaphyseal blood supply to the bone adjacent to the physis is generally normal. The results of the study indicate that free physeal transplants might be used to prevent or decrease the bone bridge formation, growth arrest, or angular deformity that can occur in these conditions.

A procedure was first developed for creating a standard focal defect in the lateral aspect of the distal femoral physis of 3–4 month old rabbits, which consistently led to the formation of a bone bridge between the distal femoral

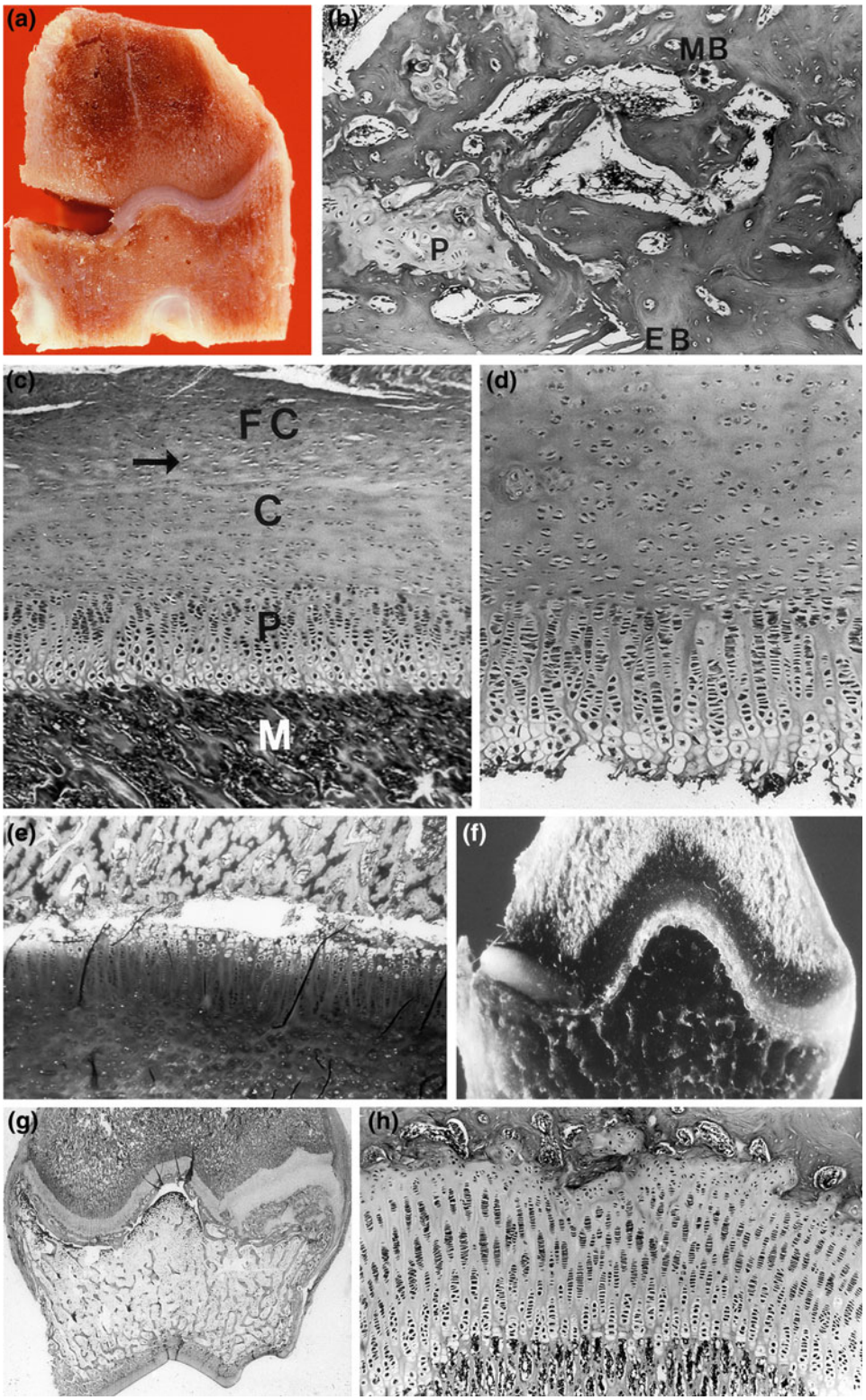

Fig. 6.27 (continued)

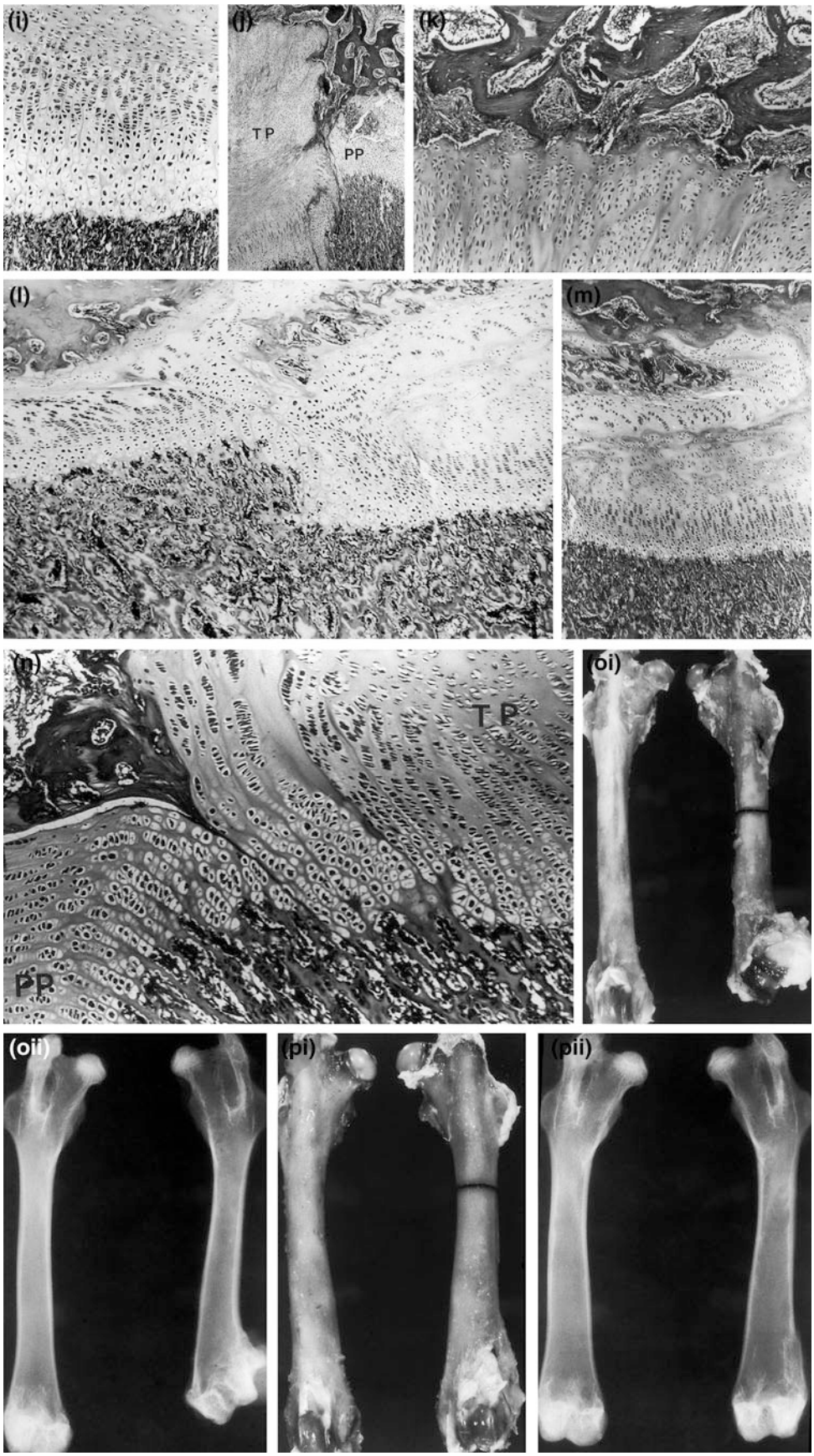

Fig. 6.27 (continued)

epiphysis and metaphysis. The defect was created by removing the outer one-half of the lateral half of the physis. The gross appearance of the defect in a mid-coronal section of the distal end of the femur is shown in Fig. 6.27a. In creating the defect, care was taken to remove all of the cartilage from the surfaces of the epiphyseal and metaphyseal bone to leave the bone intact, and thus to preserve the host's dual epiphyseal-metaphyseal blood supply to the physis.

In the early stage following creation of the defect, undifferentiated mesenchymal cells migrated into and filled the defect, but did not differentiate into cartilage. Woven bone formed, which then transformed to the lamellar conformation. By 4 weeks after surgery, a bone bridge had formed between the epiphysis and the metaphysis (Fig. 6.27b). There was no tendency for the remaining physeal cartilage to grow laterally into the defect. At the periphery of the defect, a fibrocartilaginous mass was sometimes identified, but this never developed into a growth plate. Seven of the 8 defects that were created resulted in bone bridge formation, growth arrest, and marked valgus deformity. In the one rabbit, operated on early, in which normal growth occurred, a dissecting microscope had not been used, and it was assumed that the physis had not been removed completely.

A procedure was then developed to remove and transplant a free autogenous iliac-crest physeal graft into the focal defect created in the lateral part of the femoral physis. The graft was taken from the posterior part of the iliac-crest apophysis. The overlying muscle was freed from the crest and two parallel incisions approximately 2 cm apart were made through the fibrocartilage and physis to the underlying bone. These incisions were carried through the periosteum onto the inner and outer iliac-bone surfaces and then were joined by transverse incisions. By elevating the periosteal sleeve, the iliac-crest apophysis was gently separated from the metaphysis at the junction of the hypertrophic chondrocytes and the metaphysis and was pulled free of the underlying bone. On occasion, a few spicules of metaphyseal bone came free with the cartilage fragment, but specific

◀ **Fig. 6.27** A series of illustrations shows the use of focal iliac crest physeal transplants in a rabbit model. (Reprinted with permission from Olin et al. Free physeal transplantation in the rabbit. J Bone Joint Surg Am 1984;66A:7–20). **a** Photograph demonstrating the defect in the lateral aspect of the distal femoral physis. **b** Photomicrograph showing bone bridge formation following creation of a physeal defect. The lateral femoral physis had been removed, but no graft inserted, 4 weeks before the animal was killed. The persisting physis (P) is on the left. There is no evidence of an attempt by the physeal cartilage to grow laterally to re-form cartilage tissue at site of the defect. Bone fills the defect site (right) and an extensive bone bridge unites epiphyseal bone (EB) with metaphyseal bone (MB).**c** Photomicrograph illustrating the iliac apophysis and the metaphyseal bone. Fibrocartilaginous layer (FC); cartilage of the apophysis (C), the cytologically specialized region of the cartilage referred to as the physis (P); and metaphyseal bone (M). The arrow represents the line of demarcation between the green-staining fibrocartilaginous tissue and the *red*-staining cartilaginous tissue, as demonstrated on a safranin O-fast green preparation. **d** Photomicrograph of the iliac apophysis after its separation from the metaphysis. Separation has occurred through the zone of hypertrophic cells, with a few spicules of metaphyseal bone persisting on the transplant specimen. **e** Photomicrograph showing an iliac physeal graft in position in the defect immediately after transplantation. The cartilage graft is below and the femoral metaphysis is above. A narrow space is present between the graft and the femoral metaphysis, which ensures a firm fit. **f** Photograph showing an iliac physeal graft in position in the lateral femoral physeal defect. **g–n** This series of photomicrographs demonstrates the histological appearance of the physeal graft in relation to the persisting physis and associated epiphyseal and metaphyseal bone following transplantation. Except figure **g**, the photomicrographs are positioned with the epiphyseal areas at the *top* and the metaphyses below. **g** Low-power photomicrograph illustrating the distal femoral physeal graft at the *right* 3 months after insertion. Normal growth has occurred and no distal femoral valgus deformity is present. The graft is approximately two times as thick as the persisting non-operated physeal tissue. Cartilage union has occurred at the graft-physis junction and there is no continuity between the epiphyseal and metaphyseal bone and no angular deformity. **h** Photomicrograph of the medial aspect of the nonoperated distal femoral physis, demonstrating the normal architecture. **i** Photomicrograph from the same specimen as in this figure **h**, showing physeal and metaphyseal tissue from the lateral physeal transplant. Cartilage and physeal tissue are at the *top* and metaphyseal tissue, at the *bottom*. *Note* the excellent orientation of the proliferating and hypertrophic cell layers of the transplanted physis and the smooth junction with the metaphyseal tissues. **j** Low-power photomicrograph made 3 months after physeal transplantation. The transplanted physis (TP) is at the left and the persisting physis (PP) is at the *right*. There is firm coaptation between the two physes. Persisting epiphyseal bone is at the *top* and metaphyseal bone, at the *bottom*. **k** Higher power photomicrograph from the same specimen illustrated in this figure **j** demonstrating the junction of the epiphyseal bone above and the transplanted cartilage *below*. Vascular invasion of the transplanted cartilage has not occurred. **l** Photomicrograph illustrating the physeal graft (*right*) and the persisting physis (*left*). Cartilage continuity between the two has been established. At the upper right, note the bone that has invaded the cartilage part of the transplant as distinct from the physeal part. The metaphyseal bone adjacent to the persisting physis merges imperceptibly with the metaphyseal bone adjacent to the graft. **m** Higher power photomicrograph showing, from *top* to *bottom*, epiphyseal bone, bone in the cartilaginous part of the graft, cartilage and physeal cartilage from the graft, and metaphyseal bone produced by the graft. **n** Higher power photomicrograph showing the junction between the persisting physeal cartilage (PP) and the physeal transplant (TP). There is persistence of the proliferating and hypertrophic cell zones in the graft tissue and continuity between metaphyseal bone from both segments. At the *upper left*, epiphyseal bone remains separate from metaphyseal bone. **o** Photograph demonstrating a poor result 4 months after transplantation is seen in this figure **o(i)**. When the animal was killed, the graft was found to have displaced from the defect site, allowing a bone bridge to form with significant shortening and valgus deformity. The non-operated control femur is on the *left*. Figure **o(ii)** shows radiographs of the two bones. **p** Photograph illustrating an excellent result 4 months after growth-plate transplantation in this figure **p(i)**. The control femur is on the left. Figure **p(ii)** shows radiographs of the two bones illustrated in (**i**) demonstrating an excellent result following transplantation

attempts to include bone were not made. Histological studies confirmed the separation between the hypertrophic chondrocytes and the metaphysis. The graft was trimmed under the dissecting microscope to remove the periosteal-perichondrial sleeve and much of the overlying fibrocartilage. The graft was then placed in the femoral defect with the correct orientation and the femoral periosteal sleeve was sutured to the intact femoral periosteum with 4–0 Dermalon to hold the graft in place. The animals were not immobilized postoperatively. The iliac apophysis is composed of a physis, epiphyseal cartilage, and a fibrocartilaginous layer (Fig. 6.27c). The apophysis was separated gently from the metaphysis of the iliac crest, at the junction between the lowermost hypertrophic chondrocytes and the metaphysis (Fig. 6.27d). Most of the fibrocartilaginous layer and all of the perichondrium and periosteum were removed using the dissecting microscope. The physeal graft was then placed in the femoral defect and the overlying femoral periosteal sleeve was sutured into place (Fig. 6.27e, f).

In the transplant specimens assessed as early as 1 week postoperatively, the physeal graft appeared to be intact and viable. The morphology and organization of the physis were retained. Union of the graft by cartilage at the graft-host junction was seen at as early as 2 weeks. Viability of the growth plate was evident histologically by production of metaphyseal bone, maintenance of physeal height and cytological organization, and the absence of vascular invasion or bone formation in the germinal, proliferating, and columnar cell layers. The physis maintained its bright-red stain with safranin O. The residual overlying fibrocartilaginous tissue of the graft underwent vascular invasion and ossification with time, but the growth plate itself appeared immune. A detailed description of the histological characteristics of the transplanted physis is presented in Fig. 6.27g–pi, ii.

In the definitive study of the capacity of the physeal transplant to prevent bone bridge formation, shortening, and valgus deformity, 33 rabbits received transplants. Twenty-seven of the rabbits were killed 21 days or more after surgery. The capacity of the graft to prevent growth arrest or valgus deformity was then assessed by its gross and radiographic appearance and by measurements of the distances between the femoral head and the medial and lateral condyles of the distal end of the femur. The results were classed as excellent, good, fair, or poor, as already defined.

Photographs of the gross appearance and radiographs of the femora demonstrate an obvious, striking difference between an excellent and a poor result. In the preliminary studies, when the experimental technique and the criteria for assessment were evolving, there were 7 excellent, 6 good, 4 fair, and 2 poor results. In the definitive group, when grading criteria were more stringent, 16 were excellent, 3 good, 4 fair and 4 poor (a good or excellent result in 70%).

The type of growth-plate defect created led to bone bridge formation and valgus deformity in experiments where no cartilage was interposed. Similar defects created by other investigators have also led repeatedly to bone bridge formation and angular deformity. There have been reports of defects that involved only a narrow, peripheral portion of the plate in which a bone bridge formed but the bone subsequently yielded to growth, with angular deformity not occurring as the intact physis overcame the small bridge. There also have been reports of small central bone bridges forming but not restricting growth. There thus appears to be a relationship between the size of a physeal defect and bone bridge formation and the effect of the bridge on subsequent growth.

Since normal growth did not continue in the sham experiments after creation of the growth-plate defect alone, the large number of good and excellent results following physeal transplantation is attributable to insertion of the graft. The graft may have functioned simply as a passive barrier to vascularization, keeping the epiphyseal compartment separate from the metaphyseal compartment without actually contributing actively to growth. If so, the absence of deformity might have been due to persistence of growth of the remaining growth plate alone. Separation of the two circulations is the prime function of any interpositional material, be it biological or prosthetic. Intimate communication between the epiphyseal circulation with its associated osteoprogenitor cells and the metaphyseal circulation with its osteoprogenitor cells allows a bone bridge to form. Examples of passive barriers include heterogenous deep-frozen hyaline cartilage, fat, Silastic, methyl-methacrylate, and bone wax. Physeal cartilage is avascular and also possesses an anti-angiogenesis factor which inhibits vessel ingrowth.

The histological studies of the transplants indicate that the morphology, viability, and normal function of the transplanted physis were retained. The proliferating chondrocytes remained organized in orderly rows and contributed to longitudinal growth. The persisting epiphyseal blood supply adjacent to the defect provides nourishment for the resting, germinal, and proliferating cell layers of the transplanted iliac physis; as long as the graft is sufficiently thin, is handled gently, and is well positioned, it appears that it will survive. Cartilage union at the persisting physis-graft junction was demonstrated histologically in the several specimens from animals that were killed at early time-periods. Endochondral bone formation occurred beneath the physeal transplant in a fashion almost indistinguishable from that of the persisting physis.

The importance of a narrow graft must be stressed. As the cells of the growth plate are supplied by diffusion, removing most of the overlying fibrous and fibrocartilaginous tissue from the iliac crest cartilage graft allowed vascular diffusion

from the epiphyseal side to supply the transplant almost immediately. With time, the fibrocartilage remaining on the graft underwent vascular invasion, followed shortly by endochondral bone formation such as occurs in iliac apophyseal ossification prior to skeletal maturation. This bone soon merged with that of the secondary ossification center of the epiphysis. The physeal portion of the graft, however, remained intact without suffering vascular invasion until the time that the entire distal femoral physis reached maturity. A bed of well-vascularized epiphyseal and metaphyseal bone is essential, as the nutrition of the free graft is derived exclusively from its surrounding tissue.

Lalanandham et al. transplanted scapular cartilage in the rabbit into the distal ulna following curettage of the ulnar physis in animals 5–6 weeks old [656]. They then assessed the viability and biochemical function of the transplanted chondrocytes and their histologic appearance at varying time periods. They concluded that the cartilage transplanted in an avascular fashion could remain viable, synthesize proteoglycan and also be associated with active growth (although less than normal). Histologic sections at 2 weeks showed the transplanted block of cartilage to be intact and by 8 weeks the transplanted cartilage appeared to be participating in endochondral ossification on the metaphyseal side. Histochemical studies from the graft cartilage were consistent at 2, 7, and 14 days and showed lactic dehydrogenase to be strongly present in both transplanted and unoperated control cartilage. Radiosulfate administered intravenously was clearly present throughout the transplanted tissue also at 2, 7, and 14 days. This incorporation was indicative of chondrocyte synthesis of proteoglycan. Thymidine incorporation was seen but was diminished relative to controls.

Several groups have used animal models to compare the effects of interpositional tissues. Martiana et al. used many interpositional tissues in physeal regions of the distal left femur of a 3-month-old rabbit including muscle, fat, physeal allograft, and iliac apophyseal autograft [657]. A standard defect was created in the lateral distal physis of the left femur in all rabbits. A control group had no interpositional material. At 12 weeks following surgery assessments involved limb length discrepancy and angular deformity. Muscle, fat, and iliac apophyseal autograft had less severe limb length discrepancy and angular deformity than did the control group and the physeal allograft group. In terms of limb length discrepancy and angular deformity, the best results were seen with the iliac crest autograft. The second best tissue in each regard was the interposed muscle with fat third best.

Lee et al. excised the medial half of the proximal tibial epiphyseal growth plate in the rabbit to create a partial growth arrest, then excising the bone bridge and inserted either iliac crest physis, fat, or silastic into the gap [658]. The iliac crest physeal transfer to be superior to silastic which in turn was superior to fat. The tibias that received free fat as interposition material developed severe varus angulation and failed to grow in length. The bony bridge redeveloped in all cases in the transferred adipose tissue, contrary to the findings of Langenskiold and his group. In the experimental group with iliac physeal grafts, varus angulation was much less and the amount of longitudinal growth much greater than that of the other groups with fat and silastic. In many of the animals "the transferred physis remained viable and therefore could have contributed to growth and also could have prevented reformation of the bony bridge through its spacer effect."

This experimental approach is for well localized, focal lesions, in this instance involving approximately one-quarter of the physis in the coronal plane and one-half of that segment in the sagittal plane. The shape of the iliac physis must also be considered in relation to the shape of the defective physis, as few long bone physes are as level as diagrammatic and radiographic projections often imply.

It appears that full physeal and certainly epiphyseal grafts can be successful only if they are transplanted with an associated vascular supply. The possibility of using vascularized iliac-crest apophyseal transplants has been investigated. In focal physeal lesions, however, when the host epiphyseal and metaphyseal bone is present and well vascularized, free autogenous iliac crest might be effective clinically. Although not all of the transplants were successful, the dramatic differences demonstrated between the excellent, good, and even fair results in comparison with the poor and sham results clearly indicate that free physeal transplants in the appropriate environment can function well. The graft must be freed from much of the overlying fibrocartilage and surrounding periosteum and perichondrium, and must be fitted gently but firmly into narrow defects so that coaptation is intimate. In addition, the host periosteum at the region of the groove of Ranvier should be sutured over the graft to provide both mechanical and physiological support. As the majority of lesions due to trauma and Blount's disease leave the epiphyseal and metaphyseal bone intact and well vascularized, free iliac-crest physis transplants may be useful in the treatment of focal physeal arrest in patients with such conditions.

6.11.2 Vascularized Autogenous Epiphyseal and Iliac Crest Grafts

Since studies of nonvascularized transplants over several decades stressed poor or imperfect results owing to failure of rapid revascularization, the use of vascularized transplants held great attractiveness and once vascularized bone transplants became feasible investigation was extended to this area. Nettelblad et al. transplanted successfully the proximal

third of the fibula including the entire epiphysis, adjacent metaphysis, and diaphysis in 22 puppies showing the feasibility of the technique [659]. In the experimental groups, the fibula switch was performed selecting one fibula as a vascularized graft and the other as a nonvascularized graft. Continuous growth was observed in the vascularized epiphyseal transplants and in the controls with no statistical difference noted whereas the nonvascularized transplants exhibited considerably less or no growth. Varying techniques subsequently confirmed the continued viability of the vascularized epiphyseal transplants in contrast to the nonvascularized procedures.

Teot and associates have reported on their investigations concerning vascularized partial iliac crest growth cartilage transplants [660–662]. An initial study performed in 50 childhood cadavers and 25 immature dogs assessed the vascularization of the lower end of the femur and the iliac crest [660]. They were able to identify regions of cartilage from the epiphyses that could be transplanted with anastomosis of appropriate pedicles. In a second brief presentation, the value of iliac crest cartilage as a graft source was again reviewed [661]. They utilized iliac crest vascularized transfers in an experiment in 38 puppies replacing approximately 80 % of the distal femoral growth plate region. Initial indications were of growth in the range of 85 % of that on the opposite normal side. Early report was also made of 1 case in a 2-year-old patient with a total epiphyseal arrest of the distal femur who had a vascularized iliac crest transplantation after bone bridge resection. The patient was doing well 16 months later but no further follow-up was reported. The second proposed utilization was in reestablishing acetabular growth for the dysplastic hip.

The vascular pedicle had its origin from the deep circumflex iliac artery. A more formal presentation of iliac crest pedicle graft transplantation was reported from 48 immature dogs in relation to repairing distal femoral growth plate abnormalities [662]. In 1 group the graft was pedicled on the superficial circumflex iliac vessels and reimplanted in situ. In group 2 the pedicle graft was transferred to the groin area as an island graft. These two control groups demonstrated conservation of growth activity when the graft was pedicled on its epiphyseal vessels. In group 3, the graft was transferred to the distal epiphyseal area of the femur after resection of the portion of the growth plate (approximately 2/3) located inside the perichondrial ring of Ranvier with conservation of 80 % of the outer cylinder. Microsurgical revascularization was achieved by using the saphenous vessels. In group 4 the latter technique was used without revascularization. Results were far more favorable in terms of growth restoration in the pedicled than in the nonvascularized transplant. In the vascularized distal transplant, the possibility remained that some regeneration of cartilage was from the surrounding epiphyseal plate which had been left intact. They concluded that the pedicle graft "appears to act as a catalyst in the formation of a new growth plate, preventing the formation of bony bridges between the epiphysis and metaphysis." Vascularized iliac-crest transplantation has been used experimentally to augment acetabular growth in dogs with severely deformed hips and damaged femoral growth as a result of epiphyseal lesions. Allieu also provided a brief report on the feasibility of iliac crest cartilage and bone pedicle transplants into the acetabular and proximal femur region [663].

6.11.3 Physeal Reconstruction Using Tissue from Fetal and Early Postnatal Epiphyses

Zaleske and colleagues attempted physeal reconstruction with young fetal-neonatal tissue to take advantage of its greater growth potential [664–667]. Experiments were done involving full and partial physeal reconstruction in mice with most studies involving 4-day-old postnatal distal femoral tissue. While growth in length over brief periods of time has tended to be limited to the 25 % range, autoradiographic studies using tritiated thymidine show persistence of cell proliferation after avascular transplantation. Isolated physeal regions appear to maintain their kinetic activity at least in short-term implantations. In the 4-day-old distal mouse femur, which serves both as the source of tissue and the area into which tissue is implanted, the epiphysis is completely cartilaginous and avascular. The work, summarized by Barr and Zaleske, showed that as a group the transplanted physeal blocks resulted in femurs of significantly shorter overall length [664]. Metabolic and kinetic analysis, however, showed both tritiated thymidine and radioactive sulfate incorporation indicating that cell viability continued even though normal function was not reconstituted. They concluded that blocks of cartilage containing important cell populations can be transplanted in a nonvascularized fashion with at least partial maintenance of viability. The bulk of this transplantation investigation was done with highly inbred strains allowing for syngeneic transplantation. The work was expanded using complete epiphyseal replacement via knee transplantation in the murine model but utilizing tissue of different developmental times in neonatal mice in an effort to determine whether or not a specific stage of epiphyseal chondrogenesis led to improved results. Studies were done in 4-day-old postnatal mice but the distal femoral and proximal tibial chondroepiphyses in their entirety were transplanted from a 4-day-old postnatal mouse, a 1-day-old postnatal mouse, and a 17-day-old fetal mouse. Similar histologic, metabolic, and kinetic analyses were done, as had been used previously. The animals were followed for 2 months post surgery. There was variability in morphology and growth from the transplanted syngeneic knee in all experimental groups but the important observation was felt to be the presence of an unequivocal joint with distal femoral and proximal tibial secondary centers of

ossification in adjacent physeal regions implying some continuing function of the chondroepiphyseal transplant. No differences could be noted between the three groups of slightly differing ages. Since the chondroepiphyses were transplanted prior to their vascularization, the fact that they survived and subsequently were vascularized to form secondary ossification centers demonstrated the ability to utilize developmentally immature tissue which could progress to increased development in its new position.

6.11.4 Cell-Based Therapy for Focal Growth Plate Cartilage Repair

Increased understanding of mesenchymal stem cells (MSCs) and chondrocytes has led to multiple attempts to direct them into a growth plate cartilage synthesis and repair mode [668]. The most common use of cell-based growth plate therapy is for focal lesions, usually transphyseal bone bridges following growth plate fracture separations. Experimental approaches started with efforts at implantation of chondrocytes. This tended to poor repair since already differentiated chondrocytes were ineffective in expanding to fill spaces and, more importantly, did not further differentiate into the highly structured physeal cartilage. Autogenous chondrocytes can be harvested, cultured, and expanded ex vivo prior to being implanted back into the patient. This has shown good clinical applicability for osteochondritis dissecans lesions in the knee but has not been well adapted for physeal focal defects.

Attention is now turning to working with mesenchymal stem cells and directing them to a cartilage-line differentiation. Exogenous growth factors and scaffolds are also being employed. Two lines of MSC-based treatments are being investigated: (i) cell harvesting, MSC isolation and ex vivo expansion; (ii) mobilizing endogenous MSCs to the growth plate injury site and enhancing in situ regeneration. The mesenchymal stem cell approach has also been directed toward physeal cartilage regeneration, as well defined by Chung, Foster, and Xian [668]. Planka et al. have treated a distal physeal defect by transplantation of autologous and allogeneic mesenchymal stem cells. Newly formed hyaline cartilage was demonstrated histologically in both groups [669]. Differentiation along the chondrocyte line has been enhanced by use of growth factors such as FGF-2 and various TGF-βs. Use of scaffolds has also been applied especially natural materials which are biocompatible, biodegradable, appropriate in pore size, and suitable for MSC growth and differentiation. Materials used include chitosan, collagens, fibrin gels, hyaluronan, and alginate. Injectable hydrogels allow MSCs to be embedded into them along with growth factors and can be molded easily into irregular spaces. Activation of the Wnt Planar Cell Polarity (PCP) signaling pathway has been shown to enhance the formation of columnar growth plate architecture and can be seen to function in patterning growth plate chondrocytes in vitro [670]. The ability to grow chondrocytes which synthesize a cartilage matrix in vitro has led to the hope that chondrocyte suspensions grown in tissue culture might be placed within focal physeal defects to reconstitute a functioning physis. Experimental reports of this possible approach have appeared. Hansen et al. reported on the growth of chondrocytes into cartilage discs after culturing isolated epiphyseal chondrocytes from sheep [671]. The best results are achieved in experimental animals using fetal cartilage as the source of chondrocytes. While there is some evidence that a cartilage tissue subsequently forms in the physeal defect and proliferates, there is no evidence that the cytologically specialized physis has been reconstituted. Tobita et al. transplanted autogenous chondrocytes cultured in collagen gel into growth plate defects in 8–10 week old rabbits [672]. Results in terms of angular deformity and length in the growth plate defect model were better than in the groups with the defect left empty or filled with autogenous fat tissue. Autogenous chondrocytes were harvested from cartilage of the knee joints, embedded in collagen gel and cultured for a week prior to transplantation.

6.11.5 Transplantation of Entire Physes and Epiphyses

Both nonvascularized and vascularized transplantation of epiphyseal plate autografts have been attempted, experimentally and occasionally clinically, for over 100 years. Throughout most of this time, nonvascularized transplants were studied. By the late 1960s, advances in vascularized tissue transfers allowed investigation into use of vascularized epiphyseal transfers [673].

6.11.5.1 Early Transplantation Experiments 1899–1914

The results of the initial experimental transplantations of entire growth plates in dogs were almost all poor in allografts but there were some favorable reports of reimplantation and autograft viability and growth. Haas reviewed in great detail the studies on growth plate transplantation that had been reported in the German literature between 1899 and 1914 [674, 675]. Although an optimistic report had been presented concerning the effectiveness of allograft (homoplastic) transplantation of the upper end of the radius including the epiphyseal cartilage allowing for growth in rabbits he felt that the interpretation of that work by the authors was inaccurate and remained unconvinced that actual growth had occurred since very little growth occurred normally in the proximal radius. In assessing all the reports,

there was virtually no growth noted in any of the allograft transplantations although there was on occasion some growth in the autotransplantations and often considerable growth in reimplantations. The term reimplantation refers simply to removing a segment of bone or cartilage and then replacing it in its same site. In none of these approaches were any vascular repairs performed.

Among the earliest detailed epiphyseal transplantation studies were those of Helferich [676] and Enderlen [677] who provided separate reports in 1899. The investigators, who worked together, reimplanted the epiphysis in rabbits using the lower epiphyseal cartilage of the ulna with an adjoining piece of epiphysis and diaphysis. Helferich reported on the macroscopic findings that the epiphyseal cartilage, under favorable conditions, need not lose its property of producing length growth. A lessening of this ability was noted but generally there was not a complete loss of growth. Enderlen reported on the microscopic findings and indicated that some of the reimplanted epiphyseal cartilage remained viable to a large extent in particular those parts adjacent to the perichondrium [677]. Von Tappeiner performed reimplantations and allograft transplantations on dogs 6 and 12 weeks of age using the distal half of the metatarsal [678, 679]. In the reimplantations, he found no disturbance in length growth even after 6 months while in the allograft transplantations growth was markedly diminished. Obata performed reimplantations, autografts and allografts of the entire metatarso-phalangeal joint with either a part or an entire metatarsal and phalanx [680]. He felt that shortening occurred in all cases but that it was most marked in the allograft transplantations.

An extensive study was performed by Heller who carried out reimplantations of the distal epiphysis of the radius and ulna as well as homotransplantations (allografts) [681, 682]. The epiphysis did not keep its normal length growth in any of the 45 experiments in which the epiphyseal cartilage was transplanted in the form of half joints. The best results occurred in the reimplantation group while the worst, by which is meant the greatest degree of shortening, occurred in the allograft between non-related animals. In the allograft transplantation group, there was complete cessation of epiphyseal function. He concluded that in autografts there was active regeneration of the epiphyseal cartilage from the perichondrium but that bone growth did not remain at a normal amount. The most favorable conditions for epiphyseal cartilage transplantation would be in the form of a thin sheet of physeal cartilage without adhering bone particles so that the cartilage could come directly into contact with nourishment from the host. He reported almost normal growth in instances where autograft transplantation had been performed transferring physeal cartilage only. Minoura transplanted metatarso-phalangeal joints of 2 month old rabbits into soft tissue [683]. Varying models were used but he too concluded that autografts were much superior to allografts but that even with autografts there was not regular growth of the epiphyseal cartilage even though some of the tissue survived and in no case was there lengthening of the transplanted joint. Axhausen had also transplanted the lower quarter of the femur from a growing rat to the subcutaneous tissue of another rat [684]. The physeal cartilage was noted to degenerate such that at 20 days only the peripheral parts remained alive. With further time the entire physis was replaced by fibrous tissue. Similar findings were noted when the same experiment was repeated in the rabbit. Von Tappeiner performed 3 reimplantations and 8 allografts in dogs [678, 679]. In the reimplantations, there were practically no changes in the epiphyseal cartilage line even after 6 months as assessed microscopically. Even in the allograft group some histologic evidence of continuing function was noted. The findings of Von Tappeiner were not confirmed by Haas. Obata described a progressive degeneration of the epiphyseal cartilage line in the reimplantation group until the 50th day at which time there was some repair of function [680]. He also ascribed almost normal functional properties to this regenerated epiphyseal cartilage. By 70 days however degeneration had again occurred leading Haas to interpret the fact that under some favorable circumstances some of the physes continued to function. Otherwise, the changes described by Obata were similar to those of Haas. In Obata's allograft work, the epiphyseal cartilage underwent progressive degeneration with practically no regeneration. Heller noted some favorable results in reimplantations. There was some regeneration of the epiphyseal cartilage line and some new growth but overall the bone growth was retarded. In allograft transplants, the results were invariably poor. Haas felt that use of the distal end of the radius and ulna made interpretation of one bone transplantation more difficult than in the simpler and more straightforward metacarpal or metatarsal model. The findings of Minoura agreed closely with those of Haas. In none of the experiments was there any increase in length of the bone after transplantation.

6.11.5.2 Haas

Haas reported on his 75 experimental procedures on dogs regarding the effectiveness of epiphyseal transplantation in maintaining growth [674]. The majority of the animals were from 1½ to 4 months of age at time of surgery. The metacarpals and metatarsals were selected for transplantation since they had only one epiphysis making it easy to determine whether or not growth from the transplanted region had occurred. The bones were also quite stable after repositioning because of the nonoperated adjacent bones. Review of the literature indicated failure of allograft transplantation to be effective in virtually all studies and thus Haas concentrated on reimplantation and autograft transplantation. Following reimplantation of an entire metacarpal or metatarsal

which had been removed from its position with the articular surface and periosteum intact and then immediately replaced there was complete cessation of growth of the epiphysis. Autograft transplantation of the entire metacarpal or metatarsal, in which an entire bone was transplanted from one foot to another foot of the same animal, also showed no evidence of growth. No effective growth was seen with split metacarpal reimplantation or autograft transplantation. In the group most likely to succeed, namely those having reimplantation of the epiphyseal cartilage, the cartilage was transplanted with a piece of adjoining epiphysis and diaphysis and even here there was no effective growth. A similar approach with autograft transplantation from one foot to the other showed no definite evidence of growth with the conclusion that after autograft transplantation of the epiphyseal cartilage its function for linear growth was entirely lost or present to only a minimal degree. There was also uniform failure of growth with reimplantation of varying lengths of the epiphyseal end of the metacarpal and metatarsal bones and uniform failure of growth after autotransplantation of varying lengths. Haas' conclusions were quite straightforward; the epiphyseal cartilage lost its power to function after transplantation either of the reimplantation or autograft transplantation type and with the physis transplanted either alone or with an accompanying piece of epiphysis and diaphysis. When Haas uses the term epiphyseal cartilage "alone" he still obtained a piece with small adjacent regions of epiphyseal and metaphyseal bone. He concluded that the epiphyseal cartilage was very vulnerable and that its viability was directly dependent upon its blood supply. In no instance was any vascular repair done with his transplants and the physeal cartilage rarely had direct access to the persisting vascularity of the host bone since it was always transplanted with a thin rim of bone on epiphyseal and metaphyseal sides. Haas himself addressed this question in an abstract of the discussion printed immediately following the article. He noted that "in all the excisions of the epiphyseal cartilage a piece of adjoining epiphyseal and diaphyseal bone was removed so as not to injure that particular region." Heller had commented on this matter and felt that in his work he had succeeded in transplanting the epiphyseal cartilage in the form of very thin sheets of cartilage which subsequently resulted in almost normal growth. Haas felt that Heller's conclusions were incorrect either in the sense that he could not truly effectively transplant just cartilage alone, leaving open the possibility that it was the persisting cartilage not removed for transplantation that enabled growth to occur.

In a subsequent article, Haas reported on the macroscopic, microscopic, and in some cases radiologic details from 58 of the 75 procedures [675]. The microscopic description involved not only the epiphyseal growth plate cartilage but also the articular cartilage, the marrow and bone of the secondary ossification center, the marrow and bone of the metaphysis and cortical bone. With epiphyseal cartilage reimplantation, the first evidence of degeneration of the epiphyseal cartilage was seen at 23 days and appeared as a cleavage line extending through the cartilage columns dividing the physis into a proximal 2/3 and distal 1/3. With time, progressive degeneration of the epiphyseal cartilage line occurred and by 85 days there was almost complete disappearance of the physeal cartilage. With autotransplantation the epiphyseal cartilage also showed early degeneration and at 23 days a line of cleavage was noted through what appeared to be the hypertrophic zone. By 135 days, only a slight remnant of physeal cartilage persisted. Following reimplantation with varying lengths of the epiphyseal and of the metacarpal and metatarsal bones degeneration of the cells at the junction of the proximal 2/3 and distal 1/3 of the physis was noted followed by fissuring and eventual degeneration of the entire cartilage. With autotransplantation the epiphyseal cartilage line underwent a progressive and complete degeneration. The epiphyseal cartilage line also underwent progressive and complete degeneration with either reimplantation or autograft transplantation of the entire metacarpal or metatarsal bone. Haas reconfirmed his observations that the epiphyseal cartilage ceased to function after either reimplantation or autograft transplantation in each of several approaches. The longitudinal growth ceased in each case. The cartilage degenerated, there were frequently transverse and vertical fissures followed by a disappearance of the cells, fibrous substitution and eventually bone transformation. The only evidence for regeneration was near the periphery beneath the perichondrium although the new cartilage possessed none of the length performing functions of the normal physeal pattern. He concluded that the epiphyseal cartilage was the least transplantable of any of the components of bone due to damage to the vascular supply to the epiphyseal region.

Haas later performed another series of transplantation procedures since others continued to describe some effective results with epiphyseal transplantation [685]. He concluded again however following 20 additional procedures that "the epiphyseal cartilage plate loses its power of causing length growth after transplantation." Haas defined the potential clinical value of epiphyseal transplantation but concluded after extensive and repeated experimentation that longitudinal growth ceased after reimplantation, autograft or allograft transplantation of the epiphyseal cartilage whether by itself or with a neighboring piece of epiphyseal or diaphyseal bone. Entire widths of physis in dogs were transplanted and most of the many variations used were unsuccessful, as Haas recognized, owing to failure to provide nutrition to the resting, germinal, and proliferating chondrocytes of the physis. Even transplants of what Haas referred to as the

epiphyseal cartilage line, however, included a thin rim of adjoining epiphyseal and metaphyseal bone.

6.11.5.3 Physiologic Concerns in Physeal Transplantation

Subsequent studies on physeal transplants continued to use entire ulnar, radial, metacarpal and metatarsal physes, most of which had some epiphyseal bone attached both to protect the physis from mechanical damage during removal and to ensure its complete transplantation. The results were variable. It is probable that even thin layers of bone attached to physeal transplants on the epiphyseal side inhibit rapid diffusion of nutrients to the physeal cartilage, result in chondrocyte death, and lead to growth-plate resorption and replacement by bone. In support of this contention is the report by Heller of good results in physeal transplants when a thin layer of cartilage was transplanted without a sliver of epiphyseal bone attached to the graft although Haas pointed out that growth might have been due in such situations to parts of physeal cartilage left behind which continued to function [681]. Similar good results have been reported with focal cartilage transplants performed using iliac-crest cartilage without overlying epiphyseal bone.Some grafts appear to have led to poor results after transplantation with the surrounding perichondrium intact. This tissue layer would inhibit nutrition by diffusion from the host tissues, which is essential in free transplants. In addition, most of the studies on free epiphyseal transplantation have involved total physes, which undoubtedly represent too extensive an amount of tissue for consistently good results, especially if epiphyseal bone, perichondrium, and periosteum are left attached and a firm fit in the defect site is not achieved.

6.11.5.4 Ring

Ring performed reimplantation, autograft and allograft transplantations of the entire distal ulnar epiphysis in 3–6 week old rabbits [686]. He had calculated that approximately 85 % of the growth of the ulna occurred distally. He also recognized that owing to the tight bond between the distal radius and the distal ulna there could be some lengthening of the distal ulna region after transplantation which need not represent physeal growth but was due to a mechanical pulling apart of the distal ulna by the continuing growth of the radius. After a period of time however failure of ulnar growth would be reflected by tethering of the adjacent radius and its growth in a curved pattern. The ulnar physeal cartilage was removed following knife cuts made transversely through the bony epiphysis and metaphysis such that the isolated cartilage was transplanted "with its thin attached slivers of bone" following which it was gently freed from the radius and removed together with its surrounding perichondrium. In a series of reimplantation experiments of 9 animals followed for 5 weeks of more, 6 showed little or no shortening and 3 were failures. The reimplantation procedure represents the most favorable in terms of prognosis. He then performed comparative experiments involving autograft transplantation within the same animal from right to left and vice versa and allograft transplantations from separate rabbits. Detailed and accurate length determinations of normal rabbit ulnar growth and of the transplanted animals were then made over a several week period. Histological and radiographic studies were made. He concluded that only five of the autograft transposition group could be assessed as completely successful out of 18 procedures. The ulnar growth had to exceed 75 % of that predicted and stringent radiographic criteria had to prevail to give the successful grading. In the allograft group 26 procedures were done. Using the criteria for successful transplantation developed for the other 2 groups, 21 of the 24 were clear failures and while 3 looked to have acceptable radiographic appearances in each of these the epiphyseal cartilage was narrow and in none of the 3 was the growth in the experimental limb within 75 % of the control. He thus concluded that allograft transplantation was unsuccessful in all the animals studied, a conclusion invariably reached by investigators throughout the century. In the autograft transposition group normal growth occurred in only 5 of 18 procedures. Some of the failures were due to technical difficulties in the sense that it was difficult to obtain a snug fit of the transplanted physis into its new host bone. Even when this was present however growth failure occurred because of inability to restore full revascularization in an appropriate period of time.

6.11.5.5 Harris et al.

Harris et al. achieved a 50 % success rate in autogenous transplants of immature rabbit whole distal ulnar physes by leaving the host perichondrium intact and transplanting only physeal cartilage without a sliver of epiphyseal bone, thus substantiating Heller's results at least partially, as well as the importance of allowing nutrition from the host to support the graft [687]. Extremely careful technique was utilized to obtain the graft. Following subperiosteal dissection of the distal ulnar metaphysis and adjacent epiphysis for about 1/3 of its circumference the epiphysis was broken from the shaft with ease by manual pressure. Since the physis was quite straight there was a constant line of separation through the hypertrophied cells of the zone of provisional calcification leaving the bulk of the epiphyseal plate attached to the epiphysis. They then inserted a small scalpel blade as close to the bone plate of the epiphysis as possible excising only the cartilaginous physis. Since the germinal layer was relatively thick during early development it was easier to obtain an adequate transplant in the very young animals. They performed reimplantation in 65 rabbits, autogenous

transplantation (right to left) in 65 rabbits and allograft transplantation using animals paired as closely as possible by weight in 65 animals. A stainless steel wire was then placed through the ulnar shaft approximately 0.5 cm proximal to the plate to serve as a radiographic guide for length measurements. Sacrifice ranged from 1 to 84 days with 9 time periods in the first 2 weeks and histologic studies at 21, 28, 56, and 84 days. In the allograft transplantations, 7 of 13 long-term (56 and 84 days) animals were successful. Normal growth was virtually never noted in comparison to controls regardless of the type of procedure. In the reimplantation group 11 of 25 available long-term specimens showed a normal histological appearance of the plate and 80 % or more of anticipated growth. In the allograft transplantations there was a remarkably uniform success rate up to 28 days. All physes subsequently degenerated however and were destroyed between the 56th and 84th day. They concluded that satisfactory survival with up to 80 % of normal growth for the 12 weeks of the experiment was achieved in ½ of the autografts with homografts fairing quite poorly in particular after the first 4 weeks. Technical features for a good result involved the necessity of including the germinal cells of the physis within the transplant, an adequate supply of tissue fluid (i.e. vascularization) reaching the transplant from the epiphyseal side and a snug fit of the transplant in the recipient bed. Their interpretation, which appears accurate, suggested that the transplants had to survive an avascular stage obtaining nutrition from the surrounding tissues before healing and stabilization occurred so that longitudinal growth could continue. Care had to be taken to ensure that the recipient bed in particular on the epiphyseal side had been curetted to bleeding bone since it is the vascularity of the host that provides nutrition to the transplanted or reimplanted physeal graft tissue.

6.11.5.6 Silfverskiold; Farine

Silfverskiold performed ulnar epiphyseal cartilage transfers in the rabbit and found that allograft transplantation produced a complete cessation of growth while autograft exchange produced cessation of growth in 6 of 11 animals and considerable retardation in the rest [688]. Farine also performed distal ulnar transplantation procedures in the young rabbit [689]. Sacrifice in most was from the first to the 19th day after surgery with occasional animals followed to 180 days. Operations were performed in 16 rabbits 5 weeks of age. The transplant included the entire distal ulnar physis with two thin epiphyseal and metaphyseal lamellae of bone. Autograft transposition from right to left was done in 16, and in a second group an additional 16 had reimplantation procedures performed. The results in the two groups were similar. The subsequent study was histologic and microangiographic. A major part of the cartilage transplant survived in each of the rabbits and on one occasion there was total survival. Any imperfect result was due to the production of a hematoma which limited passage of host vessels to the graft and thus limited revascularization. Measurements in terms of physeal function were not made however.

6.11.5.7 Transplantation of Vascularized Epiphyseal Plates

The biology of vascularized epiphyseal transplants was well reviewed by Boyer et al. [673]. Much work was done outlining the details of blood supply to the epiphyseal regions (which we have reviewed in previous chapters). Three types of vascularized epiphyseal plate studies were reviewed. (i) The first involved studies after vascularized epiphyseal plate orthotopic replantation. This refers to microvascular replantation into the same host in the same anatomic location. This experimental approach assesses the ability of growth plates to maintain function after (immediate) revascularization. (ii) the second approach involved studies of vascularized epiphyseal plate heterotopic transplantation, meaning transfer to different anatomic sites in the same individual. These are autogenous free tissue transfers which not only define a biologic principle but also represent some clinical applicability. (iii) the third approach studied epiphyseal plate behavior after allograft transplantation. The clinical problem limiting this work is the need for immunosuppression to maintain cell viability. Studies by Bowen et al. with microvascular growth plate transfers of the distal ulna of the immature dog illustrated the feasibility of these transfers for subsequent growth when both epiphyseal and metaphyseal circulations were maintained [690, 691]. Donski and O'Brien transferred distal ulnar growth plates contained within epiphyseal and metaphyseal bone in the distal ulna of the dog [692]. Heterotopic and orthotopic transplants were done, some vascularized and some not vascularized, although relatively few dogs were done (13) with the bilateral upper extremity surgery. Heterotopic transplants (vascularized) averaged 69 % growth, with orthotopic even higher, while grafts without microvascular anastomoses showed no growth. Nettleblad et al. performed classic free microvascular epiphyseal plate transplantation in puppies in proximal fibulas showing retention of good values [659].

Experimental work in immature rabbits by Zaleske et al. has shown that reimplantation of vascularized whole knee joints, including the epiphyses, can survive and continue growth [693]. At present, however, such procedures have little clinical applicability, primarily because the epiphyses that can be sacrificed for transplantation do not fit the anatomical and mechanical needs of the area to which they would be transferred.

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