

Passing the USMLE: Basic Science

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 Springer

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Preface

Basic sciences are the bedrock of a medical education. Though the breadth of basic medical sciences can be complicated and confusing, a firm grasp of this knowledge is essential for both passing the United States Medical Licensing Examination (USMLE) and building a successful medical career.

Step one of the USMLE examines a student's ability to understand and apply these basic sciences. Most residency programs pay a great deal of attention to this score when considering applicants, so preparing for this portion of the USMLE can be a daunting task.

This book was designed to present all the information necessary to pass this step of the exam in bullet format for easy memorization. The text includes key words, tables, figures, diagrams, and photographs for increased retention, and should eliminate the need for any other books during your preparation. Though the basic science of medicine can seem like an endless ocean of facts, this book distills large topics down to only the most pertinent facts.

With this book guide, mastering the USMLE will be just another step in your medical career.

Michigan, USA
Ahmad Wagih Abdel-Halim

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Head and Neck

Arterial Supply

- The left common carotid artery (CCA) arises directly from the *aorta*, while the right CCA arises from the *brachiocephalic trunk*.
- Each CCA bifurcates at the level of *T4* into two branches:
 1. External carotid artery (ECA): Gives multiple branches, including the *superficial temporal*, *lingual*, and *maxillary*
 2. Internal carotid artery (ICA): Passes through the *carotid foramen* into the inside of the skull and forms the *circle of Willis*; see Chapter 3, Neuroanatomy, for more details

Venous Drainage

- *Face*: Drains into the *internal jugular vein (IJV)* via the *facial vein*
- *Brain*: Drains into the dural venous sinuses; see Chapter 3, Neuroanatomy.
- *Note*: The facial vein is connected to the cavernous sinus, so an infection of the face may be transmitted intracranially, causing *cavernous sinus thrombosis*.

Carotid Sheath and Neck Triangles

- *Carotid sheath*: Contains *common carotid artery (medially)*, *internal jugular vein (laterally)*, and *vagus nerve (posteriorly)*
- *Triangles*: The sternocleidomastoid muscle divides the neck into anterior and posterior triangles (Table 1.1).

Muscle Actions

- *Levator palatini*: Elevates the soft palate during swallowing
- *Palatoglossus*: Elevates the base of the tongue

TABLE 1.1 Important triangles of the neck and their contents.

	Carotid triangle	Occipital triangle
Location	Anterior	Posterior
Artery	Common carotid artery	Subclavian artery
Vein	Internal jugular vein	External jugular vein
Sympathetic	Sympathetic trunk	–
Parasympathetic	Vagus nerve	–
Cranial nerves	XII	XI
Others	Ansa cervicalis	<ul style="list-style-type: none"> • Trunks of brachial plexus • Phrenic nerve • Cervical plexus

- *Palatopharyngeus*: Closes the oropharynx after a food bolus passes
- *Posterior cricoarytenoid*: Abducts the vocal cords
- *Lateral cricoarytenoid*: Adducts the vocal cords
- *Note*: All muscles of palate are supplied by the vagus nerve except the tensor palatini, which is supplied by the mandibular branch of the trigeminal nerve.

Larynx

- The ventricle of the larynx lies between the *vestibular folds superiorly* and the *vocal folds inferiorly*.
- *Musculature*: All muscles of the larynx are supplied by the *recurrent laryngeal nerve*, except the *cricothyroid muscle*, which is supplied by the *external branch of the superior laryngeal nerve*.
- *Recurrent laryngeal nerve*: The left recurrent laryngeal nerve hooks around the *aorta*, while the right one hooks around the *subclavian artery*.
- Injury of recurrent laryngeal nerve:
 1. Bilateral: Both vocal folds migrate toward the midline and *fatal dyspnea* ensues.
 2. Unilateral: The vocal fold on the injured side migrates toward the midline, causing *hoarseness of voice*. So when you see a patient presenting in

the USMLE with hoarseness of voice after thyroidectomy, you know what to think!

- *Superior laryngeal nerve*: Lies close to the *superior thyroid arteries*. Injury causes *loss of high-pitched tone of voice*.

Cricothyrotomy

- Urgent procedure to establish an airway
- *Technique*: A horizontal opening is created between the *2nd and 3rd tracheal rings* by piercing the *skin, cervical fascia, pretracheal fascia, and cricothyroid ligament*.
- *Tracheostomy*: A vertical incision is made more inferiorly in the neck, compared to a cricothyrotomy.
- *Complication*: *Erosion of brachiocephalic artery*. So when you see a patient in the USMLE who had a tracheostomy and *2 weeks later* started bleeding from the incision, you know what to think!

Thyroid Gland

- Develops from the floor of the primitive pharynx
- *Arterial supply*:
 1. Superior thyroid artery: Branch of *ECA*
 2. Inferior thyroid artery: Branch of the *thyrocervical trunk (from the 2nd part of subclavian artery)*
 3. Thyroid ima artery: Branch of *aorta*
- *Venous drainage*:
 1. Superior and middle thyroid veins: *IJV*
 2. Inferior thyroid veins: *Left innominate vein*
- *Note*: Parathyroid glands are four small glands on the posterior surface of the thyroid gland. They are supplied by the *inferior thyroid arteries*, and they secrete *parathyroid hormone (PTH)*.

Parotid Gland

- A salivary gland in the retromandibular fissure that secretes *serous saliva*; the duct opens in the mouth at the level of the *upper second molar tooth*.
- *Arterial supply*: *ECA*
- *Venous drainage*: *External jugular vein*
- *Nerve supply*: The facial nerve divides inside the parotid gland into five branches: *temporal, zygomatic, buccal, mandibular, and cervical*. Injury of the facial nerve during its course inside the parotid gland causes *Bell's palsy* (see Chapter 3, Neuroanatomy).
- *Crocodile tears syndrome*: Excessive *lacrimation* induced by *eating*; it occurs due to injury of the *facial nerve inside the parotid*.

- *Frey syndrome*: Excessive *sweating* induced by *eating*; it occurs due to injury of the *auriculotemporal branch of the trigeminal nerve*.
- *Sialolithiasis*: Salivary stones forming in the salivary glands and ducts. *Clinical picture*: Pain and swelling of the involved gland *upon eating*; especially *sour substances*, e.g., lemon juice. *Diagnosis*: *Sialogram*. *Treatment*: Sialogogues. Surgery is reserved for severe cases.
- *Sialoadenitis*: Infection of the salivary glands. *Cause*: Viruses, e.g., mumps, or bacteria, e.g., *Staphylococcus aureus*. *Clinical picture*: Fever, swelling, and tenderness of the involved gland *unrelated to meals*. *Treatment of bacterial sialoadenitis*: Penicillinase-resistant penicillin, e.g., dicloxacillin. *Note*: Postoperative parotitis is common after any major surgery.

Vertebral Column

Anatomic Landmarks

- Formed of *33 vertebrae*: seven cervical, 12 thoracic, five lumbar, five sacral, and four coccygeal.
- *Landmarks*:
 1. C4: *Bifurcation of CCA*
 2. T2: *Sternal notch and aortic arch*
 3. T4: *Sternal angle, and bifurcation of trachea*
 4. L1: *End of spinal cord in adults*
 5. L3: *End of spinal cord in newborns*
 6. L4: *Bifurcation of aorta*
 7. S1-S3: *Extent of sigmoid colon*

Curves, Joints, and Stabilization

- *Curves*:
 1. Primary: *Thoracic and sacral curves*
 2. Secondary: *Cervical and lumbar curves*
- *Joints*:
 1. When you nod “yes,” you are moving the *atlanto-occipital joint*, which is supported by *anterior and posterior membranes*.
 2. When you shake your head “no,” you are moving the *atlantoaxial joint*, which is supported by *transverse or alar ligaments*.
- *Ligaments*:
 1. Your eyes look toward the supporting ligaments:
 - *Nodding anteroposteriorly*: Anterior and posterior membranes
 - *Shaking your head horizontally*: Transverse ligaments
 2. Tear of transverse (alar) ligaments causes dislocation of the atlantoaxial joint, which is a *unique*

complication of rheumatoid arthritis. This results in the axis pushing on the spinal cord causing quadriplegia or on the medulla oblongata causing respiratory paralysis.

- **Stabilization:** Vertebral column is stabilized by four ligaments:
 1. Anterior longitudinal ligament
 2. Posterior longitudinal ligament
 3. Ligamentum flavum
 4. Interspinous ligaments
- **Notes:**
 1. The cervical column is one area in the vertebral column you can see *dislocation without fracture*, which is not common in the rest of the column.
 2. Venous plexuses of the spinal cord (external and internal) are connected to the thorax, abdomen, and pelvis. This is the reason some malignancies are more common than others to metastasize to the brain, e.g., *breast, lung, and kidney*.

Intervertebral Disks

- **Structure:** It is composed of:
 1. Central part: Nucleus pulposus, which is a remnant of the *notochord*
 2. Outer part: Annulus fibrosus, which is formed of *fibrocartilage*
- **Pathology:** Herniated nucleus pulposus (HNP) can compress on a nerve root causing pain and tingling sensation in the dermatome supplied by the nerve root *underneath the lesion level*, e.g., the C4-C5 disc lesion will compress the *C5 nerve root*, causing symptoms along the lateral surface of the arm.
- **Dermatomes** (Fig. 1.1)
- **Notes:**
 1. In a patient presenting with neurologic symptoms in his legs, and *cannot stand on his heels* on exam, think *L4-L5 HNP*.
 2. If he *cannot stand on his toes* on exam, think *L5-S1 HNP*.
 3. Cauda equina syndrome: A *surgical emergency* characterized by *bilateral leg pain and numbness, saddle (perineal) hypoesthesia, bowel and bladder incontinence*. Disk prolapse is discussed in detail in Chapter 3, Neuroanatomy.

Whiplash Injury

- Common after motor vehicle accident, especially getting *rear-ended*

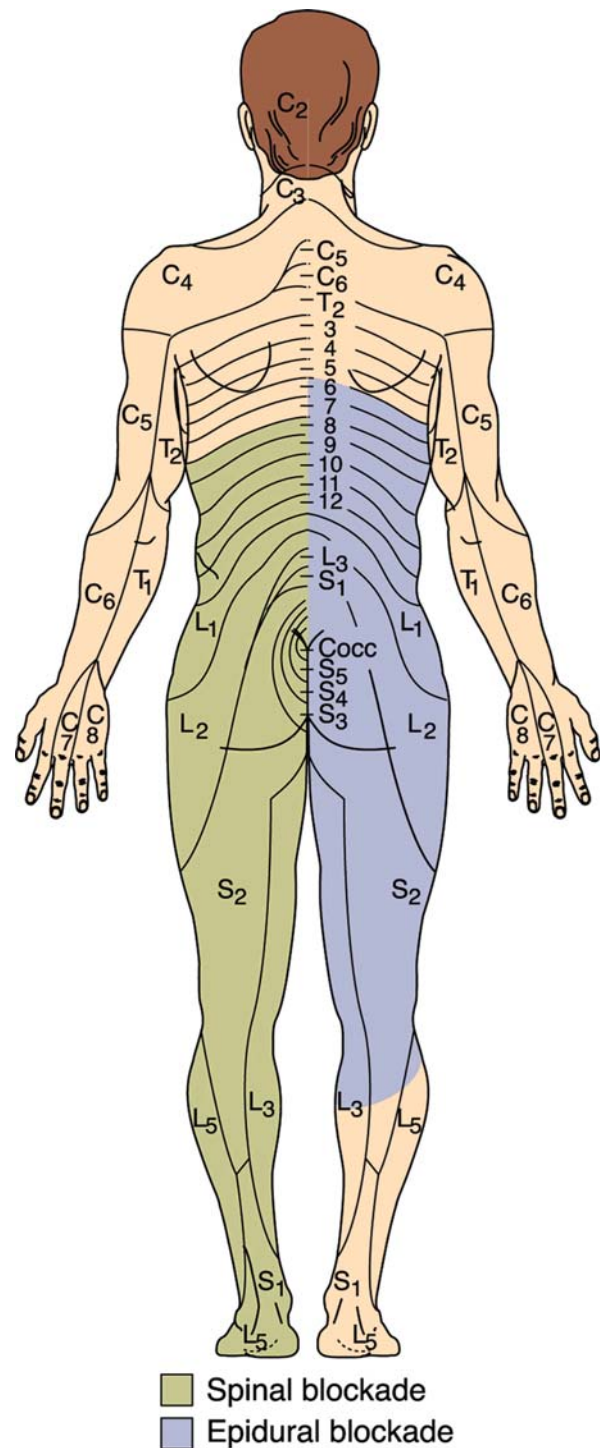


FIG. 1.1 Dermatomes

- **Pathology:** The *upper cervical vertebrae* get *hyperextended*, and *lower ones hyperflexed*. The most common joint to be injured is *C4-C5*.
- **Clinical picture:** Neck pain and stiffness
- **Treatment:** Conservative by *C-collar* and physical therapy until patient can resume full activity

Spondylosis

- **Mechanism:** Degenerative disorder of the spine and intervertebral discs characterized by *osteophytes* formation
- **Treatment:** Conservative; surgery is needed only if there are signs of cord compression.

Spondylolysis

- **Mechanism:** *Stress fracture* of the *pars interarticularis*, mainly in the *lumbar* vertebrae, and is more common in *athletes*
- **On exam:** Positive *leg hyperextension test*
- **Diagnosis:** X-ray reveals *collar-shaped fracture*
- **Note:** Do not confuse this with *spondylolisthesis*, a disorder of the *pedicles* of lumbar vertebrae causing sliding of a vertebral body and *lordosis*. It is either congenital or secondary to degeneration.

Osteomyelitis

- **Mechanism:** It is an infection of the bone, directly from a nearby septic focus or through the blood-stream in cases of bacteremia.
- **Pathology:** Bone death (*sequestrum*) and new bone formation (*involucrum*)
- **Most common organism:** *Staphylococcus aureus*; *Salmonella* is common in patients with sickle cell disease, but *S. aureus* is still the most common organism.
- **Clinical picture:** Red, warm, tender, and swollen limb
- **Diagnosis:**
 1. Gold standard: *Bone biopsy*
 2. Radiologic test of choice for acute cases: *Magnetic resonance imaging (MRI)*
 3. Radiologic test of choice for chronic cases: *X-ray (periosteal elevation)*
 4. Practically: Bone scan; it is very sensitive but *not specific*.
- **Treatment:** Admit to the hospital and start 4- to 6-week course of IV penicillinase-resistant penicillin.

Upper Limb

Arterial Supply

- **Course:**
 1. Subclavian artery (SCA): Left SCA arises directly from the *aorta*, while the right one arises from the *brachiocephalic trunk*

2. The SCA becomes the *axillary artery* as it reaches the *lateral border of the first rib*.
3. The axillary artery becomes the *brachial artery* as it reaches the *inferior border of teres major muscle*.
4. The brachial artery divides into radial and ulnar arteries in the *antecubital fossa*.

- **Branches of SCA:**

1. Internal mammary artery: Used frequently in coronary artery bypass surgery. It courses inferiorly as the *superior epigastric* to anastomose with the *inferior epigastric branch of external iliac artery*.
 2. Vertebral artery: Supplies the posterior aspect of circle of Willis
 3. Thyrocervical trunk: Gives off *inferior thyroid*, *transverse cervical*, and *suprascapular* arteries
- **Axillary artery:** It gives off the *circumflex humeral* and the *circumflex scapular arteries*. It is crossed by the *pectoralis minor* muscle dividing it into thirds: medial, inferior, and lateral (named according to their relation to the muscle).
 - **Brachial artery:** Runs in the *radial groove* with *radial nerve*, where it becomes vulnerable in humeral shaft fractures
 - **Blood supply of the hand:** *Superficial and deep palmar arches*. The deep palmar arch is deep to both tendons of flexor digitorum superficialis and profundus, so it is at risk of injury in fracture of *any* carpal bone.
 - **Shoulder joint anastomosis:**
 1. Suprascapular artery
 2. Subscapular artery
 3. Circumflex scapular artery
 4. Transverse cervical artery
 - **Elbow joint anastomosis:** In the arm, the short (Inferior) stand in the front, and the tall (Superior) in the back. Now let's go over the anastomosis:
 1. *Superior* ulnar collateral with *posterior* ulnar recurrent arteries
 2. *Inferior* ulnar collateral with *anterior* ulnar recurrent arteries
 3. Middle collateral with interosseus recurrent arteries
 4. Radial collateral with radial recurrent arteries

Venous and Lymph Drainage

- **Venous drainage:** Cephalic, basilic, and brachial veins. Basilic and brachial veins fuse to form the axillary vein at the *lower border of teres major muscle*.
- **Lymph drainage:** Axillary lymph nodes, which drain into the *thoracic duct*

Nerve Supply (Fig. 1.2)

- **Brachial plexus:** It is formed of the *ventral primary rami of C5 through T1*, which are all located between the *anterior and middle scalene muscles*.
- **Rami:** The rami fuse forming upper (C5-C6), middle (C7), and lower (C8-T1) trunks in the *posterior triangle of the neck*.
- **Trunks:** Three trunks give rise to *three anterior and three posterior divisions*.
- **Divisions:** They fuse forming *medial, lateral, and posterior cords in the axilla*.
- **Lateral cord:** Gives rise to the *musculocutaneous nerve*, and the *lateral part of median nerve*
- **Posterior cord:** Gives rise to the *axillary and radial nerves*.
- **Medial cord:** Gives rise to the *ulnar nerve*, and the *medial part of median nerve*
- **Notes:**
 1. Remember: *Rami, Trunks, Divisions, Cords (RRDD)*
 2. The cords are termed medial, lateral, and posterior according to their relation to the *axillary artery*.

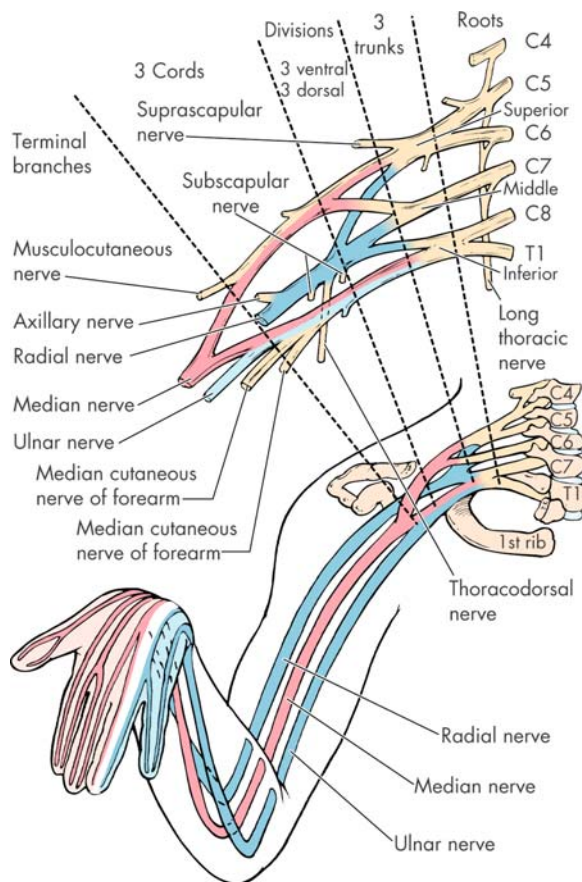


FIG. 1.2 Brachial plexus

3. The scalene lymph nodes lie *behind the clavicle* and are adherent to (the 3 P's):
 - **Pleura:** Pneumothorax is a risk during scalene node biopsy.
 - **Phrenic nerve:** Diaphragm paralysis is a risk.
 - **Lymph ducts:** Lymph leakage is a risk.

Brachial Plexus Injury

- **Injury of upper trunk:**
 1. Cause: Inferior displacement of the shoulder, e.g., shoulder dystocia
 2. Clinical picture: Arm is adducted, extended, pronated, and medially rotated. This is known as *Erb's palsy* or *waiter's tip deformity*.
- **Injury of lower trunk:**
 1. Cause: Superior displacement of the shoulder
 2. Clinical picture: *Loss of power and sensation over the medial three and half fingers of the injured hand*. This is known as *Klumpke paralysis*.

Radial Nerve Injury

- **Cause:** *Midshaft humerus fractures*
- **Clinical picture:**
 1. Motor: *Inability to extend wrist and fingers; hence wrist drop ensues*
 2. Sensory: Loss of sensation over the *dorsum of the hand*

Ulnar Nerve Injury

- **Cause:** *Compression at the elbow or wrist*
- **Clinical picture:**
 1. Motor: Paralysis of *interossei* and *medial two lumbricals*, causing *claw-hand deformity*
 2. Sensory: Loss of sensation along the *medial third of the hand*
- **Note:** *Palmar interossei Adduct fingers (PAD), while Dorsal ones Abduct fingers (DAB).*

Median Nerve Injury

- **Cause:** *Wrist injury*, as it lies *deep to flexor retinaculum*
- **Clinical picture:**
 1. Motor: Paralysis of *opponens pollicis* and *flexor digitorum superficialis*, causing *wasting of thenar eminence*, and *pointing index*, which does not flex

when making a fist. This deformity is known as *ape-hand*.

2. Sensory: Loss of sensation over *the lateral two thirds of the palm*
- *Note:* Flexor digitorum superficialis controls the proximal interphalangeal (PIP) joints, while flexor digitorum profundus controls the distal interphalangeal (DIP) joints.

Axillary Nerve Injury

- *Cause:* Fractures of the *surgical neck of the humerus* and *anterior displacement of humeral head*
- *Clinical picture:* Two muscles suffer paralysis:
 1. Deltoid: Leading to *adduction of the arm*
 2. Teres minor: Leading to *medial rotation of the arm*

Joints

- *Glenohumeral joint:* It is stabilized by:
 1. Subacromial and subscapular bursae
 2. Long head of biceps
 3. Rotator cuff muscles (*SITS*): Supraspinatus and Infraspinatus muscles (supplied by *suprascapular nerve*), Teres minor (axillary nerve), and Subscapular muscle (subscapular nerve); rotator cuff injury causes painful abduction >90 degrees.
- *Acromioclavicular joint:* Stabilized by coracoacromial, coracoclavicular, and acromioclavicular ligaments
- *Humeroulnar joint:* Stabilized by *ulnar collateral ligament*. Injury of this ligament leads to *abnormal abduction of the forearm*.
- *Humeroradial joint:* Stabilized by the *radial collateral ligament*. Injury of this ligament leads to *abnormal adduction of the forearm*.
- *Radioulnar joint:* Stabilized by the *annular ligament*. Supination and pronation occur in this joint.

Clavicular Fracture

- *Mechanism:* Occurs at the *junction of medial two thirds and lateral one third of the clavicle*, mostly due to *fall on outstretched hand*
- *Clinical picture:* *Stepladder* deformity, and tilt of the head toward the fractured side due to contraction of sternomastoid muscle
- *Treatment:* Closed reduction and sling (*figure-of-eight sling*)

Supracondylar Fracture of Humerus

- *Mechanism:* It is a fracture of the humerus just above the epicondyles, mostly due to a *fall on the tip of a flexed elbow*.
- *Clinical picture:* Pain and ecchymosis of the ante-cubital fossa
- *On lateral view X-ray:* *Fat pad sign*
- *Next best step:* *Examine radial pulse*
- *Complications:*
 1. Injury to brachial artery: Leads to acute ischemia of the limb
 2. Volkmann contracture: It is a flexion deformity of the wrist and fingers, mostly *due to ischemia causing muscle fibrosis*.
- *Treatment:* Reduction and immobilization by cast placement

Nursemaid Elbow

- *Mechanism:* Pulling on the upper limb causing the *radial head to be subluxed off the annular ligament*
- *Clinical picture:* Common in children; patient presents with *flexed and pronated forearm*
- *Treatment:* Manual reduction

Scaphoid Fracture

- *Most common cause:* Fall on an *outstretched hand*
- *Clinical picture:* Wrist pain and *tender anatomic snuffbox*
- *Complications:* Avascular necrosis of scaphoid bone in *proximal* fractures
- *Diagnosis and management:* X-ray does not show the fractures in early stages, so in suspected cases, place a *thumb splint* and repeat the X-ray in *7–10 days*.
- *Note:* The snuffbox is bounded by three *pollicis* tendons: extensor pollicis longus, extensor pollicis brevis, and abductor pollicis longus. (Helpful to remember: “The police guards the box.”)

Colles' Fracture

- *Mechanism:* *Posterior displacement of distal radius plus fractured styloid process* of the ulna
- *Clinical picture:* Pain and palpable fracture in the distal forearm
- *Diagnosis:* X-ray shows *dinner-fork* deformity
- *Treatment:* Reduction and immobilization by cast placement

Dupuytren Contracture

- **Mechanism:** Fibrosis and contraction of *palmar aponeurosis*
- **Risk factors:** Alcoholism, pregnancy, and liver cirrhosis
- **Clinical picture:** Painless flexed medial fingers
- **Treatment:** Physical therapy; *fasciectomy* is reserved for severe resistant cases.

Miscellaneous Upper Limb Injuries

- **Shoulder dislocation:** Mostly *anterior dislocation*, injuring the axillary nerve and artery. On exam: *Externally rotated* arm. Treatment: Reduction and sling.
- **Lateral epicondylitis** (“tennis elbow”): Due to inflammation of *common extensor origin*
- **Medial epicondylitis** (“golfer’s elbow”): Due to inflammation of *common flexor origin*
- **Boxer fracture:** Fracture of the *head of fifth metacarpal bone*
- **Gamekeeper fracture:** Expect it in a patient coming to the emergency room (ER) after *skiing*, complaining of *thumb pain and tenderness*. The pathology is *avulsion of medial collateral ligament* of thumb.
- **Monteggia’s fracture:** Dislocation of radial head plus diaphyseal ulnar fracture. Expect it in a patient coming to the ER who was in a fight, and used his forearm to protect his head from trauma by a blunt object.

Lower Limb

Arterial Supply

- At its termination, the aorta divides into the right and left common iliac arteries. Each common iliac divides further into the *internal* and *external iliac arteries*.
- **Obturator artery:** It is the continuation of the *internal iliac artery*. It passes through the *obturator foramen* to supply the *adductor muscles*. It also gives the *artery of ligamentum teres*, which supplies the head of femur.
- **Femoral artery:** It is the continuation of *external iliac artery*. It enters the lower limb through the *femoral triangle*. It gives off the *lateral* and *medial circumflex arteries*, the latter being the main blood supply to head and neck of femur.
- **Popliteal artery:** Once the femoral artery passes through the *hiatus of adductor magnus muscle*, its name changes into popliteal artery. It gives off two important branches:

1. **Anterior tibial artery:** Runs with the *deep peroneal nerve*, and ends as the *dorsalis pedis artery* on the dorsum of the foot. The *dorsalis pedis* is located between the *tendons of extensor hallucis longus* and *extensor digitorum longus*. The *dorsalis pedis* pulse is best palpated over the *navicular bone*.
2. **Posterior tibial artery:** Runs posteriorly with the *tibial nerve*, and ends in the sole of the foot with medial and lateral branches, which fuse to form the *plantar arch*.

- **Hip joint anastomosis (cruciate anastomosis):**

1. Superiorly: first perforator of the femoral profunda artery
2. Inferiorly: Inferior gluteal artery
3. Medially: Medial circumflex artery
4. Laterally: Lateral circumflex artery

- **Femoral head anastomosis:** Same arteries as above, except for the superior contributor being *superior gluteal artery*.

Venous and Lymph Drainage

- **Venous drainage:**

1. Superficial venous system: Multiple veins, including the *greater saphenous medially* and *small saphenous laterally*
2. Deep venous system: Drains into the *femoral vein*
3. Perforating veins: Drain superficial to deep system

- **Lymph drainage:**

1. Superficial inguinal nodes: Drain into *external iliac lymph nodes*
2. Deep inguinal lymph nodes: Drain into *lumbar lymph nodes*

Nerve Supply

- **Lumbosacral plexus:** Formed by the *ventral primary rami of L1-S4*
- **Branches:**

1. Anterior division: *Tibial* and *obturator* nerves
2. Posterior division: *Gluteal, femoral* and *common peroneal* nerves

Femoral Triangle

- Located in the *upper anterior thigh*
- **Contents:** *Mediolaterally:* femoral vein, femoral artery, femoral nerve

- **Borders:** *Sartorius*, *adductor longus*, and *inguinal ligament*
- **Floor of the triangle:** *Adductor longus*, *iliopsoas*, and *pectineus* muscles

Knee Joint

- **Ligaments:**
 1. Anterior cruciate ligament (*ACL*): Can be injured in *knee hyperextension*, which allows the tibia to move anteriorly on exam (*anterior drawer sign*)
 2. Posterior cruciate ligament (*PCL*): The mirror image of the *ACL*
 3. Medial collateral ligament (*MCL*): Prevents *valgus stress* on the knee
 4. Lateral collateral ligament (*LCL*): Prevents *varus stress* on the knee
- **Menisci:** Medial (*C-shaped*) and lateral (*O-shaped*)
- **Popliteal fossa:** Contains an artery, vein, and two nerves: *Popliteal artery*, *popliteal vein*, *tibial*, and *common peroneal nerves*.
- **Note:** Foot joints are multiple; the most important of which are:
 1. *Talocalcaneal joint*: Responsible for *plantar-* and *dorsiflexion of the ankle*
 2. *Subtalar joint*: Responsible for *inversion* and *eversion of the foot*

Peripheral Vascular Disease (PVD)

- **Causes:** Atherosclerosis, smoking, thrombosis, embolism
- **Clinical picture:**
 1. Acute: 6 P's: pain, pallor, pulselessness, paralysis, poikilothermia, and paresthesia
 2. Chronic:
 - **Atrophic changes:** Thin skin with loss of hair and possible ulcers
 - **Intermittent claudications:** Muscle cramping on walking that *resolves at rest*. This occurs due to accumulation of metabolites due to ischemia, which stimulate the nerve endings.
 - **Rest pain:** It is *ischemic neuritis*. Patient presents with pain in the affected limb even at rest, and he would tend to keep that limb uncovered and hanging by the side of the bed while sleeping. *This is a sign of impending gangrene.*
- **On exam:** Ankle/brachial pressure index (ABI) lower than 0.9 (normal >1)

- **Location:** There are key sites to look for the effects of vascular compromise:

1. Aortoiliac: Cramping of *buttocks and thighs*, and *impotence (Leriche syndrome)*
2. Femoropopliteal: Cramping of the *calf muscles*
3. Popliteal: Cramping of the *lower leg and foot muscles*

- **Diagnosis:** *Digital subtraction angiography (DSA)* is the gold standard.

- **Complication:** Gangrene and amputation

- **Treatment:**

1. Treat the cause, e.g., stop smoking. Embolic cases should be managed within *6 hours* by embolectomy and anticoagulation, or else gangrene is a risk.
2. Medications: Antiplatelets and vasodilators, e.g., aspirin, cilostazol
3. Surgery: Angioplasty or bypass graft

Deep Venous Thrombosis (DVT)

- **Risk factors:**

1. *A previous DVT is the most important risk factor.*
2. Recent prolonged immobilization, e.g., long car ride, long flight, hospitalization, limb fracture
3. Medications, e.g., *oral contraceptive pills (OCPs)*
4. Hypercoagulable state, e.g., protein C or S deficiency, antiphospholipid antibody syndrome

- **Pathology:**

1. Virchow's triad: hypercoagulability, stasis, and endothelial damage
2. The blood clot is formed of fibrin and platelets.
3. Most common site is the *lower extremities*; however, it can occur anywhere.
4. Time frame: Around the *third to seventh day* after start of immobilization

- **Clinical picture:**

1. The affected limb is red, warm, tender and swollen.
2. **Homan's sign:** Pain in the calf on dorsiflexion of the foot in cases of DVT below the knee

- **Complications:**

1. Pulmonary embolism (PE): *DVT in the lower extremities is the most common source*. So keep that in mind when you see any patient with DVT in the USMLE with sudden respiratory distress. PE is discussed in Chapter 10, Pathophysiology.
2. Varicose veins, edema, and venous ulcer

- **Diagnosis:** Gold standard is *venography*. It is practical to use Doppler ultrasound.
- **Prevention:** All hospitalized patients get subcutaneous heparin or sequential compression devices on their calves during their hospital stay.
- **Treatment:** Heparin IV drip is the first step. Coumadin is then started and continued for 3 to 6 months, maintaining an international normalized ratio (INR) target of 2 to 3.
- **Notes:**
 1. Indications of inferior vena cava (IVC) filters, e.g., Greenfield filter:
 - Patients with DVT who have an absolute contraindication to anticoagulation, e.g., GI bleeding
 - Patients with DVT already on anticoagulation and yet keep throwing emboli into the lungs
 2. Thrombophlebitis migrans: *Superficial thrombophlebitis* that lasts for short periods and disappear spontaneously. This is usually a sign of malignancy (*Trousseau's sign*), so intensive screening for malignancy should be the next step for any patient with thrombophlebitis migrans.

Compartment Syndrome

- Surgical emergency; common after trauma, fracture, or severe infection
- **Clinical picture:** The affected compartment is red, warm, tender, and swollen.
- **On exam:** Severe compartmental pain on *passive extension* of the digits
- **Diagnosis:** Elevated pressure inside the compartment by manometry (>30 mm Hg)
- **Treatment:** Urgent fasciotomy
- **Notes:**
 1. Structures in anterior compartment of thigh are *femoral artery and nerve*.
 2. Structures in anterior compartment of leg are *anterior tibial artery and deep peroneal nerve*.

Femoral Neck Fracture

- **Risk factors:** *Elderly women with osteoporosis*
- **Clinical picture:** *Tender, abducted, externally rotated, and shortened leg*
- **Complication:** *Avascular necrosis of femoral head*
- **Treatment:** Open reduction and internal fixation (ORIF), *unless there is intracapsular fracture, which requires a hemiarthroplasty*.

Knee Injuries

- **Unhappy triad:** The most serious injury after a *lateral* knee injury, which injures three structures (*MAM*): Medial collateral ligament, Anterior cruciate ligament, and Medial meniscus
- **Quadriceps tear:** Suspected if you feel a groove above the knee after a knee injury
- **Anterior cruciate ligament (ACL) tear:** Patient hears a popping sound in his knee, usually during *jogging*. On exam: anterior displacement of tibia on femur with the knee flexed 20 degrees (*Lachman's test*)
- **Meniscus tear:** Patient develops painful swelling on either side of the knee, usually after *frequent crouching and standing movement, or after a sudden twist injury to the knee*. On exam: repeated flexion and extension of the knee with internal and external rotation of the ankle reveals *palpable and audible clicking sound* in the knee joint (*McMurray test*).
- **Note:** All knee injuries described above are managed medically with pain control and immobilization. *Only if condition is not improving, MRI of the knee is obtained.*

Osgood-Schlatter Disease

- **Mechanism:** Common in *soccer players*, due to *avascular necrosis of tibial tuberosity*
- **Clinical picture:** *Pain and swelling below the knee*
- **Note:** Tibial fractures typically do not heal well and there is a possibility of malunion due to the poor blood supply.

Miscellaneous Lower Limb Injuries

- **Slipped capital femoral epiphysis:** Common in *obese African-American adolescents*. **Clinical picture:** *Thigh and knee pain and limping*. **On exam:** Passive hip flexion is associated with an *external rotational* movement. **Diagnosis:** *Medioposterior* displacement of femoral head on *frog leg lateral* x-ray views of the hip. **Complication:** *Avascular necrosis* of femoral head. **Treatment:** Surgical fixation.
- **Ankle sprain:** Due to injury of the *anterior talofibular ligament*. No fracture is involved. **Treatment:** Ice packs and early mobilization.
- **Jones' fracture:** Occurs with *foot inversion*, where the *fifth metatarsal tuberosity* is avulsed
- **Pott's fracture:** Occurs with *foot eversion*, where the *medial malleolus* is avulsed
- **Lover fracture:** Occurs in patient falling from a height landing on his heels; fracture involves the *calcaneus, neck of femur, and lumbar vertebrae*

Nerve Injuries

- *Common peroneal nerve injury (L4-S2)*: Common in *upper fibular fractures*. Clinical picture: Decreased sensation on *lateral surface of leg and foot*, along with *loss of dorsiflexion and eversion of the foot*.
- *Tibial nerve injury (L4-S3)*: Loss of *plantar flexion of the foot*
- *Superior gluteal nerve injury (L4-S1)*: *Waddling gait*
- *Femoral nerve injury (L2-L4)*: Loss of *knee reflex*

Breast

Anatomy

- *Histology*: It is a *modified sweat gland*. It contains *15–20 lactiferous sinuses* opening into the nipple via ducts.
- *Extent*: The breast lies inside the fascia of the *pectoralis major* muscle. It extends from the *2nd rib superiorly to the 6th rib inferiorly*. It also extends *medially to the sternum*, and *laterally to the midaxillary line*. The breast tapers *laterally into an axillary tail*, which is a common site of malignancy.
- *Suspensory ligaments of Cooper*: Extend from the skin overlying the breast all the way into the *deep fascia*, as means of support. If infiltrated by malignancy, Cooper's ligaments contract, causing *dimpling of skin and inversion of the nipple*.

Arterial Supply

- *One artery medially*: *Internal thoracic artery*
- *One artery laterally*: *Lateral thoracic artery*
- *Few arteries in between*: *Intercostal arteries*

Venous and Lymph Drainage and Nerve Supply

- *Venous drainage*: Mainly through the *axillary vein*, and to a lesser extent the *internal thoracic*, *lateral thoracic*, and *intercostal veins*. *Note that the intercostal veins are the portal through which cancer cells from the breast get into the vertebral venous plexuses and end up in the brain*.
- *Lymph drainage*:
 1. Medial quadrants: *Parasternal lymph nodes*
 2. Lateral quadrants: *Axillary lymph nodes*
 3. Nipple and areola: *Subareolar lymph plexus*
- *Nerve supply*: *Intercostal nerves 2nd through 6th*

Aorta

- *Branches* (Fig. 1.3)
 1. Left subclavian artery (SCA)
 2. Left common carotid artery (CCA)
 3. Brachiocephalic trunk (Innominate artery): Gives right SCA and right CCA

Coarctation of the Aorta

- *Types*:
 1. Preductal: Proximal to left subclavian artery's origin; usually associated with patent ductus arteriosus (PDA)
 2. Postductal: *More common*, and is distal to left subclavian artery's origin
- *Pathology*: There is higher flow and pressure in the upper half of the body, and lower flow into the lower half. Blood takes a detour through the intercostal arteries to be able to reach the superior epigastric artery. This leads to dilated intercostal arteries and *rib notching mainly posteriorly*, which is *pathognomonic for this disease*.

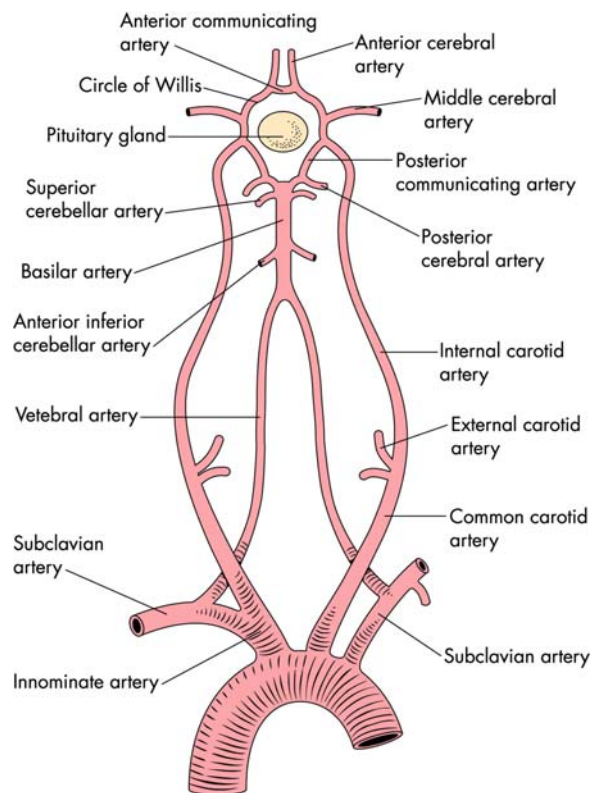


FIG. 1.3 Aortic arch and its branches

- *Clinical picture:*
 1. Significant difference between blood pressure readings of the *upper and lower* extremities
 2. Systolic murmur over the left third interscapular area, along with *machinery murmur over the collaterals*
 3. Bicuspid aortic valve: Common association causing *systolic murmur on apex*
- *Diagnosis:* Gold standard is *aortography, plus rib notching* on chest x-ray (CXR).
- *Treatment:* Surgical correction.
- *Note:* Always think about *coarctation in any case of Turner syndrome.*
- *On exam:* *Pulsatile abdominal mass*
- *Diagnosis:* *Aortography* or *ultrasound of the abdomen*
- *Treatment:*
 1. >5 cm in diameter (*6 cm in thoracic aneurysms*): Surgical
 2. <5 cm: Control blood pressure (BP) and other risk factors, and follow up by ultrasound *every 6 months*
- *Note:* True aneurysms are formed of intima, media, and adventitia, while false ones are formed only of adventitia.

Aortic Dissection

- *Clinical picture:*
 1. *Tearing chest pain radiating to the back* mainly in between the scapulae
 2. Significant difference between blood pressure readings of *left and right* upper extremities
- *Diagnosis:*
 1. CXR: *Wide mediastinum* is suggestive of aortic dissection.
 2. Diagnostic test of choice is:
 - Gold standard: *Aortography*
 - Nonemergency situations: *MRI of the chest*
 - Emergency situations: *Transesophageal echocardiogram*
 - Practically: *Spiral CT of the chest with contrast* is commonly used.
- *Treatment:*
 1. Ascending aortic dissection: Urgent surgical correction
 2. Descending aortic dissection: Medically by urgently lowering the blood pressure using beta-blockers. Avoid inotropic agents and vasodilators (e.g., nitroprusside) without beta-blockade, as this will worsen the dissection.

Aortic Aneurysm

- Aortic arch aneurysm can compress the trachea if it was huge and the pulsations could be felt at the sternal notch; however, most aortic aneurysms are below the level of renal arteries, and are secondary to *atherosclerosis* and *hypertension*. Below is the abdominal aortic aneurysms discussed in details.
- *Clinical picture:* Abdominal pain radiating to the back

Thoracic Outlet Syndrome

- *Mechanism:* Cervical rib compressing on two main structures: *subclavian artery* and *lower trunk of brachial plexus*
- *Clinical picture:*
 1. Decreased sensations along the *ulnar nerve* distribution
 2. *Atrophy of thenar, hypothenar, and interossei muscles*
- *On exam:* *Adson test:* If the patient turns his chin towards the side of the lesion while doing the Valsalva maneuver, the radial pulses in the affected hand *decrease in intensity*.
- *Diagnosis:* X-ray of chest and neck looking for the compressing object is needed.
- *Treatment:* Conservative by physical therapy and exercise. Surgery is reserved for complicated cases with severe compression signs.

Mediastinum, Ribs, and Diaphragm

- *Mediastinum:* See Table 1.2 for parts and contents.
- *Ribs:* *Intercostal vessels and nerve* run across the lower border of each rib, between the *internal and innermost intercostal muscles*.

TABLE 1.2 Mediastinal contents.

Superior mediastinum	Aortic arch, left subclavian artery, left common carotid artery, brachiocephalic artery and vein, esophagus and trachea
Anterior mediastinum	Thymus gland
Middle mediastinum	Heart, superior and inferior vena cava
Posterior mediastinum	Descending aorta, esophagus, azygos vein, sympathetic chain, and vagus nerve; <i>an artery, a vein, a tube, and two nerves</i>

- **Diaphragm:** It has a *central tendon* and *two domes*; each extends up to the level of the *fifth rib*. It is perforated at 12, 10, 8 = Artery, Tube, Vein (helpful to remember: “A TV”):
 1. T8 level: *IVC*
 2. T10 level: *Esophagus*
 3. T12 level: *Aorta* and *thoracic duct*

Lungs

Tracheobronchial Tree

- **Trachea:** It is formed of *15–20 hyaline cartilage rings*, the last of which forms the *carina*. The trachea starts at the level of the *cricoid cartilage (C6)*, and bifurcates at the level of the *sternal angle (T4)* into right and left main bronchi.
- **Bronchial system:** Right main bronchus is *shorter, larger* in diameter, and *more in line* with the trachea, hence it is *more common to aspirate into the right lung*.
- **Note:** If you face a case in the USMLE hinting at the carina being shifted from its normal position, think one of two things: *lung cancer* or *an enlarged left atrium*.

Lungs and Pleura

- **Lungs:** Right lung has three lobes, while the left lung has only two lobes. Note that each lobe receives its own bronchus.
- **Fissures:**
 1. Left lung: Oblique fissure separating upper and middle lobes
 2. Right lung: Horizontal fissure (separating upper and middle lobes), and oblique fissure (separating middle and lower lobes)
 3. Oblique fissure surface markings: *T3 spine* posteriorly to *sixth costochondral junction* anteriorly
 4. Horizontal fissure surface markings: *Right fourth costal cartilage* anteriorly, until it meets the oblique fissure at *right mid-axillary line*.
- **Pleura:** The pleural sac is divided into a visceral layer encasing the lungs, and a parietal layer lining the chest wall. Only the parietal pleura has sensory nerve supply, hence *pleurisy (chest pain on deep inspiration)*.

Blood Supply and Lymph Drainage

- **Arterial supply:** Pulmonary and bronchial arteries
- **Venous drainage:** Pulmonary and bronchial veins
- **Lymph drainage:** Hilar and mediastinal lymph nodes

Heart

- **Pericardium:** Surrounds the heart, and is formed of three layers: visceral, parietal, and fibrous pericardium. Note that the *phrenic nerve* and *pericardiaco-phrenic artery* pass through the *fibrous layer*.
- **Surfaces of the heart:**
 1. Anterior: *Right ventricle*
 2. Posterior: *Left atrium*
 3. Inferior: *Left ventricle*
- **Borders of the heart:**
 1. Left: *Left atrium and ventricle* and *aorta*
 2. Right: *Superior vena cava (SVC)* and *right atrium*
 3. Superior: *Aortic arch* and *pulmonary trunk*
 4. Inferior: *Right ventricle*
- **Arterial supply:**
 1. Left coronary artery, which gives off the following branches:
 - *Left anterior descending* artery: Supplies anterior wall of left ventricle
 - *Circumflex* artery: Supplies lateral and posterior walls of left ventricle
 2. Right coronary artery: Supplies everything else, including *sinoatrial (SA)* and *atrioventricular (AV)* nodes
- **Venous drainage:**
 1. Great, middle, and small cardiac veins: Drain into the *coronary sinus*. Note that the *middle cardiac vein* runs in the *posterior interventricular sulcus*.
 2. Anterior cardiac veins from right ventricle: Drain *inside right atrium*
- **Nerve supply:**
 1. Parasympathetic: *Nucleus ambiguus* and *dorsal nucleus of vagus nerve*
 2. Sympathetic: *Intermediolateral column of spinal cord*
- **Valves:** All valves are formed of *three cusps*, except *mitral*, which has *only two cusps*. Cusps are connected into papillary muscles of ventricles via *chordae tendineae*.
 1. Best site to listen to aortic valve: *Right second intercostal space*
 2. Best site to listen to pulmonary valve: *Left second intercostal space*
 3. Best site to listen to tricuspid valve: *Left lower sternal border*
 4. Best site to listen to mitral valve: *Left fifth mid-clavicular line*

- **Conduction system:**
 1. SA node (pacemaker): Located at junction of SVC with *right atrium*
 2. AV node: Located just right to the interatrial septum
 3. Bundle of Hiss: It runs in the interventricular septum, and gives off right bundle (to right ventricle) and left bundle (to left ventricle). Both bundles end up inside the ventricular wall as *Purkinje fibers*.

Abdomen

Abdominal Wall

- **Quadrants:** The abdomen is divided anatomically into *nine quadrants* by means of two vertical *mid-clavicular lines* and two transverse lines: *subcostal* and *transtubercular*.
- **Layers of abdominal wall:**
 1. *Centrally:* Skin, fascia of Camper and Scarpa, linea Alba, fascia transversalis, fat, and peritoneum
 2. *Peripherally:* Exactly the same; the only difference here is *external and internal oblique and transversus abdominis muscles*, which replace the linea Alba.
- **Abdominal wall's vs. scrotum's layers:** A common question on the USMLE is about the abdominal layers as they continue into the scrotum, and they are:
 1. Skin: Continues as *skin*
 2. Fascia of Camper and Scarpa: Continues as *Colles' fascia* and *Dartos muscle*
 3. External oblique muscle: Continues as *external spermatic fascia*
 4. Internal oblique muscle: Continues as *cremasteric muscle and fascia*
 5. Transversus abdominis muscle: *Does not continue into the scrotum*
 6. Fascia transversalis: Continues as *internal spermatic fascia*
 7. Fat: Continues as *fat*
 8. Peritoneum: Continues as *Tunica vaginalis*
- **Inguinal ligament:** The lower border of the *external oblique* muscle thickens to form the *inguinal ligament*, which extends from the *anterior superior iliac spine* into the *pubic tubercle*.
- **Inguinal canal:** It carries the *spermatic cord* in males, and *round ligament of uterus* in females, and it extends between two rings:
 1. Deep ring: Lies in *fascia transversalis*, just *lateral to inferior epigastric artery*
 2. Superficial ring: Lies in *external oblique muscle*, just *lateral to pubic tubercle*

Hernia

- **Predisposing factors:** *Chronic* straining increasing intraabdominal pressure, e.g., heavy lifting, chronic cough
- **Clinical picture:** Swelling that gives *expansile impulse on cough* and is *reducible by lying down*
- **Complications:**
 1. Strangulation: A hernia emergency that occurs due to interruption of the blood supply to the herniated intestinal loop. Patient presents with a once-reducible hernia that now is *red, warm, tender, tense, irreducible, and does not give impulse on cough*.
 2. Incarceration: Trapping of the herniated intestine inside the hernial sac. On exam: Failure to reduce the herniated intestine. It is a common cause of strangulation. Treatment: Muscle relaxants, placement in Trendelenburg position, and urgent surgical intervention.
 3. Infection or obstruction
- **Treatment:** Surgical repair. It usually involves reduction of the herniated intestinal segment and covering the defect with a mesh. In surgical repair of inguinal hernia, it is common to injure the *iliohypogastric nerve*, which supplies the abdominal wall, and the *ilioinguinal nerve*, which supplies the testicles, penis, and medial thighs.
- **Inguinal hernia:**
 1. Oblique: Descends into the scrotum, *lateral to inferior epigastric artery* with *positive internal ring test* on exam. Note: Intestine passes through *both superficial and deep inguinal rings*.
 2. Direct: Intestine passes through *superficial inguinal ring* into *Hesselbach triangle*. This triangle is bounded by a *lateral border of rectus abdominis medially, inferior epigastric artery laterally, and inguinal ligament inferiorly*.
- **Femoral hernia:** Common in *females*, where intestine passes down the femoral ring and canal. Hernia is *below and lateral to the pubic tubercle* that could be reduced *downward and medially*. Strangulation is common, mainly due to *proximity to lacunar ligament* and to a lesser extent due to the *narrow neck* of hernial sac.
- **Umbilical hernia:**
 1. Congenital (*omphalocele*): Due to *failure of the midgut to return into the abdomen*. Treatment: Excision of the sac.
 2. Adults: Due to *defect in the linea Alba or divarication of recti*.
- **Incisional hernia:** Hernia at the site of an incision, mostly due to dehiscence of wound layers. The first sign of abdominal wound dehiscence is *serosanguinous discharge* from the wound.

Peritoneum

- It is arranged into two major sacs and two major omenta.
- *The greater sac*: Forms the *paracolic gutters*, which are connected to subphrenic recess, rectovesical, and rectovaginal pouches
- *The lesser sac*: Created by the embryologic 90-degree rotation of the *stomach*, and is bounded by:
 1. Anterior: Stomach
 2. Posterior: Diaphragm
 3. Left: Gastrosplenic ligament
 4. Right: Liver
- *Foramen of Winslow*: Connects lesser and greater sacs, and is bounded by two veins: *portal vein anteriorly* and *IVC posteriorly*.
- *The greater omentum*: It is the provider and protector of the abdomen (“policeman of the abdomen”), surrounding inflammation sites to limit spread.
- *The lesser omentum*: Extends from the *lesser curvature of the stomach* to the *porta hepatis* in the form of *gastroduodenal* and *gastrohepatic ligaments*. Free border of the lesser omentum contains the *portal triad*:
 1. Portal vein: Posteriorly.
 2. Common bile duct: Anteriorly to the *right*
 3. Hepatic artery: Anteriorly to the *left*
- *Retroperitoneal organs*:
 1. Second, third, and fourth parts of the duodenum and what they bound in between, i.e., head, neck, and body of pancreas
 2. Kidneys and its neighbors, i.e., adrenal glands and ureters
 3. Colon segments: Ascending, descending, and rectum
 4. Two big vessels: Aorta and IVC

Blood Supply of Abdomen

- *Aorta*: It gives off the following unforgettable branches:
 1. T12: *Celiac trunk* to supply the *foregut* (from esophagus down to the ampulla of Vater, including liver, gallbladder, and pancreas)
 2. L1: *Superior mesenteric artery (SMA)* to supply the *midgut* (from ampulla of Vater all the way to the end of the proximal two thirds of the transverse colon)
 3. L3: *Inferior mesenteric artery (IMA)* to supply the *hindgut* (Rest of colon)
- *IVC*: It starts at *L5* by the fusion of two common iliac veins, and it drains all venous return from the abdomen into the *right atrium*.

- *Helping veins*:
 1. One on the right side of the body: *Azygos vein*, which branches off from the *IVC* and drains into *SVC*
 2. One on the left side: *Hemiazygos vein*, which branches off from the *left renal vein* and drains into the *azygos vein*
- *Portal vein*: Forms behind the neck of pancreas by fusion of the *splenic* and *superior mesenteric veins*. Note that the inferior mesenteric vein ends in the splenic vein before the portal vein is created.

Esophagus

- It pierces the diaphragm at *T10 level* (remember “A TV”).
- *Sphincters*: Two sphincters: Upper one is *skeletal*, while lower one is *smooth muscle*.
- *Constrictions*: Three constrictions:
 1. High: At *pharyngoesophageal junction* by *crico-pharyngeus muscle*
 2. Midway: Compressed by *aortic arch* and *left main bronchus*
 3. Low: At *diaphragm hiatus*
- *Histology*: Esophagus is not surrounded by serosa, so malignancy spreads easily to thorax.
- *Arterial supply*:
 1. Cervical portion: *Inferior thyroid arteries*
 2. Thoracic portion: *Esophageal branches of aorta*
 3. Abdominal portion: Left gastric; branch of celiac artery
- *Venous drainage*: *Azygous*, *hemiazygous*, and *gastric veins*
- *Nerve supply*: *Vagus nerve trunks* and *sympathetic chains*

Stomach

- *Parts*: Cardia, fundus, body, and antrum. The antrum extends from the *incisura angularis* to the pylorus.
- *Arterial supply*:
 1. Lesser curvature: *Right and left gastric arteries*
 2. Greater curvature: *Right and left gastroepiploic arteries*
 3. Fundus and body: *Short gastric and posterior gastric arteries*
 4. Distal stomach: *Common hepatic artery*
- *Venous drainage*: All branches drain to *portal vein*

- *Lymph drainage: Gastric and pancreaticoduodenal lymph nodes.* Note that gastric cancer is notorious for metastasizing to the left supraclavicular lymph node (Virchow lymph node).
- *Nerve supply:*
 1. Vagus nerves: *Left vagus forms anterior trunk and right forms posterior trunk.*
 2. Sympathetic: *Greater splanchnic nerve*
- *Ileal resection or disease: Leads to B₁₂ deficiency and oxalate stones.*
- *Arterial supply: Branches of SMA. Remember, it is midgut.*
- *Venous drainage: Superior mesenteric vein (SMV), which joins the splenic vein to form the portal vein*
- *Nerve supply: Vagus and splanchnic nerves*
- *Lymph drainage: Superior mesenteric and ileocolic lymph nodes*

Duodenum

- *Parts: C-shaped structure divided into four parts:*
 1. First part: Duodenal bulb; a common site of duodenal ulcer. Related posteriorly to *gastro-duodenal artery and tuber omental of pancreas*, so posterior wall ulcer can cause pancreatitis, and might cause fatal bleeding on perforation. This part of duodenum is marked intraoperatively by the *prepyloric vein of Mayo*.
 2. Second: *Ampulla of Vater* opens into its *posteromedial wall*.
 3. Third: Squeezed between the *aorta and IVC* posteriorly and *SMA* anteriorly
 4. Fourth: Its fusion with the jejunum is supported by *ligament of Treitz*, which represents the *cranial end of the dorsal mesentery*. Note: GI bleeding proximal to ligament of Treitz causes *melena (black soft tarry stool)*, while bleeding distal to the ligament causes *bright red bleeding per rectum*.
- *Arterial supply:*
 1. Proximal to ampulla of Vater (*foregut*): Branches of *celiac artery*; namely *gastroduodenal and superior pancreaticoduodenal*
 2. Distal to ampulla of Vater (*midgut*): Branch of *SMA*; namely *inferior pancreaticoduodenal artery*
- *Venous drainage: Small veins, which all drain into portal vein*
- *Nerve supply: Vagus nerve (parasympathetic), and splanchnic nerves (sympathetic)*
- *Lymph drainage: Pancreaticoduodenal lymph nodes*

Jejunum and Ileum

- Main site of absorption *thanks to the extensive villous system and the long blood vessels*; however, the ileum remains essential for absorption.
- Vitamin B₁₂ gets absorbed at the *terminal ileum*.

Colon

- It is the part of large intestine that *absorbs water and forms stool*.
- *Parts:*
 1. Cecum and ascending colon: Arterial: *Ileocolic and right colic branches of superior mesenteric artery (SMA)*; venous: *SMV*.
 2. Transverse colon: Proximal two thirds are a part of the midgut, so it gets its blood supply from the *SMA* through the *middle colic branch*. Venous: *SMV*.
 3. Descending colon: Along with the distal one third of transverse colon are parts of *hindgut*. Arterial: *Left colic branch of IMA*. Venous: *IMV*.
 4. Sigmoid colon: Being part of the hindgut, its arterial supply is still the *IMA* through *sigmoid branches*. Venous: *IMV*. *Remember, the IMV ends in the splenic vein before the portal vein is formed.*

Rectum

- *Extent: From S3 down to the tip of the coccyx, where the puborectalis muscle forms a U-shaped sling around it forming the perineal flexure*
- *Lumen: The rectum contains three transverse folds of Houston in the lumen. Folds are formed of mucosa, submucosa and an inner circular muscle layer.*
- *Arterial supply (hindgut): IMA; through superior rectal branches*
- *Venous drainage: IMV*
- *Notes:*
 1. *Ampulla of the rectum is where the stools are stored.*
 2. When the defecation reflex is stimulated (*splanchnic nerves S2-S4*), the wall contracts and sphincters relax. *Note that the external anal sphincter is under somatic control.*

Anal Canal (Table 1.3)

TABLE 1.3 Anal canal.

	Upper anal canal	Lower anal canal
Embryologic origin	Endoderm	Ectoderm
Extent	From perineal flexure down to dentate line	From the dentate line down to the anal verge
Arterial supply	IMA	Inferior rectal branches of the internal pudendal artery
Venous drainage	IMV	Inferior rectal branches of IVC
Notes	<ul style="list-style-type: none"> The mucosa is arranged in columns ("columns of Morgagni"); lower ends of these columns form the dentate (Pectinate) line Anal glands open via their valved ducts into dentate line 	Digital rectal exam (DRE) is now recommended annually for all patients 40 years of age and older for: <ul style="list-style-type: none"> Early detection of anal and prostate tumors Fecal occult blood testing (FOBT): if positive, colonoscopy is the next step

IMA, inferior mesenteric artery; IMV, inferior mesenteric vein; IVC, inferior vena cava.

Liver

- **Lobes:** two lobes; the left one contains two important ligaments:
 1. Falciform ligament: Part of the *ventral mesentery*
 2. Ligamentum teres: A remnant of the *umbilical vein*
- **Arterial supply:** *Portal vein*, and to a lesser extent the *hepatic artery* (branch of the celiac artery)
- **Venous drainage:** Hepatic veins, draining into the *IVC*
- **Note:** Hepatic veins in the liver, just like pulmonary veins in the lungs, are used as landmarks for segments during segmental resection surgeries.

Gallbladder

- **Parts:** Fundus, body, neck, and cystic duct
- **Cystic duct:** It contains endoluminal ridges (spiral valves of Heister) to *keep the duct open and to prevent reflux*. Cystic duct joins the common hepatic

duct to form the common bile duct (CBD), which in turn joins the main pancreatic duct and opens into the second part of the duodenum, via the *ampulla of Vater*.

- **Function:** *Stores and processes bile formed by the liver*
- **Arterial supply:** *Cystic branch of the right hepatic artery*
- **Venous drainage:** *Cystic vein*, which drains into the *portal vein*
- **Nerve supply:** Vagus and greater splanchnic nerves

Pancreas

- **Parts:** Head, neck, body, tail, and uncinuate process. The head of the pancreas overlies the *IVC* and *right renal vessels*.
- **Histology:** Pancreatic acinar cells contain *zymogen granules*.
- **Arterial supply:**
 1. Head: *Superior and inferior pancreaticoduodenal arteries*
 2. Neck, body, tail, and uncinuate process: *Pancreatic branches of the splenic artery*
- **Venous drainage:** *Pancreatic veins*, which then drain into the *splenic vein*
- **Lymph drainage:** *Pancreaticosplenic lymph nodes*
- **Nerve supply:** Vagus and greater splanchnic nerves

Spleen

- Located in the left upper quadrant (LUQ) underneath the *9th, 10th, and 11th ribs*
- **Functions:**
 1. Strong immunologic filter: Due to its rich lymphocytic content
 2. Blood reservoir: Spleen can store large amounts of blood.
 3. Scavenger for the remnants of red blood cells (RBCs): The presence of *Howell-Jolly bodies* in the peripheral blood indicates that the spleen is *absent or nonfunctioning*.
- **Support:**
 1. Connected to the stomach via the *gastrosplenic ligament*, through which the *short gastric* and *left gastroepiploic* vessels run
 2. Connected to the left kidney via *splenorenal ligament*, through which the *splenic vessels* and *tail of pancreas* run

- *Arterial supply* (Foregut): Splenic branch of celiac artery
- *Venous drainage*: *Splenic vein*, which joins the *SMV* to form the *portal vein*
- *Lymph drainage*: *Pancreaticosplenic lymph nodes*

Pelvis and Perineum

Anatomy

- *Pelvic inlet*: Outlined by the *promontory of sacrum posteriorly* and the *linea terminalis anterolaterally*
- *Pelvic outlet*: Outlined by the *coccyx posteriorly*, *ischial tuberosities laterally*, and *symphysis pubis anteriorly*
- *Greater and lesser sciatic foramina*: They are bounded by *sacrospinous* and *sacrotuberous* ligaments.
- *Greater sciatic foramen*: The following structures pass through the greater sciatic foramen (just remember the word *Sippin'* or the acronym *SSIIPPN*):
 1. Superior gluteal vessels and nerve
 2. Inferior gluteal vessels and nerve
 3. Internal pudendal vessels and nerve
 4. Piriformis muscle: This muscle divides the greater sciatic foramen into *two*.
 5. Three nerves: Sciatic nerve, Posterior cutaneous nerve of the thigh, and Nerve to obturator internus
- *Lesser sciatic foramen*: The following structures pass through the lesser sciatic foramen: *internal pudendal vessels and nerve*.
- *Pudendal block*: Can be done transvaginally by injecting the anesthetic *around the ischial spine*, aiming at the pudendal nerve
- *Geometry of the pelvis*:
 1. True conjugate line: Extends from the promontory of sacrum to upper border of symphysis pubis
 2. Diagonal conjugate line: From promontory of sacrum to lower border of symphysis pubis. *It is the best diameter to assess pelvic capacity.*
 3. Transverse diameter: Extends horizontally between ischial tuberosities
 4. Interspinous diameter: Extends horizontally between ischial spines
 5. Posterior sagittal diameter: The narrowest pelvic diameter; less than 10 cm
- *Perineum*: It is formed mainly of two triangles, *urogenital* and *anal*. It also contains two important spaces:
 1. Deep perineal space: Lies between the superior and inferior fascia of urogenital diaphragm. *Contents*: Urogenital diaphragm (*external*

urethral sphincter and *transverse perineal muscles*), pudendal vessels and nerve, and urethra (membranous part in males, and the entire urethra in females)

2. Superficial perineal space: Lies between the inferior fascia of urogenital diaphragm and superficial perineal fascia. *Contents*: All other perineal structures

Kidneys

- *Anatomy*:
 1. A retroperitoneal, double-capsulated organ that extends between *T12 and L3 on the left*, and *L1 and L4 on the right* (due to presence of the liver)
 2. Kidneys overlie the *quadratus lumborum* muscle on either side.
 3. The kidney is surrounded by a *perirenal space*, which contains the *adrenal gland, ureter, fat, and the gonadal vessels*.
 4. At the renal hilum: Vessels are arranged as anteroposteriorly, i.e., renal vein, renal artery, and finally the renal pelvis (VAP)
 - *Function*: *Filtration* of the blood; discussed further in Chapter 10, pathophysiology
 - *Histology*: The kidney is formed of two zones:
 1. Cortex: Contains *columns of Bertin*
 2. Medulla: Contains five to 10 *pyramids of Malpighi*; these join into five to 10 minor calyces, which further join into two to three major calyces and open into the renal pelvis
 - *Arterial supply*: *Renal branches of the aorta*, which divide into *segmental arteries* inside the medulla. Segmental arteries further divide into *interlobar* branches, which all join together to form the *arcuate artery* at the *corticomedullary junction*. From the arcuate artery originates the *interlobular* arteries supplying the cortex.
 - *Venous drainage*: *Renal veins*, which drain into *IVC*
 - *Lymphatic drainage*: *Lumbar* and *common iliac lymph nodes*
- ## Ureter
- It is a muscular tube for transporting urine.
 - *Anatomy*: Starts at the ureteropelvic junction and descends along the *psoas muscle*. It then crosses over the *common iliac vessels* and opens into the urinary bladder as one of the heads of the *trigone*.

Along its route, it crosses *underneath* one structure in each gender:

1. Males: *Vas deferens*
 2. Females: *Uterine artery*
- **Constrictions:** The ureter has three constrictions along its course, at which stones are more likely to cause obstruction:
 1. High: Junction with the renal pelvis
 2. Midway: While entering the pelvis
 3. Low: Junction with the urinary bladder
 - **Arterial supply:** Ureteric branches of the *renal and gonadal arteries*
 - **Venous drainage:** Ureteric veins, which drain to *renal and gonadal veins*
 - **Lymph drainage:**
 1. Abdominal portion: Just like the kidney
 2. Pelvic portion: *Internal iliac lymph nodes*
 - **Note:** In a female patient presenting with unexplained right hydronephrosis, suspect right *ovarian vein thrombosis* compressing the right ureter.

2. Anterior surface: Faces the symphysis pubis
3. Superior surface: Covered by *peritoneum in males* and by *uterus in females*
4. Neck: Related to *the prostate in males*, and the *urogenital diaphragm in females*
5. Apex: Related to three structures:
 - *Median umbilical ligament (Urachus):* Remnant of *allantois*
 - Two *medial umbilical ligaments:* Remnants of the *right and left umbilical arteries*.
 - Two *lateral umbilical ligaments:* Created by the *right and left inferior epigastric vessels*
- **Arterial supply:** Vesical branches of the *internal iliac artery*
- **Venous drainage:** Vesical venous plexus, which drains into the *internal iliac vein*
- **Lymph drainage:** External and internal iliac lymph nodes
- **Nerve supply:** Sympathetic (hypogastric nerve [T10-L2]), parasympathetic (pelvic nerve [S2, S3, S4]), and somatic (pudendal nerve)
- **Note:** Most common cause of vesicoureteric reflux in children is *incomplete development of the intramural part of the ureter*.

Urinary Bladder

- It starts as an abdominal organ in children, descending into the pelvis by *age 6*.
- **Parts:**
 1. Base: It is the posterior surface, which is adjacent to the *vagina in females*, and to the *rectum in males*.

Urinary Incontinence

- It is a pathologic process, *even in the elderly*.
- **Next best step:** The first thing to order in a patient with urinary incontinence is *urine analysis* to rule out infection.
- **Types:** See Table 1.4.

TABLE 1.4 Types of urinary incontinence.

	Urge incontinence	Stress incontinence	Overflow incontinence
Cause	Detrusor muscle overactivity	Defect in the outlet, whether a sphincter problem or hypermobile bladder neck	Obstruction, e.g., benign prostatic hypertrophy, or anticholinergic medication overuse
Clinical picture	Urge to urinate followed by incontinence before the patient can make it to the toilet; it usually <i>follows</i> increased intraabdominal pressure, but <i>does not coincide with it</i>	Incontinence that <i>coincides</i> with any increase in intraabdominal pressure, e.g., coughing or laughing	The normal urge to urinate is lost, and small amounts of urine leak continuously
Treatment	<ul style="list-style-type: none"> • Frequent scheduled voiding • Antimuscarinic medications, e.g., Oxybutynin or imipramine 	<ul style="list-style-type: none"> • Pelvic floor exercises and topical steroids into the external urethral meatus • Alpha-blockers, e.g., phentolamine. 	Identify and correct the underlying cause
Notes	<ul style="list-style-type: none"> • It is the <i>most common</i> form of incontinence • Always ask about history of sexual abuse in these patients 	Flow rate, residual volume and bladder compliance are all <i>within normal limits</i>	It is more common among <i>elderly men</i>

TABLE 1.5 Neurogenic bladder.

	Spastic neurogenic bladder	Atonic neurogenic bladder
Lesion	Upper motor neuron lesion	Lower motor neuron lesion
Bladder wall	Thick	Thin and dilated
Detrusor muscle	Hyperreflexia	Hyporeflexia
Symptoms	Urinary frequency and urgency	Overflow incontinence
Treatment	Antimuscarinic medications, and urinary catheterization	Treat the cause, and urinary catheterization

- *Neurogenic bladder*: See Table 1.5.
- *Note: Urethral diverticulum*: More common in females. *Clinical picture (DDD triad)*: Dysuria, urine Dribbling, and Dyspareunia

Male Urethra

- It is 15–20 cm long.
- *Parts*:
 1. Prostatic urethra (2–3 cm): Ejaculatory ducts open into the posterior wall forming the *urethral crest* in the midline. Prostatic ducts open on either side of the crest.
 2. Membranous urethra (1–2 cm): *This is the narrowest part*. It crosses the urogenital diaphragm, and is surrounded by the *external urethral sphincter*.
 3. Penile urethra (~15 cm): Runs inside the *corpus spongiosum*, dilates into *fossa navicularis*, then narrows again and opens as the *external urethral meatus*. *Bulbourethral glands open into the proximal portion of this part*.
- *Arterial supply*:
 1. Prostatic urethra: Prostatic branches of *inferior vesical artery*
 2. Membranous and penile urethra: *Dorsal artery of penis*
- *Venous drainage*:
 1. Prostatic urethra: *Prostatic venous plexus*
 2. Membranous and penile urethra: *Penile veins*

Female Urethra

- It is only 4 cm long.
- *Anatomy*: Starts at the internal urethral meatus at the neck of urinary bladder, crosses the urogenital

diaphragm, and then opens just anterior to the vaginal introitus *between the labia minora*

- *Arterial supply*: *Internal pudendal and vaginal arteries*
- *Venous drainage*: *Internal pudendal and vaginal veins*
- *Notes*:
 1. The female urethra is not completely surrounded by the external sphincter, which is why stress incontinence is more common in females.
 2. Micturition reflex is just like the defecation reflex discussed earlier, mediated by *splanchnic nerves S2-S4*.

Bladder and Urethral Trauma

- *Anatomical key*:
 1. Superior surface of bladder: Urine leaks *inside* the peritoneum.
 2. Anterior surface of bladder or urethra above urogenital diaphragm: Urine leaks into the *retropubic space of Retzius* (extraperitoneal space).
 3. Urethra below the urogenital diaphragm: Common in *straddle injury*. Urine accumulates in the *superficial perineal space*, which is bound by *Colles' fascia* and *external spermatic fascia*.
 4. Penile urethra: Urine leaks extraperitoneally underneath the *fascia of Buck*.
- *Kidney rupture*: After major trauma. Patient presents with severe flank pain and hematuria. Diagnosis: Order a computed tomography (CT) of the abdomen and pelvis. Treatment: Surgical repair after resuscitation.
- *Urinary bladder rupture*: Patient presents with *strong persistent desire to urinate, but when he does, only a few drops of bloody urine are voided*. On exam: Prostate is *not* dislocated. Diagnosis: Ascending cystography: *Teardrop sign*. Treatment: Surgical closure of bladder. Note: Intraperitoneal rupture will show on abdominal x-ray as *ground-glass appearance*.
- *Membranous urethra rupture*: Patient presents with same symptoms as rupture of the bladder, above, but the prostate here is *dislocated and floating* inside the pelvis. Treatment: Suprapubic cystostomy followed by surgical urethral closure.
- *Penile urethra rupture*: Common in *straddle injury*, e.g., jumping over a fence or a horse. Clinical picture: *Penile and scrotal swelling, and blood at the external urethral meatus*. Treatment is similar to that of membranous urethral rupture.

Suprarenal (Adrenal) Glands

- One pyramidal gland above each kidney, *but not attached to it*.
- *Histology*: Each gland has a cortex and medulla. The medulla synthesizes catecholamines, i.e., epinephrine, and norepinephrine, while the cortex is formed of three zones arranged from outside in as follows:
 1. Zona glomerulosa: Synthesizes mineralocorticoids, i.e., aldosterone
 2. Zona fasciculata: Synthesizes glucocorticoids, i.e., cortisol
 3. Zone reticularis: Synthesizes sex hormones, mainly dehydroepiandrosterone (DHEA)
- *Arterial supply* (from bottom to top; “RAP”):
 1. Superior suprarenal: Branch of *Inferior Phrenic artery*
 2. Middle suprarenal: Branch of *Aorta*
 3. Inferior suprarenal: Branch of *Renal artery*
- *Venous drainage*:
 1. Right gland: Right suprarenal vein drains into the *IVC*.
 2. Left gland: Left suprarenal vein drains into the *left renal vein*.

Ovary (Fig. 1.4)

- *Anatomy*: Almond-shaped and sized. It is located *posterior to the broad ligament*, and is attached to the lateral

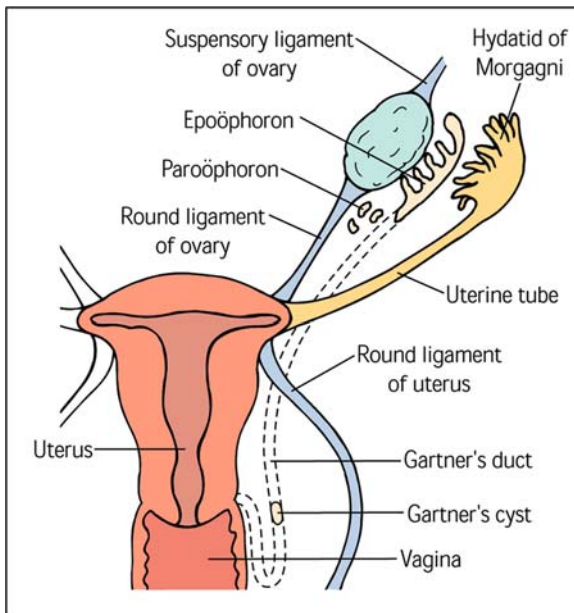


FIG. 1.4 Female genital duct system

pelvic wall by the *suspensory ligament of the ovary*. This ligament carries the ovarian vessels and nerve.

- *Arterial supply*: Ovarian branch of the *aorta*
- *Venous drainage*: Similar to suprarenal glands
- *Lymph drainage*: *Lumbar lymph nodes*

Fallopian Tubes (Fig. 1.4)

- *Parts*: Infundibulum, ampulla, isthmus, and intrauterine parts. The *ampulla* is where *fertilization* takes place, and it is the most common location of *ectopic pregnancies*.
- *Blood supply and lymph drainage*: Similar to ovaries.

Uterus (Fig. 1.4)

- *Parts*: Cornu, fundus, body, isthmus, and cervical parts. The *isthmus* is the *narrowest part of the body*, and it separates the body from the cervix. The isthmus is the preferred site for incision in a C-section.
- *Supporting ligaments of uterus*:
 1. Urogenital diaphragm: Formed by *external urethral sphincter* and *transverse perineal muscles*
 2. Pelvic diaphragm: Formed by the *levator ani* and *coccygeus* muscles
 3. Round ligament of uterus: A remnant of the *gubernaculum*
 4. Transverse cervical ligaments of Mackenrodt: Contain the *uterine arteries*
 5. Uterosacral ligaments: Maintain *anteversion of the uterus*.
 6. Broad ligament of the uterus: Contents (acronym “FOUR O”):
 - Fallopian tubes and ureters
 - Ovarian vessels and nerves
 - Uterine vessels and nerves
 - Remnants of mesonephros: epoöphoron, paroöphoron, and Gartner’s duct
 - Ovarian and round ligaments of the uterus
- *Arterial supply*: Uterine branches of the *internal iliac artery*
- *Venous drainage*: Uterine veins, which drain into the *internal iliac veins*
- *Lymph drainage*:
 1. Cornus: *Superficial inguinal lymph nodes*
 2. Fundus and upper body: *Lumbar lymph nodes*
 3. Lower body: *External iliac lymph nodes*
 4. Cervix: *Obturator and internal iliac lymph nodes*
- *Note*: The clitoris is formed by *fusion of the vestibular bulbs*, and, just like the penis, is formed of two corpora cavernosa; however, it does not have a corpus spongiosum.

Testes (Fig. 1.5)

- Each testicle is surrounded by two layers: the *inner tunica albuginea* and the *outer tunica vaginalis*. Note that *tunica vaginalis does not cover the posterior surface of testicles*
- **Arterial supply:**
 1. Testicular artery (*main supply*): Branch of *abdominal aorta*
 2. Cremasteric artery: Branch of the *inferior epigastric artery*
 3. External pudendal artery: Branch of the *femoral artery*
 4. Artery of vas: Branch of the *internal iliac artery*
- **Venous drainage:** *Pampiniform venous plexus*; around the *testicular artery*
- **Lymph drainage:** *Deep lumbar* and *para-aortic* lymph nodes.

Epididymis and Vas Deferens (Fig. 1.5)

- *Epididymis*: Head, body, and tail. The head and body are where the sperm maturation process takes place as it is where the sperms are stored.

- *Vas deferens*: A transportation tube that starts at the inferior pole of each testicle. It runs through the spermatic cord and joins the *seminal vesicle* to form the *ejaculatory duct*. Remember, ejaculatory ducts open into the urethral crest of prostatic urethra.

Prostate (Fig. 1.5)

- A gland that secretes a fluid rich in *prostaglandins* and *citric acid* to liquefy semen; hence facilitate ovum penetration by sperm.
- **Parts:** *Five lobes*, which contain deposits known as *corpora amylacea*
- **Arterial supply:** Inferior vesical branches of *internal iliac artery*
- **Venous drainage:** Prostatic venous plexus, which drains into the *IVC*. Remember, *this plexus is connected to the vertebral venous plexus*.
- **Notes:**
 1. Benign prostatic hypertrophy (BPH) targets prostate's *periurethral zones*.
 2. Prostate cancer targets prostate's *posterior lobes*.
 3. *Seminal fluid is only for sperm nutrition*, so it is very rich in *fructose* and *choline*.

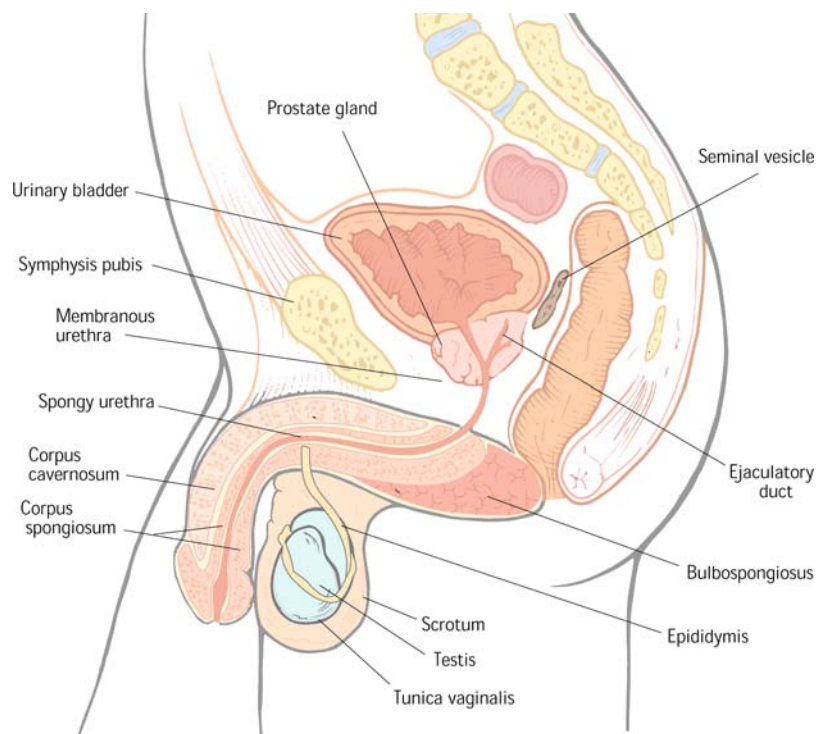


FIG. 1.5 Male genital system

Penis (Fig. 1.5)

- *Structure:*
 1. Two corpora cavernosa, whose roots are called *crurae*
 2. Corpus spongiosum, which contains the urethra. Its root is called the *bulb*.
- *Arterial supply:* Deep and dorsal arteries of penis, which are branches of internal pudendal artery
- *Venous drainage:* Deep and superficial dorsal veins of penis, which drain into IVC
- *Nerve supply:* Dorsal nerve of penis, a branch of pudendal nerve
- *Notes:*
 1. Erection is a *parasympathetic* process, emission is a *sympathetic* process, and ejaculation is controlled by *visceral and somatic* nerves.
 2. An important USMLE question is about the male and female genitalia equivalents:

- Corpus spongiosum = *Vestibular bulbs*
- Cowper glands = *Bartholin glands*
- Prostate = *Urethral and para-urethral glands*
- Ventral surface of penis = *Labia minora*
- Scrotum = *Labia majora*

Spermatic Cord

- *Contents:*
 1. Three arteries: Testicular, cremasteric, and artery of vas
 2. One vein: Testicular venous plexus
 3. Three nerves: Sympathetic, parasympathetic, and genitofemoral nerves
 4. One tube: Vas deferens
 5. Lymphatics

Chapter 2

Embryology

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Gametogenesis

- The gametes originate in the *yolk sac* and migrate to the gonads in the form of *primordial germ cells*.
- The primordial germ cells transform into either sperm or ova depending on the individual's sex.

Meiosis (Figs. 2.1–2.3)

- *Meiosis I*:
 1. This phase begins with *oogonia* in females and *spermatogonia* in males; both types of cells have *46 chromosomes* and *2N DNA*.
 2. Meiosis I concludes with the formation of secondary gametocytes (*23, 2N*).
 3. Processes occurring during meiosis I are *DNA replication* and *crossing over*.
 4. Note: *The centromere does not divide during meiosis I*.
- *Meiosis II*: This phase begins with *secondary gametocytes* (*23, 2N*), which undergo *splitting of the centromere* resulting in a gamete (*23, 1N*).

Spermiogenesis

- It is the process by which *spermatids* are converted to *mature sperms*.

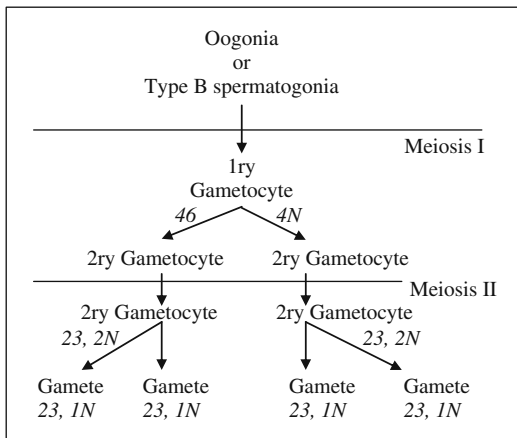


FIG. 2.1 Gametogenesis. 1ry, primary; 2ry, secondary

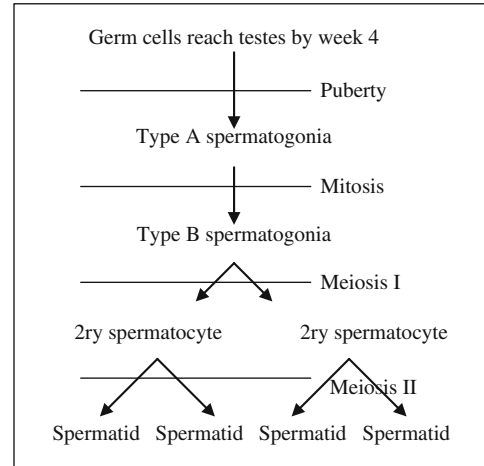


FIG. 2.2 Spermatogenesis

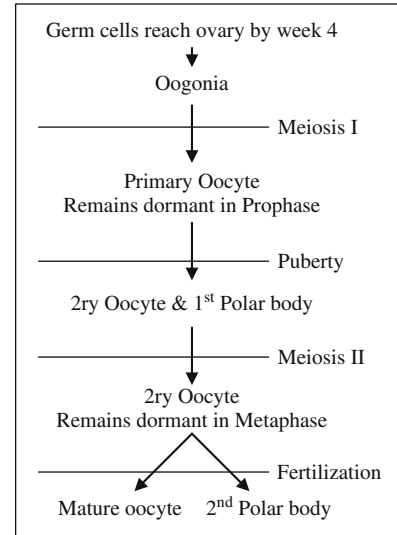


FIG. 2.3 Oogenesis

- The entire *spermatogenesis process* in adults takes place in the *seminiferous tubules*, and it takes approximately *75 days*.
- *The sperm's parts*:
 1. Head: Covered by an *acrosomal cap* and contains the genetic material

2. Middle segment: Contains *mitochondria*
 3. Tail: For *movement*
- *Source: The acrosomal cap is derived from the Golgi apparatus, while the tail is derived from a centriole.*
 - *Capacitation: It is an uncoating process that takes place inside the female genital tract, in order for the sperm to penetrate an ovum. Capacitation is characterized by an increase in the sperm's potassium content.*
 - *Normal semen:*
 1. Character: Viscid; liquefies within *0.5 hour*
 2. Volume: *2–4 mL*
 3. Color and odor: Whitish and odorless
 4. pH: *Alkaline*, due to a *phosphate buffer released by the prostate*
 5. Sperm count: *20–100 million/mL*
 6. Motility: At least *60%* are motile
 7. Morphology: At least *60%* are normal in shape
 - *Sources of seminal fluid:*
 1. *60%* from the seminal vesicles: Releases *fructose* for sperm nutrition
 2. *20%* from the prostate: Releases a *phosphate buffer* to protect the sperm from vaginal acidity
 3. *10%* from the testes
 4. *10%* from other glands

Embryogenesis

Fertilization

- *Location: Ampulla* of the fallopian tube
- *Timing: Within the first 24 hours after ovulation*
- *Steps:*
 1. Physiologically, after the sperm pierces the zona pellucida, zonal block occurs to prevent further penetrations, and similarly, when the sperm penetrates the vitelline membrane, vitelline block occurs. *Failure of the block systems results in multiple pregnancy.*
 2. Once the sperm comes in contact with the *zona pellucida* of the *secondary oocyte*, the sperm's pronucleus forms and its mitochondria degenerates.
 3. This triggers oogenesis, as mentioned earlier, and the ovum's pronucleus is formed.
 4. Sperm's and ovum's pronuclei fuse to form the *zygote*.

Cleavage and Implantation

- *Morula: The zygote (postfertilization day 2) undergoes mitosis repeatedly to form the blastula, then the morula (32-cell stage, postfertilization day 3)*

- *Blastocyst: It forms on postfertilization day 5, when the morula secretes fluid creating an internal cavity separating the cell mass into two: an inner cell mass (embryoblast) and an outer one (trophoblast).*
- *Implantation: The zona pellucida then degenerates to allow the blastocyst to implant in the posterior superior wall of the uterus by postfertilization day 6 or 7.*
- *Trophoblast: Immediately following implantation, the trophoblast cell mass divides into:*

1. Outer syncytiotrophoblast:

- Grows inside the endometrium secreting human chorionic gonadotropin (β -HCG)
- β -HCG stimulates the corpus luteum to secrete progesterone, which maintains pregnancy until the placenta can produce its own progesterone (*8th week of gestation*).
- Urine HCG is the best initial test to detect pregnancy, and it becomes positive on *post-fertilization days 8–10*.

2. Inner cytotrophoblast: Undergoes mitosis and forms the *chorionic villi*.

- *Embryoblast: It divides into:*

1. Epiblast: Forms the *amniotic cavity*
2. Hypoblast: Forms the *yolk sac*

- *Epiblast: The epiblast and hypoblast fuse, forming the prechordal plate, the superior end of which forms the mouth. The epiblast also gives rise to the extra-embryonic mesoderm, which divides into two layers:*

1. Visceral layer: *Covers the yolk sac*
2. Somatic layer: Lines the *chorion*. Note that the chorion is formed of the *somatic layer of extra-embryonic mesoderm, the syncytiotrophoblast, and the cytotrophoblast*.

- *Twins:*

1. *Dizygotic twins: Two sperms fertilizing two separate ova*
2. *Monozygotic twins: One sperm fertilizing a single ovum, after which embryoblast splitting occurs. If splitting is partial or incomplete, conjoined twins form.*

- *Note: Folding of the embryo is regulated by the HOX gene complex.*

Gastrulation

- It is the formation of the *embryonic disk*.
- *Parts: The disk divides into ectoderm, endoderm, and mesoderm (Table 2.1):*

TABLE 2.1 Embryonic disk derivatives.

Ectoderm	Brain, spinal cord, parafollicular cells of thyroid, most of the eye structures except extraocular muscles, lower half of anal canal
Endoderm	Epithelial lining of all body lumina
Mesoderm	All muscles including extraocular muscles

1. Ectoderm: Gives rise to the *neuroectoderm* and the *neural crest*
 2. Mesoderm: Divides into *para-axial mesoderm* (35 pairs of somites), *intermediate mesoderm*, and *lateral mesoderm*
 3. Endoderm: Remains *intact*
- *Sacrococcygeal teratoma*: A tumor arising from the remnants of the disk. It lies in the lower back and has multiple contents, e.g., hair, nails, teeth, etc. Treatment: Surgical removal before 6 months of age, as malignant transformation is likely.

Placenta

- *Parts*:
 1. Maternal: *Decidua basalis*
 2. Fetal: *Chorion frondosum* (tertiary villi)
- *Surfaces*: The maternal surface has a *cobblestone* appearance and contains approximately 20 *cotyledons*, while the fetal surface is *smooth and membranous*.
- *Histology*:
 1. Early pregnancy: Placenta is formed of *syncytiotrophoblast*, *cytotrophoblast*, *connective tissue*, and *endothelium of fetal blood vessels*.
 2. Late pregnancy: Placenta is formed only of the *syncytiotrophoblast* and *endothelium of fetal blood vessels*.
- *Twins*:
 1. Dizygotic twins: *Two placentae, two chorions, and two amnions*
 2. Monozygotic twins (in most cases): *One placenta, one chorion, two amnions*.
- *Pathologic forms of placenta*:
 1. *Placenta succenturiata*: Accessory lobe, which may be retained and cause postpartum hemorrhage
 2. *Placenta circumvallate*: Chorionic plate is smaller than decidual plate, which may lead to abortion. The placenta has a white decidual ring on its margin.
 3. *Placenta membranacea*: It is a large membranous placenta due to persistence of *chorion laeve*.
 4. *Small placenta*, e.g., preeclampsia

5. *Large placenta*, e.g., diabetes mellitus (DM), syphilis, or Rh isoimmunization
6. *Pathologic adherence into myometrium*, e.g., placenta accrete, increta, or percreta
7. *Abnormal cord attachments*:

- Central or marginal
- Velamentous (in membranes): Associated with placenta membranacea, and if the traversing vessels pass below the fetal presenting part (*vasa previa*), *antepartum hemorrhage of fetal origin* could ensue and is a medical emergency.
- *Note*: The placenta lacks major histocompatibility complex (MHC) antigens, so it does not elicit any immune response from the mother i.e.: No rejection or foreign body reaction.

Umbilical Cord

- *Contents*:
 1. Right and left umbilical arteries
 2. Left umbilical vein: Carries oxygenated blood to the fetus
 3. Connective tissue, e.g., Wharton jelly, allantoic duct, and amniotic epithelium
- *Abnormalities of the cord after delivery*:
 1. Patent urachal fistula: Presents with *urine* from the umbilicus
 2. Vitelline fistula: Presents with *meconium* discharge from the umbilicus
 3. Omphalocele: A *gray sack* surrounding the umbilicus
- *Note*: The presence of a single umbilical artery in the cord (5%) is common in pregnant patients with DM, and is associated with *fetal cardiovascular anomalies* and *Edward's syndrome*.

Amniotic Fluid

- *Sources*:
 1. Fetal: *Urine*, starting the 10th week of gestation
 2. Maternal: *Transudation* from placental vasculature
- *Maximum volume*: 1000 mL, normally reached by the 36th week of gestation
- *Composition*:
 1. Mainly water with some glucose and proteins
 2. Sodium and bilirubin content of the fluid decrease throughout pregnancy.
 3. Creatinine and phospholipids content of the fluid increase throughout pregnancy.

- *Oligohydramnios*: Fluid volume less than 400 mL. Causes: Premature rupture of membranes (*most common cause*), renal agenesis (Potter syndrome), or posterior urethral folds.
- *Polyhydramnios*: Fluid volume greater than 2000 mL. Causes: Esophageal atresia, anencephaly, or maternal DM.
- *Amniotic band syndrome*: Bands in the amnion form in this syndrome. The fetus suffers *craniofacial anomalies, adhesions, and spontaneous amputations*.

Cardiovascular System

Blood

- Formation begins on *day 17* in the *extraembryonic visceral mesoderm, around yolk sac*
- *Steps*:
 1. The mesoderm gives rise to *angioblasts*, which in turn give rise to *angiogenic cell clusters*.
 2. The clusters form the blood cells until the *8th week*, at which point the liver takes over, followed by the spleen, and finally the bone marrow, as follows:
 - 3rd to 8th week: *Yolk sac*
 - 8th to 30th week: *Liver then spleen (Hb: alpha2, gamma2)*
 - 30th week onwards: *Bone marrow (Hb: alpha2, beta2)*

Blood Vessels

- *Arteries of the head and neck*: Form from the *aortic arches* as follows:
 1. 3rd arch: Gives rise to the *common carotid and internal carotid arteries*
 2. 4th arch: Gives rise to the *right subclavian artery and aortic arch*
 3. 6th arch: Gives rise to the *pulmonary arteries and ductus arteriosus*
- *Arteries of the rest of the body*: Arise from the *dorsal aorta* as follows:
 1. *Posterolateral branches*: Give rise to the *arteries of the extremities and intercostals arteries*
 2. *Lateral branches*: Give rise to the *renal, suprarenal and gonadal arteries*
 3. *Ventral branches*: Gives rise to the *celiac, superior and inferior mesenteric arteries*
- *Venous system*:
 1. *Umbilical veins*: The left vein becomes the *ligamentum teres* after birth.

2. *Vitelline veins*: Gives rise to the *superior mesenteric vein (SMV), inferior mesenteric vein (IMV), and splenic, portal, and hepatic veins*
3. *Cardinal veins*: Gives rise to *superior vena cava (SVC), inferior vena cava (IVC), internal jugular vein (IJV), and azygos and hemiazygos veins*

Fetal Circulation

- *Fetal circulation (with its remnants after delivery in parentheses)*: Left umbilical vein (*ligamentum teres*) → ductus venosus (*ligamentum venosum*) → IVC → right atrium → foramen ovale (*fossa ovale*) → left atrium → left ventricle → ductus arteriosus (*ligamentum arteriosum*) → aorta → umbilical arteries (*medial umbilical ligaments*)
- *After delivery*: Circulation changes to adult circulation, due to:
 1. *Decreased right atrial pressure due to occlusion of the placental vessels*
 2. *Elevated left atrial pressure due to increased venous return from the lungs*

Heart

- *Heart tube*: Two heart tubes form in the *mesoderm*. Lateral folding fuses the two tubes into one *primitive heart tube*. The primitive heart tube gives rise to the *endocardium*, while the mesoderm surrounding the tube gives rise to the *myocardium and epicardium*.
- *Heart tube dilatation*: Five dilatations:
 1. *Truncus arteriosus*: Gives rise to *aorta and pulmonary trunk*
 2. *Bulbous cordis*: Gives rise to the *smooth parts of right and left ventricles (conus arteriosus), and the aortic vestibule*
 3. *Primary ventricle*: Gives rise to the *trabeculated parts of both ventricles*
 4. *Primary atrium*: Gives rise to the *trabeculated parts of both atria*
 5. *Sinus venosus*: Gives rise to the *smooth part of right atrium, the oblique vein of left atrium, and the coronary sinus*
- *Note*: The *smooth part of left atrium* is formed by *fusion of the pulmonary veins and left atrial wall*.
- *Crista terminalis*: It is the line between the smooth and trabeculated parts of the atria.
- *The aorticopulmonary septum*: Formed from the *neural crest*, and it extends to *separate the aorta and pulmonary trunk*.

- *The atrioventricular (AV) septum:* Formed by fusion of the ventral and dorsal AV cushions. Abnormal septum formation results in a *unilateral heart* or *tricuspid atresia*.
- *Interatrial septum:*
 1. Septum primum grows *craniocaudally* toward the AV septum carrying the foramen primum in its lower edge.
 2. As the septum primum fuses with the AV septum, the foramen primum disappears and foramen secundum forms in the *middle part* of the septum primum.
 3. Septum secundum grows *caudocranially* just to the right of the septum primum carrying *foramen ovale* in its wall.
 4. After birth, the septum primum and secundum fuse and the foramen ovale closes.
- *Interventricular septum:*
 1. Muscular portion: Grows *caudocranially* and stops before reaching the AV septum
 2. Membranous portion forms the remaining part and joins the muscular portion, completing the IV septum.
- *Note:*
 1. *Heart formation is complete and functioning by the 4th week of gestation*
 2. Congenital heart diseases: Incidence rate is 1%, which increases to 6% among newborns with family history of congenital heart disease.
 3. In the congenital heart diseases listed below, they are all *left to right shunts* except for three (the three T's): TGA, Truncus arteriosus and Tetralogy of Fallot.

Persistent Truncus Arteriosus

- *Mechanism:* If the aorticopulmonary septum does not develop completely, the truncus arteriosus persists with a right-to-left shunt through a large ventricular septal defect (VSD).
- *Clinical picture:* Cyanosis, water hammer pulse, and a systolic murmur
- *Treatment:* Diuretics and digoxin followed by surgical correction

Transposition of Great Arteries (TGA)

- *The most common cyanotic cardiac anomaly*
- *Mechanism:* Improper twisting of the aorticopulmonary septum, leading to the aorta originating from right ventricle, and pulmonary artery from left ventricle

- *On exam:* Right ventricular heave and harsh pansystolic murmur
- *Pathology:* These patients have right ventricular hypertrophy giving the heart an *egg-shaped* silhouette on chest x-ray (CXR).
- *Treatment:* Digoxin, diuretics, and prostaglandin E₁ to keep the ductus arteriosus open until surgical correction can be performed
- *Note:* Without a patent ductus arteriosus (PDA), these patients die in a couple of months.

Tetralogy of Fallot

- *Mechanism:* Abnormal migration of neural crest cells, leading to displacement of the infundibular septum
- *Tetralogy:* Pulmonary stenosis, right ventricular hypertrophy, overriding aorta, and VSD
- *Clinical picture:*
 1. Cyanosis: Starts at 3–6 months of age (*never at birth*)
 2. Cyanotic (Tet) spells: Attacks of infundibular spasm associated with any exercise or infection
- *On exam:*
 1. Patient is in *squatting position*: Increases venous return, hence decreases hypoxia
 2. Systolic murmur at the left sternal border
- *CXR:* Boot shaped heart
- *Treatment:* Surgical correction, e.g., Blalock-Taussig
- *Treatment of Tet spells:* Put the patient in squatting position and administer oxygen, beta blockers, and fluids.

Ebstein Anomaly

- *Mechanism:* Prolapse of the tricuspid valve into a hypoplastic right ventricle
- *Pathology:* Most patients have patent foramen ovale, resulting in a dilated left atrium.
- *Associations:* Supraventricular tachycardia and Wolff-Parkinson-White syndrome
- *Treatment:* Digoxin, diuretics, and prostaglandin E₁

Ventricular Septal Defect (VSD)

- *Mechanism:* Failed fusion of the right and left bulbar ridges with the AV cushions
- *Location:* Most commonly in the membranous portion of the IV septum
- *Pathology:* Begins as a left-to-right shunt at birth but the shunt reverses due to pulmonary

hypertension. This shunt reversal is known as *Eisenmenger syndrome*.

- **Clinical picture:**
 1. *Cyanosis* and *recurrent chest infections*
 2. *Harsh pansystolic murmur* all over the precordium
- **CXR:** Biventricular enlargement and left atrial dilatation
- **Treatment:** The defect usually closes spontaneously by age 7; otherwise, surgical correction is required.

Atrial Septal Defect (ASD)

- **Mechanism:** *Persistent ostium secundum*, and less commonly an *ostium primum* defect
- **Clinical picture:** Most cases are asymptomatic and have a *wide fixed and split S2*.
- **CXR:** Right atrium and right ventricle dilatation
- **Treatment:** Most cases do not require treatment.
- **Note:** *Holt-Oram syndrome: ASD and multiple congenital skeletal anomalies*

Patent Ductus Arteriosus (PDA)

- **Pathology:** Ductus arteriosus normally closes *2 weeks after birth*. PDA is more common in *premature infants* and in *congenital rubella syndrome*, due to *high prostaglandin E levels*.
- **Clinical picture:**
 1. *Hyperdynamic circulation*
 2. *Wide pulse pressure*, i.e., high systolic and low diastolic pressure
 3. *Machine-like murmur:* Heard best in the pulmonary area (*left 2nd intercostal space*)
- **Treatment:** Anti-prostaglandin E, e.g., *indomethacin*

Hypoplastic Right Heart Syndrome

- **Causes:** Tricuspid atresia, or pulmonary atresia with an intact septum
- **Pathology:** Most cases also have VSD, ASD, or PDA, resulting in *left ventricular hypertrophy*.
- **Treatment:** *Prostaglandin E₁* until surgical correction can be performed

Hypoplastic Left Heart Syndrome

- **The most common congenital heart disease to cause death in the first month of life**
- **Pathology:** Hypoplastic left ventricle, along with mitral and aortic atresia

- **Association:** PDA and ASD to maintain circulation through a left to right shunt
- **Treatment:** *Prostaglandin E₁* (PGE₁) and heart transplant

Gastrointestinal System

Embryology

- The primitive gut tube is a part of the *yolk sac*. Its lining proliferates until the tube is plugged, then *recanalization* occurs with differentiation.
- **Esophagus:** Formed by the completion of the *tracheoesophageal septum*
- **Stomach:** Forms during the *4th week* and undergoes *clockwise rotation*
- **Liver:** Forms from the *liver diverticulum*, a part of the *mesoderm*. Note: *This part of the mesoderm also gives rise to the diaphragm and ventral mesentery*.
- **Biliary system:** Forms as an *outpouching* at the *junction of the liver diverticula and the foregut*
- **Pancreas:** Originates from the *dorsal pancreatic bud*, with the exception of the *uncinate process and a portion of the head*, which arise from the *ventral pancreatic bud*. Note: The dorsal bud originates from endoderm of *duodenum*, while the ventral bud arises from endoderm of *hepatic diverticulum*.
- **Midgut:** It herniates in the *6th week* of gestation and rotates *270 degrees counterclockwise* before migrating back into the abdomen during the *12th week*. Note that the *ileum* is the last segment of the gastrointestinal (GI) tract to recanalize.
- **Hindgut:** The cloaca divides into *urogenital sinus anteriorly* and *rectoanal canal posteriorly*:
 1. *Rectoanal canal:* Gives rise to the *rectum* and *upper half of anal canal*
 2. Lower half of anal canal rises from the *proctoderm*, and is separated from the upper half by the *anal membrane*. This membrane ruptures during the *7th week* forming the *dentate (pectinate) line*.
- **Mesentery:**
 1. The remnant of the *ventral mesentery* is the *lesser omentum*.
 2. The remnant of the *dorsal mesentery* is the *greater omentum*.

Congenital Esophageal Atresia

- It is usually associated with a *tracheoesophageal fistula*.
- **Types:** Multiple; the most common is an esophagus with an upper blind pouch, and a *lower pouch connected to the trachea*.

- *Clinical picture:*
 1. Continuous regurgitation of saliva and food *from the first day of life*
 2. Meconium aspiration pneumonia, chemical pneumonitis, and *bilious sputum*: Due to regurgitation of gastric contents into the airways
- *Diagnosis:* Failure to pass a feeding tube from nose to stomach (*Normal = 10 cm*)
- *Treatment:* Urgent surgical correction

Congenital Hypertrophic Pyloric Stenosis (CHPS)

- *Mechanism:* Congenital anomaly leading to *hypertrophy of pyloric muscles* and dilatation of the stomach
- *Clinical picture:*
 1. Vomiting: *Never* at birth (2–6 weeks after birth) and *never* bilious
 2. Constipation and failure to thrive
- *On exam:* *Olive-like mass* in the epigastrium
- *Labs:* Hypokalemic alkalosis and hyponatremia
- *Diagnosis:* *Gastrografin study*
- *Treatment:* *Pyloromyotomy*
- *Note:* Duodenal atresia is the most common congenital cause of intestinal atresia. Vomiting here *is since birth* and *is bilious* (mirror image of CHPS). *Diagnosis:* *Double-bubble sign* on abdominal x-ray. *Treatment:* Surgery.

Volvulus Neonatorum

- *Mechanism:* *Rotation of the midgut loop clockwise instead of counterclockwise*
- *Clinical picture:* *Abdominal pain, constipation, and bilious vomiting*
- *Diagnosis:* *Abnormal location of the cecum* on an upper GI series, and *bird beak* appearance on barium enema
- *Treatment:* Best next step is *rectal tube insertion* to deflate the colon, followed by surgical untwisting and fixation of the intestine to abdominal wall.

Intussusception

- *Mechanism:* *Invagination of an intestinal loop into another*; commonly seen in the ileocecal area
- *Clinical picture:* Abdominal pain and *red current jelly stools*
- *On exam:* An abdominal *sausage-like mass* may be appreciated on palpation

- *Diagnosis:* X-ray shows air fluid levels, while barium enema shows *claw sign*.
- *Treatment:* Reduction by enema; surgery and manual reduction if enema fails

Hirschsprung Disease (Congenital Megacolon)

- *Mechanism:* It is a congenital disease that occurs due to presence of an aganglionic segment in the colon; lacking Meissner and Auerbach nerve plexuses. This leads to a *spastic colon segment*, proximal to which is a *transitional zone* and a *dilated segment*.
- *Clinical picture:*
 1. *Constipation since birth:* Newborn passes stools only once or twice a week, but it is huge in amount and extremely malodorous.
 2. Growth retardation
- *On exam:* Digital rectal exam reveals a spastic segment, and on withdrawal a *gush of malodorous stool* follows.
- *Diagnosis:*
 1. Test of choice is *anorectal biopsy*: Shows *absent ganglia* and *hypertrophied nerve trunks*
 2. Barium enema *without preparation*: Colon has to be full with stools to visualize the spastic and dilated segments.
- *Treatment:* Surgical excision of the aganglionic segment. Complication: *Impotence* in males, due to injury of pelvic autonomic nerves
- *Note:* Secondary megacolon is dilated sigmoid colon and rectum all the way down the anal canal *without any spastic segment*. It is mostly due to constipation, or less likely *Trypanosoma cruzi* (Chagas disease). Biopsy is normal and treatment entails laxatives and healthy bowel habits.

Meckel's Diverticulum

- It is a remnant of *vitello-intestinal (omphalomesenteric) duct*.
- *Rule of 2's:* Present in 2% of population, 2 feet proximal to ileocecal valve, 2 inches long, and contains 2 types of epithelium, namely *gastric* and *pancreatic*
- *Clinical picture:* *Bright red bleeding per rectum, mostly in children*
- *Diagnosis:* Technetium (*Tm-99*) scan, uptake shows a *hot spot*
- *Complications:* Bleeding, diverticulitis, intussusception or perforation

- *Treatment:* Excision
- *Note:* The most common cause of bleeding per rectum during the first year of life is anal fissures. After the first year, the most common cause is Meckel's diverticulum.

Imperforate Anus

- *Mechanism:* Failure of canalization; could be high, intermediate, or low
- *Clinical picture:* Failure to pass meconium since birth
- *On exam:* A dimple at the anal area that bulges upon crying
- *Diagnosis:* Invertogram in lateral view, upside down and with flexed hips
- *Treatment:* Surgery

Annular Pancreas

- *Mechanism:* Fusion of the dorsal and ventral pancreatic buds, which results in the pancreas forming a ring around the duodenum
- *Clinical picture:* Intestinal obstruction presenting with abdominal pain, constipation, nausea, and bilious vomiting
- *Treatment:* Surgery

Omphalocele

- It is a congenital umbilical hernia.
- *Mechanism:* Failure of the midgut loop to reenter the abdomen after rotation.
- *Treatment:* Surgery

Serosa and Diaphragm

Embryology

- *The intraembryonic coelom (embryonic body cavity):* Forms between visceral and somatic intraembryonic mesoderm. This large single coelom is then divided by two pleuropericardial membranes and diaphragm.
- *Pleuropericardial membranes:* Fuse to form the fibrous pericardium
- *Diaphragm:* Formation is completed by the 4th week. In the 8th week, the diaphragm descends to the L1 level, pulling its phrenic nerve. Diaphragm formation is as follows:
 1. Central tendon: Arises from septum transversum
 2. Crura of diaphragm: Arise from dorsal esophageal mesentery

3. Rest of diaphragm: Arise from pleuroperitoneal membranes and body wall

Congenital Diaphragmatic Hernia

- *Mechanism:* Defect in the posterolateral diaphragm, a.k.a. Bochdalek hernia
- *Clinical picture:* Shortness of breath and cyanosis
- *On exam:* Scaphoid abdomen
- *Diagnosis:* CXR shows the stomach inside the thorax.
- *Treatment:* Mechanical ventilation until surgery is urgently arranged

Urinary System

Embryology

- This process is regulated by the genes *c-Ret* and *WT-1*.
- *Nephrogenic cord:* It forms in the intermediate mesoderm. The cord differentiates into the pronephros, mesonephros, and metanephros:
 1. Pronephros: Degenerates without a remnant
 2. Mesonephros: Degenerates, leaving the mesonephric duct (Wolffian duct)
 3. Metanephros: Forms the urinary system:
 - The mesoderm: Forms the kidneys
 - The ureteric bud: Forms the distal tubules, calyces, and ureters
- *Kidneys:* They originate in the pelvis and ascend into the abdomen due to disproportionate growth of the embryo caudal to the metanephros. While ascending, the kidneys rotate 90 degrees medially and the pelvic blood supply is replaced by the abdominal renal vessels.
- *Urinary bladder:*
 1. Formed from the upper part of the urogenital sinus. Wolffian duct opens into the posterior wall of the bladder, forming the trigone.
 2. The apex of the bladder is attached to the allantois, which later becomes the urachus. The urachus becomes the median umbilical ligament.
 3. Renal agenesis (Potter syndrome) may cause oligohydramnios, due to low or absent fetal urine output. Accordingly, the fetus may be compressed by the uterus, deforming the face and limbs.
- *Adrenal glands:*
 1. Adrenal cortex: Arises from the mesoderm. The zona reticularis is the only layer of the cortex that

is not completely developed at birth. It does not completely development until 3 years of age.

2. Adrenal medulla: Arises from the *neural crest*, and contains *chromaffin tissue*

Polycystic Kidney Disease

- **Mechanism:** Mutation of *PKD1* gene; autosomal dominant AD in adults and autosomal recessive AR in children
- **Clinical picture:** Patients, children or adults, might present with hematuria, proteinuria, hypertension (HTN), or even chronic kidney disease (CKD).
- **Diagnosis:**
 1. Ultrasound of kidneys: Polycystic kidneys
 2. Intravenous pyelogram (IVP): *Spider leg deformity*
- **Treatment:** Supportive; the *drug of choice* for treating HTN is an *angiotensin-converting enzyme inhibitor (ACEI)*.
- **Note:** These patients tend to have *polycystic liver* and *Berry aneurysms*, so when you face a case in the USMLE of a patient with some form of congenital kidney disease who is presenting with subarachnoid bleeding, you know what to think!

Wilms' Tumor (Nephroblastoma)

- **Origin:** Embryonic nephrogenic cells
- **Mechanism:** Deletion of *WT-1* gene on chromosome 11
- **Clinical picture:** Mostly in children as an abdominal mass
- **Treatment:** It is a rapidly growing malignant tumor, treated surgically.
- **Remember:** *GRAWL* association: genitourinary anomalies, mental retardation, aniridia, and Wilms' tumor.
- **Note:** Neuroblastoma is a *chromaffin tissue tumor* that occurs due to a deletion of *chromosome 1* and shows *Homer Wright rosettes* on microscopy (Fig. 2.4). Patients with neuroblastoma have high vanillylmandelic acid (VMA) in the urine. *Suspect this disease in any child with unexplained ecchymosis of eyelids.*

Horseshoe Kidney

- **Mechanism:** Fusion of the kidneys at the lower poles during ascent
- **Location:** Posterior to *inferior mesenteric artery*
- **Diagnosis:** IVP shows a "flower vase" appearance
- **Treatment:** Conservative

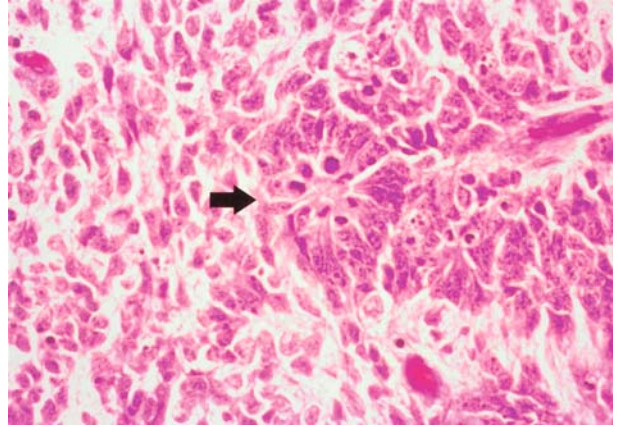


FIG. 2.4 Homer Wright rosettes (arrow)

Genital System

Embryology

- *As a rule, know that the wolffian duct forms the male genitalia and the müllerian ducts form the female genitalia.*
- **External genitalia:** Start to form by the 12th week and are fully differentiated by the 20th week; that is when you can determine the gender of the fetus.
- **Differentiation:** It is regulated by *Sry* gene on the Y chromosome, which activates the *testis-determining factor (TDF)*. This leads to the formation of:
 1. Leydig cells: Secrete *testosterone*
 2. Sertoli cells: Secrete *müllerian inhibiting factor (MIF)*
- Logically, if the *Sry* gene is not present, none of these structures will be formed and the fetus will stay the way it is—a *female*.
- **Uterus and vagina:** Mullerian (*paramesonephric ducts*) push into the posterior wall of the urogenital sinus, forming *vaginal bulbs*:
 1. Mullerian ducts: They fuse to form the *uterus*.
 2. Vaginal bulbs: They fuse to form the *vaginal plate*, which later becomes the *inferior two thirds of the vagina*.
- **Upper one third of vagina, the female urethra, and vaginal glands:** All these develop from the lower end of the urogenital sinus.
- **Male urethra:** The lower end of the urogenital sinus also forms all the male urethra, *except the fossa navicularis, which is formed by canalization of an ectodermal plate.*
- **Prostate:** Dihydrotestosterone stimulates the urethra to form an outgrowth that later becomes the prostate. *Remember: Finasteride is used to treat*

benign prostatic hyperplasia (BPH), as it blocks conversion of testosterone to dihydrotestosterone.

- *Changes after birth:*
 1. Female gubernaculum becomes the *ovarian ligament* and *round ligament of uterus*.
 2. Male gubernaculum becomes *gubernaculum testes*.
 3. Female processus vaginalis *obliterates*.
 4. Male processus vaginalis becomes *the tunica vaginalis*.
- *Note:* Incomplete fusion of *müllerian ducts* or *vaginal bulbs* can lead to many anomalies such as double uterus, double vagina, vaginal atresia, etc.

Undescended Testes (Cryptorchidism)

- *Embryology:* Testes develop from the *testicular ridge* (L2 level) and starts their descent due to *differential body growth, high abdominal pressure, and the pulling effect of the gubernaculum testes*. This descent is complete by the time of birth.
- *Causes:* Hypopituitarism, short spermatic cord, or fibrosis
- *Clinical picture:* Empty and underdeveloped scrotal sac
- *Complications:* Malignancy, mainly *seminoma*, and sterility due to high intraabdominal temperature, which destroys testicular cells
- *Next best step:* computed tomography (CT) scan of abdomen and pelvis or laparoscopy to locate the undescended testicle
- *Treatment:* HCG. Orchiopexy is performed *if still undescended by 1 year of age*.
- *Notes:*
 1. *Retractile testis:* It is a sensitive testicle *due to a strong cremasteric reflex*. Any stimulus causes retraction of testicle up to *superficial subinguinal pouch*. Testes could be felt and easily pulled down to the floor of the scrotum.
 2. *Ectopic testes:* It is a testicle that descends outside normal line of descent *due to the pulling effect of one of the gubernaculum's tails (Lockwood theory)*. Most common ectopic site is *femoral triangle*. Treatment: Surgery.

Spadias

- *Epispadias:* It is opening of the urethra into the dorsum of the penis due to *abnormal positioning of the genital tubercle*. Association: *Exstrophy of urinary bladder*.
- *Hypospadias:* It is opening of the urethra to the *undersurface* of the penis due to *failed fusion of*

urethral folds. Associations: *Bifid scrotum* and *undescended testes*. Clinical picture: Corpus spongiosum distal to the opening is fibrosed, causing the penis to curve ventrally, a condition known as *chordee*. Treatment: Surgical at the age of 2. *Circumcision is contraindicated*.

Congenital Adrenal Hyperplasia (CAH)

- *Mechanism:* 21α - or 11β -hydroxylase enzyme deficiencies, *which are necessary for cortisol production*. It is linked in some cases to human leukocyte antigen (HLA) *BW47*.
- *Clinical picture:* *Hirsutism, virilization, and precocious puberty*, due to increased adrenocorticotropic hormone (ACTH) stimulation of androgen production
- *Diagnosis:* High serum *17-hydroxyprogesterone* levels
- *Note:* This should be your first suspicion when you see a newborn with ambiguous genitalia. If confirmed, the next step would be to *check the patient's electrolytes* as they might have life-threatening mineralo- or glucocorticoid deficiency.

Testicular Feminization Syndrome

- *Mechanism:* *Mutation of androgen receptors*, through deletion of the DNA binding protein of the receptors, so *testosterone is produced but it cannot act*
- *Clinical picture:* External female appearance with a vagina, *but no ovaries or uterus*
- *Workup:* It reveals *undescended testes* and *46 XY chromosomes*.

Male Phenotypic Genital Anomalies

- *Mechanisms:* 5α -reductase or 17β -hydroxysteroid dehydrogenase deficiency
- *Clinical picture:* Underdeveloped male genitalia
- *Diagnosis:* High serum *testosterone* or *androstenedione* levels, *respectively*, due to lack of conversion to the active forms

Respiratory System

Embryology

- A respiratory diverticulum sprouts from the ventral surface of the foregut tube and forms the trachea, budding at its distal end to form the bronchial tree.

- *Stages of lung development:*
 1. Glandular (*weeks 5–15*): Cuboidal epithelium
 2. Canalicular (*weeks 15–25*): Respiratory bronchioles form.
 3. Terminal sac (*week 25 to birth*): Flat type I and cuboidal type II pneumocytes form.
 4. Alveolar (*Birth to 8 years*): Alveolar ducts and alveoli form.
- *Note:* Pulmonary hypoplasia may be associated with renal agenesis (Potter syndrome) or a large congenital diaphragmatic hernia.

Hyaline Membrane Disease (Respiratory Distress Syndrome)

- *Mechanism:* Deficiency of surfactant released by type II pneumocytes
- *Incidence:* More common among premature and low birth weight infants
- *Pathology:* Surfactant production is suppressed by asphyxia and increased by thyroxin and cortisol.
- *Clinical picture:* A newborn in respiratory distress and cyanosis due to collapsed alveoli.
- *CXR:* Diffuse ground glass appearance (Fig. 2.5)
- *Detection:* Amniotic fluid's lecithin/sphingomyelin ratio < 1.5
- *Complication:* Bronchopulmonary hypertrophy and squamous dysplasia
- *Treatment:*
 1. Steroids (betamethasone) to mother before premature delivery to accelerate fetal lung maturity
 2. Mechanical ventilation and artificial surfactant

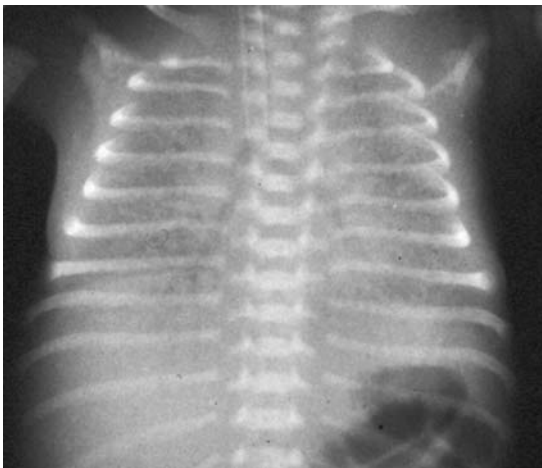


FIG. 2.5 Chest x-ray showing hyaline membrane disease

Cystic Fibrosis

- *Mechanism:* Mutation of *CFTR* gene on the long arm of chromosome 7, which controls chloride channels. It is an autosomal recessive disease, due to 3 base deletion of phenylalanine.
- *Clinical picture:*
 1. Recurrent respiratory infections: Mainly *Pseudomonas cepacia* and *Staphylococcus aureus*
 2. Malabsorption and steatorrhea: Deficiency of vitamins A, D, E, and K
 3. Infertility and meconium ileus: Due to viscid secretions
 4. Dehydration: Hyponatremia and metabolic alkalosis
- *On exam:* Clubbing is present in almost all cases.
- *CXR:* *Bleb sign*
- *Pulmonary function tests (PFTs):* Mixed obstructive and restrictive pattern
- *Diagnosis:* *Sweat chloride test;* a level of more than 60 mEq is diagnostic.
- *Treatment:* Chest physiotherapy, antibiotics, and pancreatic enzymes

α_1 -Antitrypsin Deficiency

- *Mechanism:* Inherited deficiency leading to congenital pan-acinar emphysema
- *Pathology:* Emphysema is dilatation of the air spaces distal to terminal bronchioles, and is normally centro-acinar, except in this disease where it is pan-acinar.
- *Clinical picture:*
 1. Congenital dyspnea and wheezing
 2. Recurrent hepatitis. So keep your eyes open in the USMLE for a patient who was born with emphysema and is presenting with elevated transaminases.
- *Diagnosis:*
 1. Low or undetectable α_1 -antitrypsin level
 2. PFTs: Show obstructive picture (*forced expiratory volume in 1 second [FEV₁]/forced vital capacity [FVC] < 80*)
 3. Chest x-ray: Hyperinflated lungs and flattened diaphragm
- *Treatment:* α_1 -antitrypsin replacement
- *Note:* Patients with emphysema have a tendency to form bullae. The bullae here are mainly basal, while in acquired emphysema or chronic obstructive pulmonary disease (COPD), they are apical.

TABLE 2.2 Derivatives of pharyngeal arches.

Arch	Nerve supply	Mesoderm derivatives	Neural crest derivatives
I	Cranial nerve V	Muscles of Mastication: Masseter, temporalis, and pterygoids	Maxilla, Mandible, Malleus, incus
II	Cranial nerve VII	Muscles of the face: posterior belly of digastric and Stylohyoid	Stapes, Styloid and lesser horn of hyoid bone
III	Cranial nerve IX	CCA ICA	Greater horn of hyoid bone
IV	Cranial nerve X (superior laryngeal branch)	Muscles of soft palate and pharynx	None
VI	Cranial nerve X (recurrent laryngeal branch)	Muscles of larynx	None

CCA, common carotid artery; ICA, internal carotid artery.

Kartagener Syndrome

- **Pathology:** Also known as *immotile cilia syndrome*; occurs due to *defective dynein arm*
- **Clinical picture:** The four S's: recurrent sinusitis, sterility, situs inversus (e.g., dextrocardia), and bronchiectasis

Head and Neck

Pharyngeal Apparatus

- It is the source of all head and neck structures, and is regulated by the *HOX gene complex* and *retinoic acid*. Tables 2.2–2.5 list derivatives of the pharyngeal apparatus.

TABLE 2.3. Derivatives of pharyngeal pouches.

Pouch	Derivatives
I	Lining of middle ear and eustachian tube
II	Lining of palatine tonsils
III	Inferior parathyroid glands, thymus
IV	Superior parathyroid glands

TABLE 2.4 Derivatives of pharyngeal grooves.

Groove	Derivatives
I	Lining of external auditory meatus
II, III, IV	Degenerate

TABLE 2.5 Pharyngeal membranes derivatives.

Membrane	Derivatives
I	Tympanic membrane
II, III, IV	Degenerate

- **Note:** Grooves are invaginations in ectoderm, while pouches are invaginations in endoderm. Membranes connect grooves to pouches.
- **Pharyngeal apparatus anomalies:**

1. Treacher Collins syndrome: Failure of formation of the first arch; occurs due to *insufficient migration of neural crest cells*. Patient has *malformed mandible and ears*.
2. Pharyngeal cyst: Occurs due to a *persistent pharyngeal groove or cervical sinus*. Patient presents with a cystic mass near the *angle of the mandible*.
3. Pharyngeal fistula: Occurs due to a *persistent 2nd pharyngeal groove and pouch*. Patient presents with a fistula opening exteriorly on the *anterior border of sternomastoid muscle* and interiorly into the *tonsillar area*.
4. DiGeorge syndrome: Occurs due to errors in *differentiation of 3rd and 4th pharyngeal pouches*. Clinical picture (helpful to remember: “George always shows TLC”):

1. Tetany: Due to *hypocalcemia, caused by absent parathyroid gland*
2. Lack of a *thymus*: Recurrent infections
3. Cardiovascular anomalies

Thyroid Gland

Embryology

- Develops from the *thyroid diverticulum*, which rises from the *floor of the mouth*. The gland hangs on the thyroglossal duct until it descends to the anterior neck.
- **Note:** *Foramen cecum* is the opening of the *thyroglossal duct in the tongue*.
- **Thyroglossal cyst:** Occurs due to *persistence of the thyroglossal duct*. Clinical picture: Painless midline cystic swelling in the neck that *moves up with tongue protrusion*. Treatment: Surgical resection.

Tongue

Embryology

- Muscles of the tongue originate from *occipital somites of para-axial mesoderm*. Table 2.6 lists the embryology of the tongue.
- *Nerve supply*: They are all supplied by the *hypoglossal nerve (XII)*, except the *palatoglossus muscle*, which is supplied by the *vagus nerve (X)*.

Face and Palate

- *Face*: Forms by fusion of *one frontonasal*, *two maxillary*, and *two mandibular prominences*
- *Nose*: Forms by fusion of the *nasal placodes* created on either side of the frontonasal prominence
- *Face prominences*:
 1. *Medial nasal prominences*: Fuse together forming the *nasal septum*, *philtrum of the lip*, *the four incisors*, and the *primary palate*
 2. *Maxillary prominences*: Form *palatine shelves*, which grow medially until they fuse and form the *secondary palate*
- *Palate*:
 1. *Hard palate*: Formed by the primary palate and the anterior part of the secondary palate
 2. *Soft palate and uvula*: Formed by the posterior part of the secondary palate
 3. *Note*: The landmark between the primary and secondary palate is the *incisive foramen*.

Ear

- *Auricle*: Formed by fusion of *six hillocks*
- *External auditory canal*: Arises from the *first pharyngeal groove*
- *Tympanic membrane*: Arises from the *first pharyngeal membrane*

TABLE 2.6 Embryology of the tongue.

	Anterior two thirds	Posterior one third
Source	Pharyngeal arch I	Pharyngeal arches II, III, and IV
Composition	Median and two distal tongue buds	Copula and hypobranchial eminence
Sensory supply	Lingual branch of trigeminal nerve	Glossopharyngeal nerve
Taste sensation	Chorda tympani of facial nerve	Glossopharyngeal nerve

- *Middle ear and eustachian tube*: Arise from the *first pharyngeal pouch*
- *Malleus*: Arises from the *first pharyngeal arch*, and is attached to the *tympanic membrane* by *tensor tympani muscle*
- *Incus (Meckel cartilage)*: Arises from the *first pharyngeal arch*
- *Stapes (Richter cartilage)*: Arises from the *second pharyngeal arch*, and is attached to the *oval window* by *stapedius muscle*
- *Inner ear*: Arises from the *ectodermal otic placode*. It contains:
 1. *Utricle and saccule*: Regulate *linear acceleration*
 2. *Semicircular canals (SCC)*: Regulate *angular acceleration*
 3. *Scala vestibuli and tympani*: Contain *Na-rich perilymph*
 4. *Scala media*: Contain *K-rich endolymph*, *basilar membrane*, and *organ of Corti*

Eye

Embryology

- *All eye structures are neuroectodermal* in origin, except:
 1. *The lens*: Arises from the *ectodermal surface* of the head
 2. *Extraocular muscles, ciliary body, sclera, central artery, and vein of retina*: Arise from *mesoderm*

Retinoblastoma (Cat's Eye)

- *Incidence*: It is the most common ocular malignancy in children.
- *Mechanism*: Mutation of the *RB gene* (due to deletion of long arm of chromosome 13), which activates binding of a dephosphorylated protein to transcription factor E2F, causing *G1 arrest*
- *Clinical picture*: White pupil
- *Treatment*: Surgical plus chemotherapy and radiation
- *Notes*:
 1. *Cataract* is the most common cause of white pupil (*leukocoria*).
 2. *Causes of congenital cataracts*: *Toxoplasmosis*, *galactosemia*, or *Down syndrome*

Retinitis Pigmentosa

- *Mechanism*: *Genetic*, but could also occur due to *abetalipoproteinemia*

- *Clinical picture: Tubular vision and night blindness*
- *Treatment: Supportive, and vitamin A in abetalipoproteinemia*

Cleft Lip

- It is typically unilateral, mostly on the *left*.
- *Mechanism: Failure of the maxillary prominences to fuse with medial nasal prominences, or failure of the mandibular prominences to fuse with each other*
- *Cause: Familial, or an injury during the first trimester, e.g., Rubella*
- *Complications: Difficulty in feeding*
- *Treatment: Surgical at age of 10 weeks*

Cleft Palate

- *Mechanism: Failure of fusion of both palatine shelves to either each other, or to the primary palate*
- *Cause: Same as for cleft lip*
- *Complications: Difficulty in feeding and speech*
- *Treatment: Surgical at the age of 10–12 months*
- *Note: Pierre Robin syndrome is a cleft palate syndrome associated with posteriorly displaced mandible (retrognathia) and tongue.*

Miscellaneous

- *Buphthalmos: Congenital glaucoma, either genetic or secondary to congenital rubella syndrome. The eyes and pupils are usually enlarged with deep anterior chambers and impending damage to the optic nerve.*
- *Retrolental fibroplasia: Oxygen-induced retinopathy in premature infants*
- *Coloboma iridis: Defect in the iris, due to failure of closure of choroid fissure*
- *Retinal detachment: Typically occurs between pigment and neural layers*

Nervous System

Embryology

- *Neural tube: It is connected to the amniotic cavity by anterior and posterior neuropores. These pores close normally in the 4th week as long as there is sufficient folic acid.*

- *Failure of closure of the anterior neuropore: Upper neural tube defects, e.g., anencephaly (absence of the brain)*
- *Failure of closure of the posterior neuropore: Lower neural tube defects, e.g., spina bifida*
- *Maternal serum alpha-fetoprotein (MSAFP): A marker for neural tube defects; is elevated (>2.5 mOsm) in neural tube defects; low MSAFP (<0.4 mOsm) is an indicator of Down syndrome*
- *Brain: By the 4th week, the neuropores close and the neural tube develops three dilations to form the forebrain, midbrain, and hindbrain. These dilations are known as prosencephalon, mesencephalon, and rhombencephalon, respectively, and they undergo further differentiation 2 weeks later, as shown in Table 2.7.*
- *Ventricles:*
 1. Lateral ventricles: Arise from *telencephalon*
 2. Third ventricle: Arises from *diencephalon*
 3. Fourth ventricles: Arise from *met- and myelencephalon*
 4. Aqueduct of Sylvius: Arises from *mesencephalon*
- *Meninges:*
 1. Pia and arachnoid: Arise from the *neural crest*
 2. Dura: Arise from *mesoderm*
- *Neurons: All preganglionic neurons (being close to the neural tube) arise from the tube, whereas postganglionic neurons arise from the neural crest.*
- *Neuroectoderm: Gives rise to the following:*
 1. Neuroblasts: Give rise to *all neurons of the central nervous system (CNS)*
 2. Glioblasts: Give rise to the following:
 - Choroid plexus: Forms the *blood–brain barrier* and *secretes cerebrospinal fluid (CSF)*
 - Ependymocytes: Line the ventricles
 - Oligodendrocytes: Secrete myelin *only in CNS. Oligodendrocytes are destroyed in demyelinating diseases, e.g., multiple sclerosis. The equivalent of oligodendrocytes in the peripheral nervous system is Schwann cells.*

TABLE 2.7 Neural tube derivatives.

Structure	Derivative
Prosencephalon (forebrain)	Thalamus, hypothalamus, epithalamus, optic nerve, mammillary bodies, cerebrum, hippocampus
Mesencephalon (midbrain)	Midbrain
Rhombencephalon (hindbrain)	Pons, medulla, cerebellum

- Microglia: Macrophages of the CNS
- Astrocytes and glial cells: Secrete glial fibrillary acidic protein (GFAP)
- *Pituitary gland:*
 1. Anterior pituitary gland: Formed from *Rathke's pouch*, which is an *ectodermal pouch raising from the roof of the mouth*. This process is regulated by transcription factor *Pit-1*.
 2. Posterior pituitary gland: Formed from *neuroectoderm of prosencephalon*

Craniopharyngioma

- *It is the most common cause of hypopituitarism in children.*
- *Mechanism: Remnant of Rathke's pouch, resulting in an anterior pituitary tumor*
- *Clinical picture:*
 1. *Headache, nausea, vomiting, and bitemporal hemianopia.*
 2. *Growth hormone, antidiuretic hormone (ADH), and gonadotrophin deficiency*
- *Treatment: Excision of the tumor*

Skin

Embryology

- *Epidermis: Ectodermal* in origin, and the layers from deep to superficial are arranged as per the mnemonic "*BabeS Love Good Cops*": stratum basale, stratum spinosum, stratum lucidum, stratum granulosum, and stratum corneum.
- *Langerhans cells: Arise from bone marrow, and serve as antigen presenting cells*
- *Melanoblasts: Arise from neural crest and color the skin*
- *Merkel cells: They are of unknown origin, and serve as mechanoreceptors.*
- *Dermis: Mesodermal* in origin, except in the head and neck area, where it is mainly *neuroectodermal*
- *Sweat glands: Ectodermal* in origin, including mammary glands
- *Sebaceous glands: Ectodermal, from the epithelium of hair follicles*

Icthyosis

- *X-linked disease causing defective keratinization of the skin*
- *Location: Neck and trunk, sparing the extremities*

- *Clinical picture: Dry scaly skin, frequently compared to fish scales*
- *Pathology: Thick stratum corneum layer*
- *Treatment: Topical emollients*

Hemangioma

- *Types: Strawberry, salmon patch, and port wine*
- *Prognosis: The former two disappear spontaneously during the first year of life. Port-wine hemangioma does not disappear spontaneously, and it affects the trigeminal area of the face (Fig. 2.6).*
- *Management: X-ray of the skull is necessary for patients with port-wine hemangioma to look for calcifications of cerebrum and meningeal vessels (Tram track calcifications), which if present, constitutes Sturge-Weber syndrome.*

Ehler-Danlos Syndrome

- *Mechanism: Autosomal dominant disease resulting in defective collagen, mainly types I and III; underlying disorder is failed hydroxylation of collagen's lysine*
- *Clinical picture: Hyperelastic skin and joints*



FIG. 2.6 Port-wine hemangioma (nevus flammeus)

Skull and Vertebral Column

Embryology

- **Neural crest:** It gives rise to the *neurocranium*, which forms the flat bones of the skull, and the *viscerocranium*, which forms everything else.
- **Sutures and fontanelles:** At birth, the skull has:
 1. **Five sutures:** Frontal, coronal, sagittal, lambdoid, and squamosal. Skull sutures are immobile *synarthrotic* joints, unlike mobile *diarthrotic* or *amphiarthrotic* joints, e.g., vertebral column.
 2. **Six fontanelles:** Anterior, posterior, two mastoid, and two sphenoid. Posterior and sphenoid fontanelles close at *6 months of age*, while anterior and mastoid fontanelles close at *18 months of age*. Note that the anterior fontanelle lies just on top of the superior sagittal sinus.
- **Mastoid process:** It is not present at birth; it forms at *2 years of age*. Therefore, the facial nerve could easily be injured at that site during delivery, due to lack of protection.
- **Notes:**
 1. Vertebral column and ribs are all *mesodermal* in origin.
 2. Congenital *brevicollis*: A disorder characterized by a *short neck, due to fusion of cervical vertebrae*
 3. Vertebral bodies can suffer many anomalies due to *failure of segmentation*, e.g., block vertebrae or vertebral bar.

Spina Bifida (Fig. 2.7)

- **Mechanism:** Defect in the vertebral arch, which allows contents of the spinal canal to herniate outside the body. It is common in the *lumbosacral* spine area.
- **Prevention:** *Folic acid* supplementation during pregnancy
- **Screening:** Ultrasound in the first trimester shows the *Lemon sign*.
- **Treatment:** Surgical
- **Notes:**
 1. Hypertrichosis in the lower lumbar area could be a sign of *spina bifida occulta*.
 2. If the same defect occurs in the back of the skull, it is called *encephalocele*.

Craniosynostosis (Craniosynostosis)

- **Definition:** Premature closure of one or more of the cranial suture lines

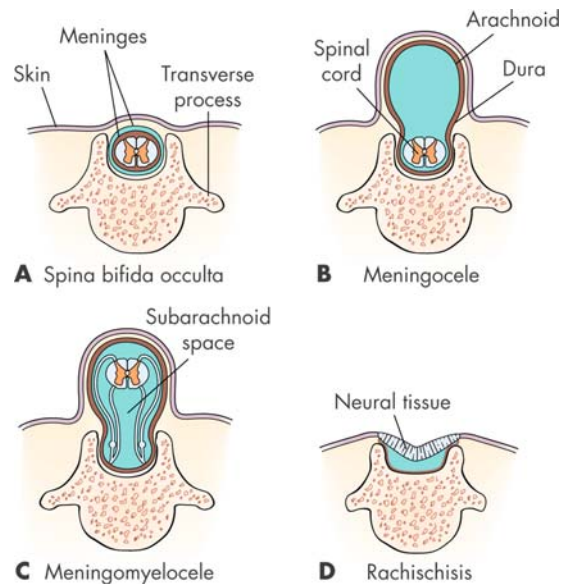


FIG. 2.7 Spina bifida

- **Types:**
 1. **Acrocephaly:** Due to premature closure of *coronal* and *lambdoid* sutures
 2. **Scaphocephaly:** Due to premature closure of *sagittal* suture
 3. **Plagiocephaly:** Due to unilateral closure of *coronal* suture
- **Clinical picture:**
 1. Abnormally shaped skull
 2. Increased intracranial pressure: Headache, blurry vision, nausea, and vomiting
 3. Ophthalmology: *Optic atrophy and blindness*
- **Diagnosis:** Palpable ridge over the prematurely closed suture line, while the skull x-ray shows *silver beaten appearance*
- **Treatment:** Craniotomy and opening of the suture

Musculoskeletal System

Embryology

- **Somites:** Each of the 35 pairs of somites in the paraaxial mesoderm divides into three structures:
 1. **Sclerotome:** Forms *bones and cartilage*
 2. **Dermatome:** Forms *skin*
 3. **Myotome:** Gives rise to the *epimere for back muscles, and hypomere for front muscles*
- **Myotomes:** They develop anterior and posterior condensations:

1. Anterior condensations: *Flexors and pronators of upper limb*, plus *flexors and adductors of lower limb*
 2. Posterior condensations: *Extensors and supinators of upper limb*, plus *extensors and abductors of lower limb*
- *Extraocular muscles*: Arise from *1st, 2nd, and 3rd myotomes*
 - *Smooth muscles*: Arise from *mesoderm*
 - *Cardiac muscle*: Arise from the *mesoderm surrounding the heart tube*
 - *Skeletal muscles*: Arise from *mesoderm*, which forms myogenic cells. These cells undergo mitotic division and differentiation under the regulation of *MyoD* protein, until they form the muscle fibers. Muscle fibers grow by addition of *satellite cells*.

Marfan Syndrome

- *Mechanism*: Autosomal dominant disease resulting in defective *fibrillin-1*
- *Clinical picture*:
 1. Very tall patient with *arm span exceeding height*, and elastic joints
 2. *Dilated ascending aorta, aortic regurgitation, and mitral valve prolapse*
 3. *Thoracic aortic aneurysm*: Due to *cystic medial necrosis*
- *Complication*: *Aortic dissection*. So when you see a patient on the USMLE with features of Marfan presenting with tearing chest pain radiating to his back, and a big difference of blood pressure between right and left arms, you know what to think!

Osteogenesis Imperfecta

- *Mechanism*: Deficiency of *type 1 collagen*, due to mutation of *COL1A1* gene
- *Clinical picture*: Fragile bones with multiple fractures, and *blue sclera* due to thin connective tissue

Congenital Absence of Muscles

- *Poland syndrome*: Defect in formation of the *pectoralis major* muscle
- *Prune belly syndrome*: One or more *abdominal muscles* are absent. It is usually associated with *hydro-nephrosis and undescended testes*.

Limbs

Embryology

- *Limb buds*:
 1. They sprout from the *lateral plate mesoderm* during the *4th week*, with an *ectodermal ridge* on each tip.
 2. This ridge produces fibroblast growth factor (*FGF*) to regulate its own growth.
 3. The base of the bud releases a growth-regulating protein known as *Sonic Hedgehog*, which needs *retinoic acid* to work effectively.
- *Rotation*: It is the last process of limb formation. *Upper limb buds rotate 90 degrees laterally*, while the *lower limb buds rotate 90 degrees medially*. This step occurs during the *8th week* after which the limbs are complete.
- *Fingers and toes*: They are formed by means of *apoptosis*.
- *Ossification centers at birth*: *Distal femur, proximal tibia, proximal humerus, and the cuboid bone*.
- *Main fetal blood supply to limbs is*:
 1. Upper limb: *Subclavian artery*
 2. Lower limb: *Umbilical artery*
- *Notes*:
 1. Apoptosis also participates in the formation of *testes and the thymus*.
 2. *Limb buds form bones and vessels of limbs; muscles come from mesoderm*.

Achondroplasia

- *Mechanism*: Mutation of fibroblast growth factor (*FGF-3*)
- *Clinical picture*: Newborn born as a dwarf with *short arms and normal IQ* (Fig. 2.8)
- *Complication*: Neck x-rays are important to rule out *odontoid process hypoplasia*, as that is a risk factor for subluxation and spinal cord compression.

Famous Congenital Anomalies

- *Congenital rubella syndrome*:
 1. Ear, nose, and throat (ENT): *Sensorineural hearing loss*
 2. Eye: Glaucoma, cataract, and *salt-and-pepper retinopathy*
 3. Cardiovascular system: Patent ductus arteriosus (PDA) and *myocardial necrosis*
 4. Bone: Longitudinal radiolucent areas in metaphyses of long bones



FIG. 2.8 Achondroplasia

- *Congenital toxoplasmosis syndrome*
 1. CNS: Hydrocephalus and *scattered intracranial calcifications*
 2. Eye: Chorioretinitis
- *Congenital cytomegalovirus syndrome*
 1. CNS: Hydrocephalus and *periventricular intracranial calcifications*
 2. Eye: Chorioretinitis
 3. ENT: Sensorineural hearing loss
- *Congenital herpes simplex syndrome*: Skin, eye, mouth (*SEM syndrome*), presenting with vesicular skin lesions and chorioretinitis. Most infections occur during passage of fetus through an infected birth canal. Prevention: Delivery by *C-section before rupture of membranes*.
- *Congenital varicella zoster syndrome*: Limb hypoplasia and multiple scarring.
- *Fetal alcohol syndrome*:
 1. Microcephaly
 2. Midfacial hypoplasia
 3. Short palpebral fissures
 4. Long philtrum of the lip
- *Fetal hydantoin syndrome*:
 1. Cleft lip or palate, and mental retardation
 2. Cupid bow
 3. Nail and digits hypoplasia
- *Medications associated with congenital anomalies* (teratogenesis occurs at any time during pregnancy, but is maximal during the *first 8 weeks of pregnancy*):
 1. Cocaine: *Intestinal atresia, and limb reduction defects*
 2. Lithium: *Ebstein anomaly*
 3. Progesterone: *Virilization and hypospadias*
 4. Radiation and iodine: *Goiter and hypothyroidism*
 5. Isotretinoin: *Thymus hypoplasia, microtia, and cardiac defects*
 6. Thalidomide: *Limb defects (Phocomelia)*
 7. Diethylstilbestrol (DES): *Vaginal clear cell adenocarcinoma, and incompetent cervix leading to repeated abortions*

Chapter 3

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Cerebrum

Anatomy (Figs. 3.1 and 3.2)

Cerebral Cortex

- *Histology*: The cerebral cortex is formed of six layers: Molecular → external granular → external pyramidal → internal granular → internal pyramidal → multiform.
- *Hemispheres*: The dominant hemisphere in most humans is the *left*, and it serves for *speech and language*, while the right hemisphere serves other functions.

Lobes (Fig. 3.3)

- *Frontal lobe*:
 1. Areas 4, 6: Injury causes *contralateral spastic paresis*.
 2. Area 8: Injury causes *ipsilateral eye deviation*.
 3. Areas 44, 45 (inferior temporal gyrus): Injury causes expressive (*Broca's*) *aphasia*, in which the patient understands *but cannot articulate*.
 4. Areas 9, 10, 11, 12: Injury causes *sphincter and gait disturbances*.
- *Temporal lobe*:
 1. Areas 41, 42: Injury causes *sensorineural hearing loss*.

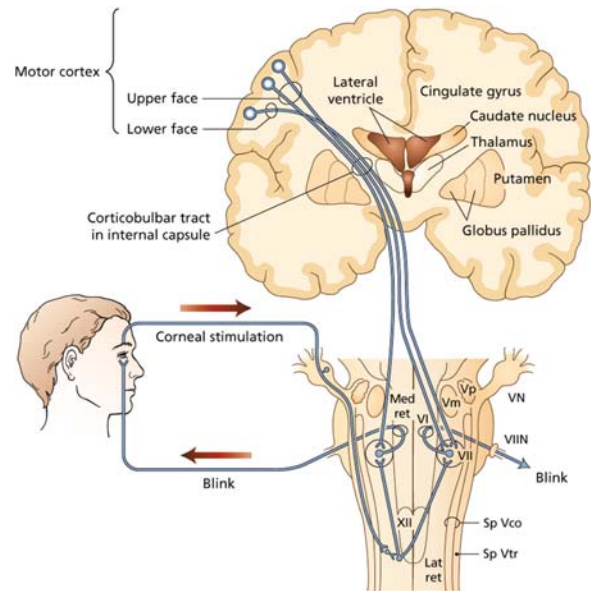


FIG. 3.2 Transverse section of the brain

2. Area 22 (superior temporal gyrus): Injury causes receptive (*Wernicke's*) *aphasia*, in which the patient *cannot understand language or symbols*. The patient *can articulate, but does not make any sense*; that is why it is known as *fluent aphasia*.
3. Anterior temporal lobe: Injury causes *Klüver-Bucy syndrome*.

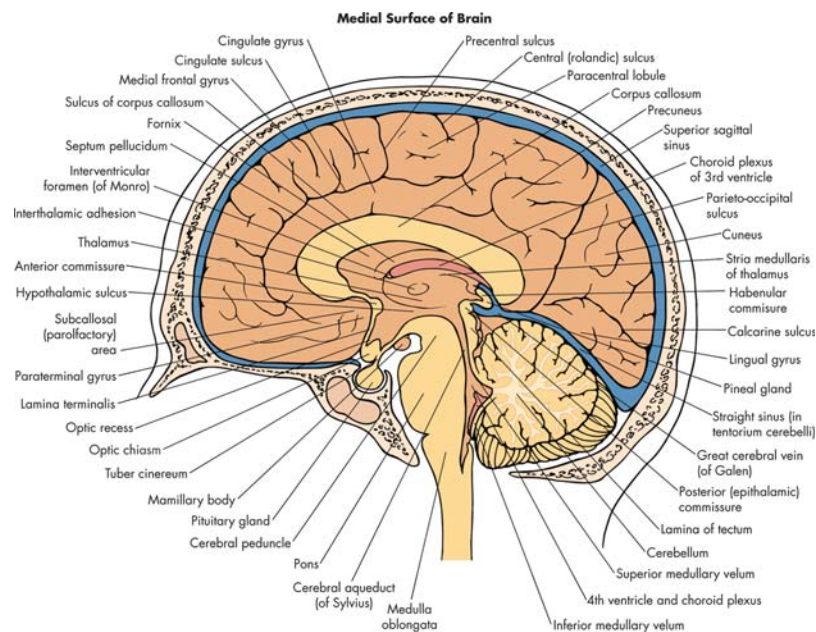


FIG. 3.1 Brain anatomy

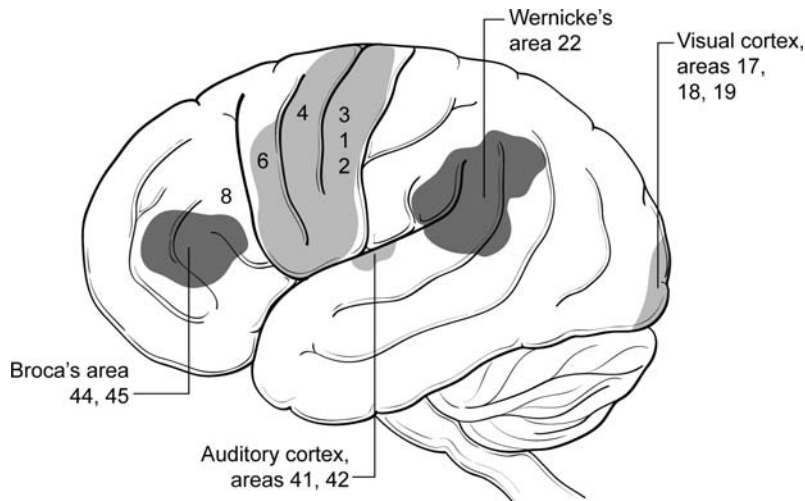


FIG. 3.3 Brain areas

- 4. Inferomedial occipitotemporal cortex: Injury causes *prosopagnosia*, in which the patient *cannot recognize faces*.
- **Parietal lobe:**
 1. Sensory cortex areas 3, 1, 2: Injury causes *contralateral hemihyperesthesia*.
 2. Superior parietal areas 5, 7: Injury causes *contralateral sensory neglect*.
 3. Inferior parietal area: Injury causes *Gerstmann syndrome*, which is full of *Dys's*—*dyslexia, dysgraphia, dyscalculia*.
- **Occipital lobe:**
 1. Unilateral injury: *Contralateral hemianopia*
 2. Bilateral injury: *Complete blindness*
- **External carotid artery (ECA):** Gives multiple branches, the most important being the *superficial temporal, lingual, and maxillary*. Note: *The maxillary artery gives rise to the middle meningeal artery, which bleeds in epidural hemorrhage*.
- **Internal carotid artery (ICA):** Passes through the *carotid foramen* into the skull and forms the *circle of Willis*, giving rise to the following branches:
 1. Ophthalmic artery: Runs with *optic nerve* and ends as the *central artery of retina*. Injury: *Blindness*.
 2. Anterior cerebral artery: Supplies most of the *medial cortex* that controls the *lower limbs*. Injury: Motor and sensory loss in the *contralateral lower limb*.
 3. Middle cerebral artery: Supplies most of the *lateral cortex* that controls the *face and upper limbs*, as well as giving off *lenticulostriate branches (artery of stroke)* to the *basal ganglia*. Injury: *Motor and sensory loss in the contralateral half of the body, plus homonymous hemianopia*.
 4. Posterior cerebral artery: Supplies the *occipital cortex*. Injury: *Contralateral sensory loss and homonymous hemianopia with macular sparing*.
 5. Anterior communicating artery: Connects the *anterior cerebral arteries* to each other. Injury: e.g., rupture of *Berry aneurysm, subarachnoid hemorrhage (SAH)*, and *bitemporal lower quadrantanopia*. Note: The most common location of *Berry aneurysms* is *at the bifurcation* of the *anterior communicating artery*
 6. Posterior communicating artery: Connects the *middle cerebral* with *posterior cerebral artery*.

Blood–Brain Barrier

- It is a membrane that protects the brain, allowing *only lipophilic materials* to pass through.
- **Composition:** Three components: Epithelium of choroid plexus, endothelium of cerebral capillaries, and arachnoid layer

Arterial Supply (Fig. 3.4)

- **Common carotid artery (CCA):** Left CCA arises directly from the *aorta*, while the right CCA arises from the *brachiocephalic trunk (branch of aorta)*. The CCA then bifurcates at the level of *T4* into external and internal branches.

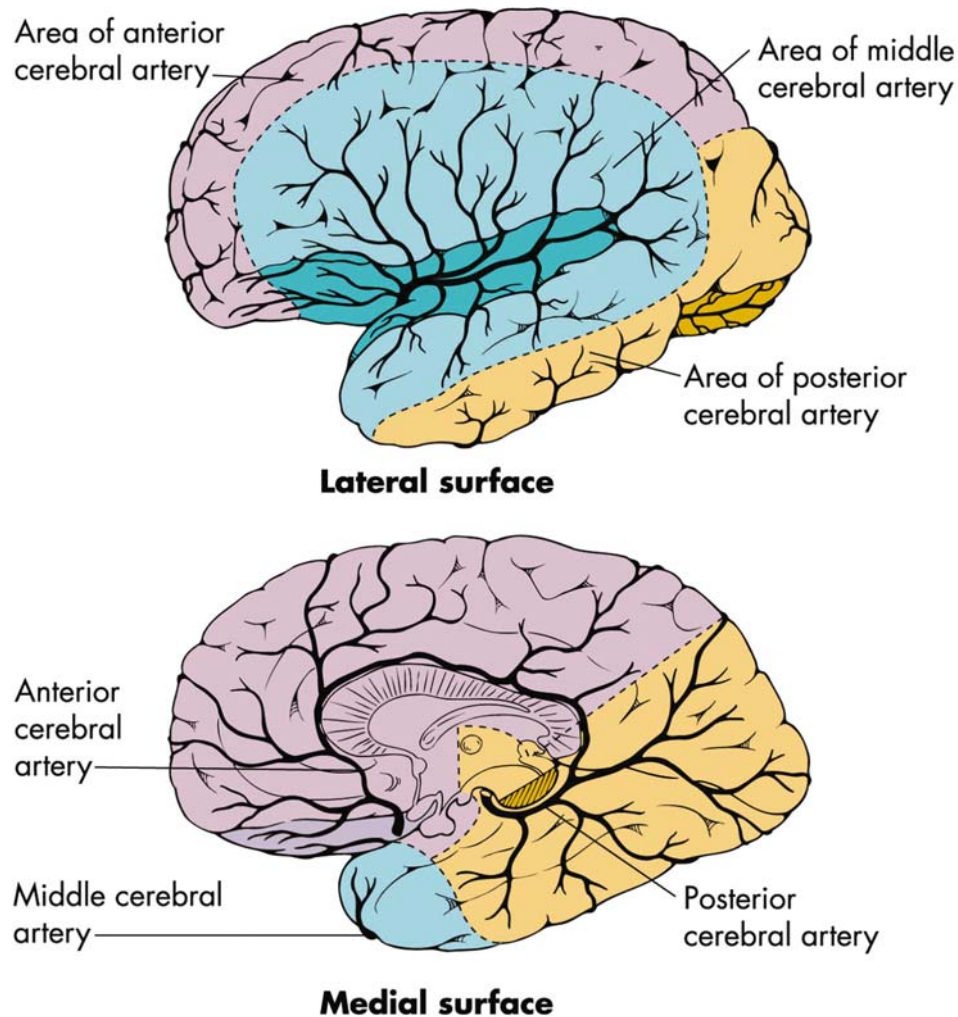


FIG. 3.4 Blood supply of the brain

Injury: *SAH* and injury of *third cranial nerve*. Suspect in a patient presenting with *SAH plus ptosis and diplopia*.

- *Circle of Willis*: It is formed of *three anterior arteries, three posterior arteries*, and the *ICA*:
 1. Three anterior: Anterior communicating artery, both anterior cerebral arteries
 2. Three posterior: Posterior communicating artery, both posterior cerebral arteries
 3. Internal carotid artery
- *Vertebral artery*: Arises from the *subclavian artery* on both sides, and they fuse together at the *lower border of the pons* to form the *basilar artery*.
- *Basilar artery*: It ends by dividing into *two posterior cerebral arteries*. Remember, the *anterior and middle cerebral arteries are branches of the internal carotid artery*.

Venous Drainage (Fig. 3.5)

- *Venous sinuses*: Located between *periosteal and meningeal layers of the dura*:
 1. Superior sagittal sinus: Contains *arachnoid granulations*
 2. Inferior sagittal sinus
 3. Straight sinus: Formed by fusion of the *inferior sagittal sinus* with *greater vein of Galen*
 4. Occipital sinus: Lies in the *attached border of Tentorium cerebelli*
 5. Confluence of sinuses: Grouping of 1, 3, and 4, above. It drains through the *transverse and sigmoid sinuses* into the *internal jugular vein*.
 6. Cavernous sinus: It lies on either side of the *sella turcica*. It drains through the *transverse and petrosal sinuses* into the *internal jugular vein*. Structures passing through the cavernous sinus are:

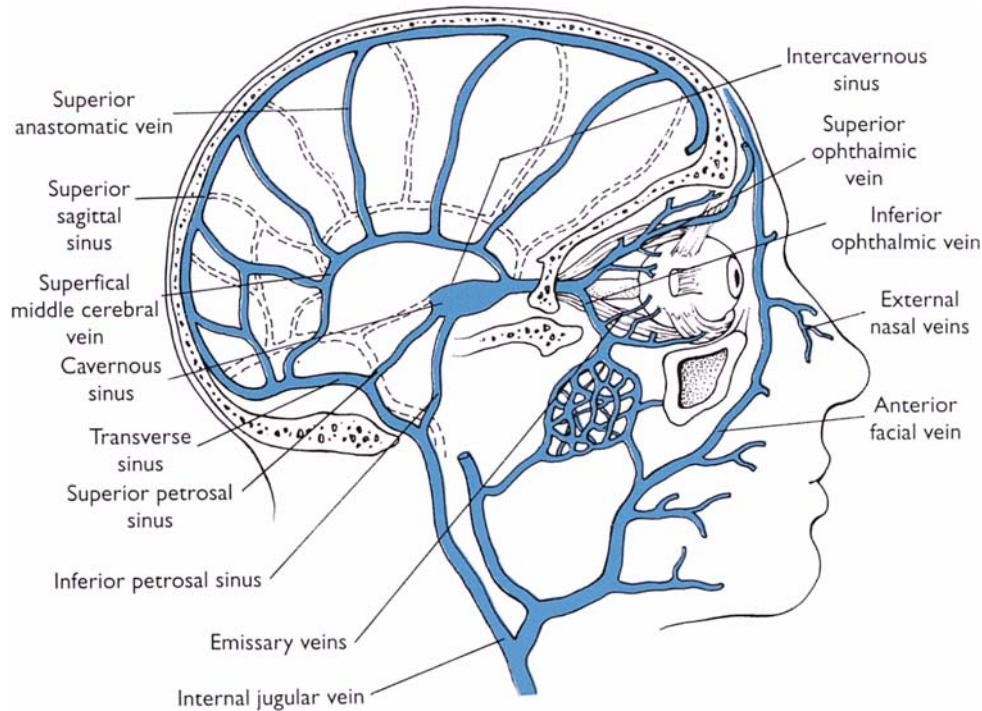


FIG. 3.5 Dural venous sinuses

Internal carotid artery and cranial nerves III, IV, V (1st and 2nd divisions only), and VI.

Cerebrovascular Accident (CVA)

- Also known as *stroke*; it could be ischemic or hemorrhagic.
- *Risk factors*:
 1. Ischemic stroke is common in patients with *arrhythmia*, e.g., atrial fibrillation.
 2. Hemorrhagic stroke is common in patients with head injury, e.g., falls.
 3. Amyloid deposition in intracranial vessels of the elderly could be a risk factor.
- *Clinical picture*:
 1. Middle cerebral artery (MCA) stroke: *Slurred speech*, *contralateral hemiplegia* and *hemihypoesthesia*. Common with internal capsule (lacunar) stroke. *Remember, MCA is the mother artery of the lenticulostriate artery.*
 2. Anterior cerebral artery (ACA) stroke: *Contralateral hemiplegia* and *hemihypoesthesia*, *more pronounced in the lower extremity*
 3. Posterior cerebral artery (PCA) stroke: *Contralateral homonymous hemianopia with macular sparing*
- 4. Vertebrobasilar stroke: *Vertigo*, *vertical nystagmus*, and *incoordination* signals suggestive of cerebellar injury, e.g., *ataxia*, *dysmetria*
- 5. Right parietal lobe infarction (neglect syndrome): Patient has *sensory neglect to left side of the body but moves it normally*, plus *visual field defects*.
- 6. Left parietal lobe infarction: Patient has *speech and language abnormalities*.
- *Diagnosis*: *Computed tomography (CT) of the head* is diagnostic, but most ischemic cases do not develop changes until *48 hours* after the insult (Fig. 3.6).
- *What to order*:
 1. *Repeat CT head in 24–48 hours*
 2. *Carotid Doppler*
 3. *Echocardiogram and electrocardiogram (ECG)*
- *Treatment*:
 1. Never drop the blood pressure too quickly, as it is usually high to maintain cerebral perfusion (*Cushing reflex: hypertension, and bradycardia*).
 2. Ischemic cases: Thrombolytic therapy with tissue-type plasminogen activator (tPA) if patient presented within the *first 3 hours* after onset of CVA. Other options include *antiplatelet agents*, e.g., aspirin, dipyridamole, clopidogrel



FIG. 3.6 Head CT showing bilateral ischemic cerebrovascular accident (CVA) (arrows)

3. Hemorrhagic cases: Treated conservatively unless hemorrhage is severe, e.g., *midline shift*, then surgical drainage is necessary.

Intracranial Hemorrhage

- *Clinical picture*: Patient has trauma followed by headache, photophobia, blurry vision, nausea, and vomiting.
- *Epidural*: *Convex-shaped*; bleeding is from *middle meningeal artery*, which runs between the *two roots of auriculotemporal nerve* (Fig. 3.7).
- *Subdural*: *Crescent-shaped*, and is the *most common traumatic intracranial injury*. Bleeding is from *superior cerebral (Bridging) veins* (Fig. 3.8).
- *Subarachnoid*: Patient has the “*worst headache of his/her life*.” Fundus exam might show *retinal hemorrhage*. Most common cause is trauma followed by rupture of an aneurysm, mostly in *communicating arteries*. Diagnosis: *Lumbar puncture, showing xanthochromia*. CT head can also show subarachnoid hemorrhage in most, but not all, cases (Fig. 3.9), so lumbar puncture remains the test of choice.

Cavernous Sinus Thrombosis

- *Causes*: Progression of infection from the sinuses or the orbit
- *Clinical picture*: Conjunctival congestion, with proptosis, fever, chills, and ophthalmoplegia

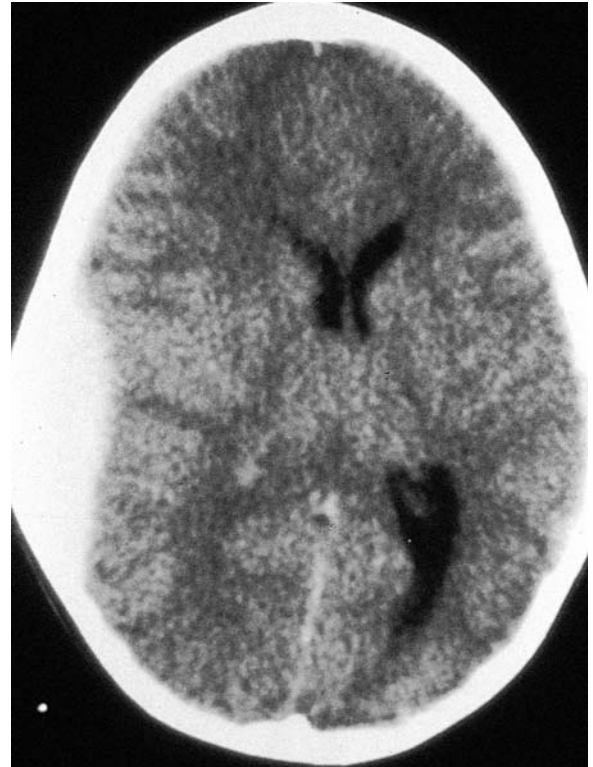


FIG. 3.7 Head computed tomography (CT) showing epidural hematoma

- *Treatment*: Antibiotics; surgical drainage is reserved for resistant cases.

Concussion

- *Mechanism*: Temporary loss of consciousness *due to failure of neurological signaling*. It is usually caused by mechanical brain injury, e.g., head trauma.
- *Phases*:
 1. Concussion: Immediate but temporary loss of consciousness
 2. Lucid interval: Full consciousness is regained, but a hematoma is building up.
 3. Compression: Due to the compressive effect of the hematoma
- *Complication*: *Recent memory loss*; regained gradually over up to 6 months
- *Diagnosis*: Clinical; *the radiology workup is normal*.
- *Treatment*: Conservative; resolves spontaneously

Alzheimer's Disease

- *It is the most common cause of dementia in the elderly*, with multi-infarct dementia ranking second.

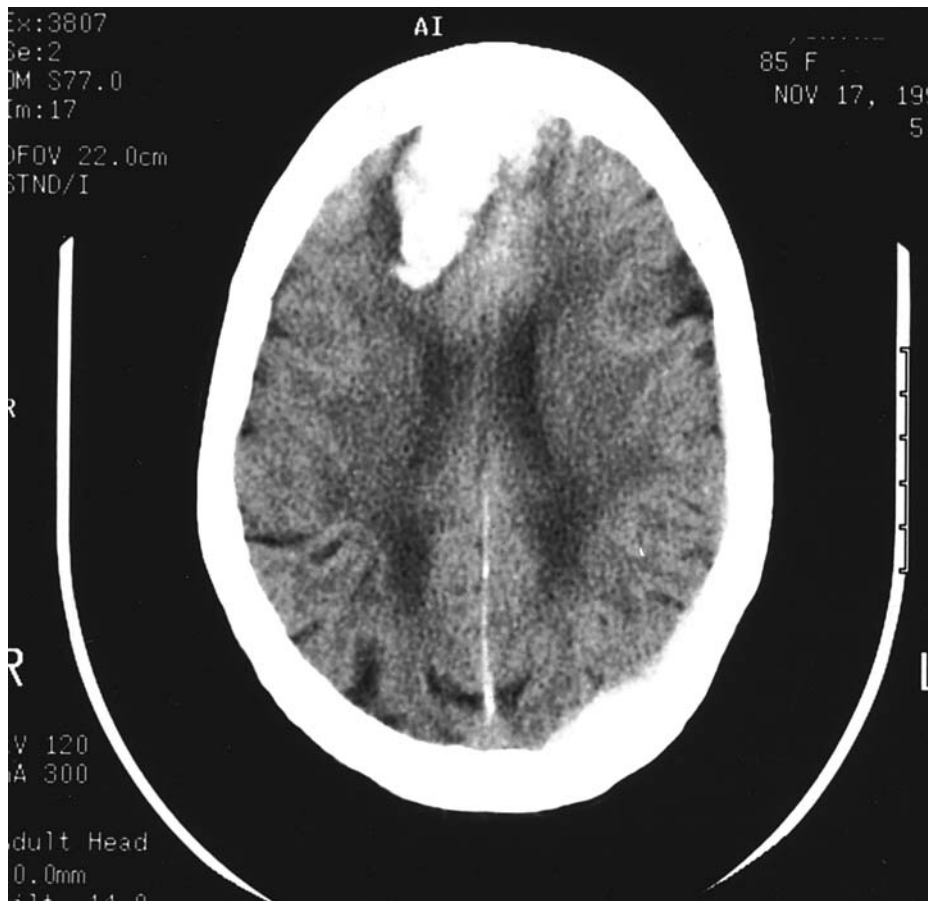


FIG. 3.8 Head CT showing subdural hematoma

- *Mechanism:* Decreased choline acetyltransferase (*CAT*) enzyme responsible for *acetylcholine synthesis*, and *loss of cholinergic neurons in the forebrain*
- *Genetics:* Abnormality in chromosomes 1, 14, and 21 has been suggested, also the presence of at least one copy of the *E4* gene on chromosome 19.
- *Clinical picture:* *Gradual, steady dementia*; in contrast, multi-infarct dementia is *stepwise*. In both cases, *recent memory is the first thing to be affected*, followed by *language* (patient cannot find the words), and finally *spatial ability*.
- *CT head:* *Ventricular dilatation* and *cortical atrophy*
- *Pathology:* *Amyloid plaques*, *Hirano bodies*, and *neurofibrillary tangles*; also, *degeneration of the nucleus of Meynert*
- *Treatment:* *Cholinesterase inhibitors*, e.g., donepezil
- *Notes:*
 1. Pick's disease: Dementia that affects the *frontal and temporal lobes*, and is unique for the *intracytoplasmic inclusion bodies* known as *Pick bodies*
 2. Normal pressure hydrocephalus: Another cause of dementia with the unique triad of *dementia*, *wide-based ataxia*, and *urinary incontinence*

Glioblastoma Multiforme

- It is the *most common primary brain tumor*; also called *butterfly glioma*.
- *Pathology:* *Grade IV astrocytoma* with a very poor prognosis. Histology shows *pseudopalisading* of cancer cells around a central area of hemorrhage and necrosis.
- *Clinical picture:* High intracranial pressure, e.g., early morning headache, vomiting, and blurry vision due to papilledema
- *Diagnosis:* CT of the head shows a mass with necrotic center surrounded by edema.
- *Notes:*
 1. Brain tumors in adults are mainly *supratentorial*, with *metastatic tumors* being the most common brain tumor.



FIG. 3.9 Head CT showing subarachnoid hemorrhage

2. Brain tumors in children are mainly *infratentorial*, with *astrocytoma* being the most common brain tumor.
3. Metastatic brain tumors show a *ring enhancement* on the CT scan.

Pseudotumor Cerebri

- **Mechanism:** Elevated intracranial pressure without a space-occupying lesion
- **Age group:** *Overweight adolescent girls*
- **Causes:** Vitamin A toxicity, tetracyclines, steroid withdrawal, and oral contraceptive pills (OCPs)
- **Clinical picture:** Early morning headache, vomiting, and blurry vision due to papilledema
- **Diagnosis:** Diagnosis of exclusion; CT of the brain and lumbar puncture (LP) are normal
- **Complication:** Long-standing untreated cases can lead to permanent blindness.
- **Treatment:**
 1. Treat the cause.
 2. Steroids and acetazolamide: To decrease intracranial pressure
 3. Resistant cases: Shunt operation

Meningitis

- **Definition:** It is infection of the meninges, whether by bacteria or viruses.
- **Cause:** Most common organisms differ with age and condition:
 1. Newborn group: *Group B streptococcus*
 2. Children: *Streptococcus pneumoniae*
 3. Adults: *Neisseria meningitidis*
 4. Elderly: *Streptococcus pneumoniae*
 5. HIV patients: *Cryptococcus neoformans*, a form of yeast with *extracapsular halo*, found in *pigeon's droppings*, diagnosed by *India ink* staining and cultured on *Sabouraud agar*
- **Clinical picture:** Fever, headache, photophobia, and *neck stiffness*
- **On exam:** Stiff neck, positive *Kerning's* and *Brudzinski's* signs
- **Diagnosis:** Examining the cerebrospinal fluid (CSF) after an LP. *Agglutination test to detect soluble antigens in CSF is the most sensitive and specific test to diagnose meningitis.*
 1. CSF in bacterial meningitis: *High protein content, high pressure, high white blood cell (WBC) count, and low glucose level*
 2. CSF in viral meningitis: *High protein and high lymphocyte count with normal glucose level. In TB meningitis, CSF will show the same exact thing as the CSF in viral meningitis, except that the glucose level will be very low.*
- **Complications:**
 1. Adrenal hemorrhage (*Waterhouse-Friderichsen syndrome*): Seen as *shell-like calcifications* on the x-ray
 2. Encephalitis: Shown on electroencephalogram (EEG) as *sharp triphasic complexes*. Note that herpes encephalitis is unique in causing olfactory hallucinations and showing mononuclear pleocytosis and red blood cells (RBCs) in the CSF.
- **Treatment:**
 1. Drug of choice: *Third-generation cephalosporin + vancomycin*
 2. Treatment of *Cryptococcus neoformans*: *Amphotericin B + flucytosine*
- **Prophylaxis for close contacts:** Drug of choice is *rifampicin*
- **Notes:**
 1. TB meningitis causes injury of cranial nerves *III, VI, VII, and VIII* only.

- If you face a case on the USMLE with meningitis, along with extremely elevated amylase level with no clear abdominal source, think of *acute viral parotitis*.

Meningioma

- These tumors arise from the *arachnoid villi* of meninges.
- 90s rule*: 90% of meningiomas are benign, and 90% are supratentorial.
- Clinical picture*: Asymptomatic, or present with a focal deficit
- Diagnosis*: CT or magnetic resonance imaging (MRI) of the brain; confirmation of diagnosis by biopsy
- Treatment*: Surgical only if symptomatic
- Pathological clue*: Suspect meningioma on the USMLE if a case is presented with increased intracranial pressure along with *psammoma bodies* on pathology report.
- Notes*:
 - Oligodendrogliomas* arise from frontal lobes, are slow-growing tumors, and very commonly show calcifications.
 - Psammoma bodies* could be seen in *Papillary carcinoma of thyroid*, *Meningioma*, and *Serous ovarian cyst (PMS)*.

Ventricles and Cerebrospinal Fluid

Anatomy

- Two lateral ventricles*: Open into the third ventricle via *two foramina of Monro*
- Third ventricle*: Opens into the fourth ventricle via the *aqueduct of Sylvius*
- Fourth ventricle*: Drains into the *subarachnoid space* (which surrounds the entire brain and spinal cord) via the *foramina of Luschka and Magendie*
- Choroid plexus*: Lie inside the ventricles, and form the CSF. These plexuses are formed of folded blood vessels from the *pia*.
- Notes*:
 - CSF is *formed by the choroid plexus* and is *absorbed by arachnoid villi*. These villi drain the fluid back to the *superior sagittal sinus*, and the closed cycle restarts.
 - The ventricles are lined by *ependymocytes*.
- CSF*: It normally contains *no RBCs*, and its composition at a glance is:

- Protein: 20–50 mg/dL
- Glucose: 50–80 mg/dL
- Pressure: 80–180 mm H₂O

Hydrocephalus

- Communicating*: Obstruction is in the *subarachnoid space*.
- Noncommunicating*: Obstruction is before the CSF reaches the subarachnoid space. There is a true obstruction as follows:
 - Congenital aqueductal stenosis: *X-linked hydrocephalus* causing dilatation of *lateral* and *third* ventricles (Fig. 3.10)
 - Dandy-Walker deformity: Obstruction in the foramina of *Luschka and Magendie*, which leads to dilatation of the *4th ventricle*, along with an *atrophied cerebellum* and *occipital meningocele* (Fig. 3.11)
- Remember*: If a hydrocephalus question mentions:
 - Dilated *lateral and third* ventricles: Obstruction is at the *aqueduct*
 - Dilated *4th ventricle* and normal 3rd and lateral: *Dandy-Walker*
- Normal pressure hydrocephalus*: It occurs due to *failure of the arachnoid villi to absorb the CSF*. Patients are usually elderly with a slow progression of symptoms, or just had a recent traumatic brain injury and intracranial hemorrhage. Clinical picture: Triad—*dementia, urinary incontinence, and wide-based ataxia*.

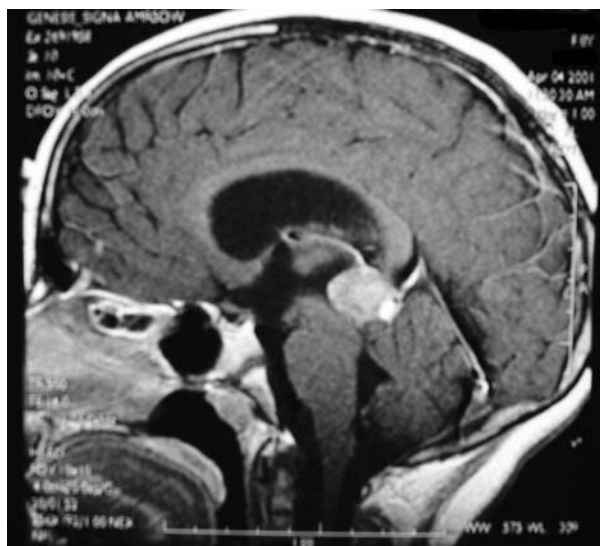


FIG. 3.10 Hydrocephalus secondary to obstruction of aqueduct of Sylvius by a tumor

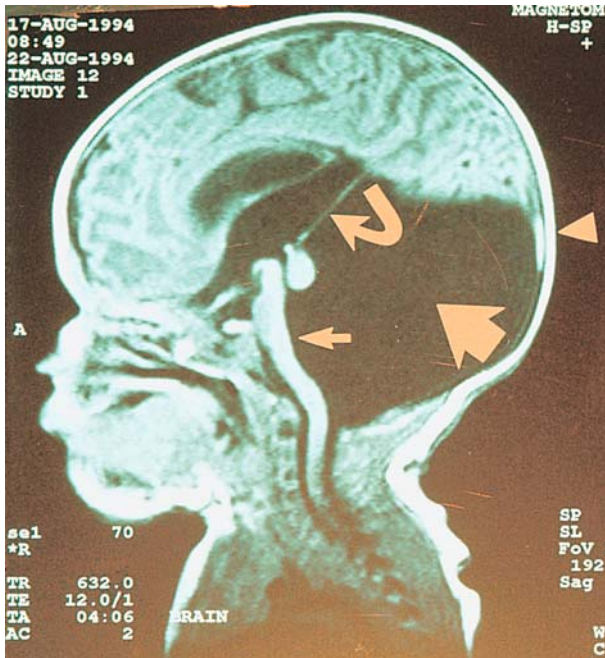


FIG. 3.11 Hydrocephalus (Dandy-Walker) Thick arrow: Dilated 4th ventricle. Thin arrow: Anterior displacement of atrophied cerebellum and brain stem

- *Treatment of hydrocephalus: Surgical placement of a shunt*

Arnold-Chiari Malformation

- *Mechanism: Elongation of the cerebellum and medulla oblongata through the foramen magnum, compressing cranial nerves IX, X, and XI*
- *Clinical picture: Stridor, dysphagia, vocal cord paralysis, and hydrocephalus. (Helpful to remember: "Arnold is a kid with big head who cannot talk, breathe, or eat.")*
- *Treatment: Surgical placement of a shunt*

Cerebellum

Anatomy

- The cerebellum is the center of *coordination and balance*. Accordingly, cerebellar diseases all lead to *hypotonia* and *loss of coordination*, e.g., intention tremors and dysmetria.
- *Peduncles: Inferior afferent, middle, and superior efferent peduncles*
- *Layers:*
 1. Molecular layer
 2. Purkinje layer: Releases *inhibitory gamma-aminobutyric acid (GABA)* upon stimulation by *climbing and parallel fibers*

3. Granular layer: Releases *stimulatory glutamate* upon stimulation by *mossy fibers*. Note that *stimulation of Golgi fibers inhibits glutamate production*.

Cerebellar Vermis Syndromes

- *Cerebellar anterior vermis syndrome: Common in alcoholics. Clinical picture: Lower extremity incoordination.*
- *Cerebellar posterior vermis syndrome: Common in children; a classic cause is medulloblastoma. Clinical picture: Trunk and upper extremity incoordination.*

Cerebellar Tumors

- Most midline tumors are Medulloblastomas, while most lateral ones are Astrocytomas.
- The most common brain tumors in children are *posterior fossa tumors*, mainly *infratentorial*. *Astrocytoma is the most common cerebellar tumor in children.*
- *Clinical picture: Incoordination, ataxia, nystagmus, and high intracranial pressure*
- *Treatment: Surgical resection, and possibly radiation and chemotherapy*

Hypothalamus and Thalamus

Hypothalamus

- As a rule, the *posterior part of the hypothalamus regulates the sympathetic system*, while the anterior part regulates the parasympathetic.
- *Supraoptic nucleus: Regulates antidiuretic hormone (ADH) secretion*
- *Paraventricular nucleus: Regulates oxytocin secretion*
- *Anterior nucleus: Regulates the process of cooling*
- *Posterior nucleus: Regulates the process of heating*
- *Lateral nucleus: Regulates the process of hunger*
- *Medial nucleus: Regulates the process of satiety*
- *Septate nucleus: Regulates sexual urges and emotions*
- *Wernicke'-Korsakoff syndrome: A common question on the USMLE is about the hypothalamic structure injured in alcoholism and Wernicke's encephalopathy. The answer is the mammillary bodies. Clinical picture:*
 1. *Wernicke's encephalopathy: Encephalopathy, ataxia, and nystagmus; due to thiamine (B1) deficiency*

2. Korsakoff's confabulations: *Anterograde amnesia* and *fabrication of stories*; due to injury of *hippocampus*

Thalamus

- Supplied by *posterior cerebral* and *posterior communicating* arteries
- *Anterior nucleus*: Regulates *emotions*
- *Pulvinar*: Largest thalamic nucleus; it regulates visual and auditory input as follows:
 1. The visual pathway: Relays through the *lateral geniculate body* (LGB) before it reaches *area 17*
 2. The auditory pathway: Relays through the *medial geniculate body* (MGB) before it reaches *areas 41, 42*
- *Note*: A common question on the USMLE is about the thalamic structure injured in alcoholism and Wernicke's encephalopathy. Answer: *Mediodorsal thalamic nucleus*.

Internal Capsule and Limbic System

Internal Capsule

- *Parts*: *Anterior limb*, *genu*, and *posterior limb*
- *Anterior limb*: Contains *striate branches of the anterior and middle cerebral arteries*.
- *Genu and posterior limb*: *Anterior choroidal artery* passes through them

Limbic System

- *Functions*: *F's*, e.g., *feel, feed, fear, fight, and flight*
- *Hippocampus*: *Center of learning and memory*, and is injured in *Korsakoff syndrome*
- *Amygdala*: *Center of fear*. If damaged, e.g., *Klüver-Bucy syndrome*, the patient becomes *placid, hyperphagic, and hypersexual*.
- *Note*: To sum up, the injury sites in alcoholism are:
 1. Wernicke's encephalopathy: Due to vitamin B₁ (thiamine) deficiency:
 - *Mammillary bodies of hypothalamus*
 - *Mediodorsal nucleus of thalamus*
 2. Korsakoff's syndrome: *Hippocampus*

Basal Ganglia

Anatomy

- *Parts*: *Caudate nucleus*, *putamen*, and *globus pallidus*

- *Striatum* = Caudate nucleus + putamen
- *Lentiform nucleus* = Putamen + globus pallidus

Parkinson's Disease

- *Mechanism*: Depletion of dopamine-producing neurons in the *substantia nigra*, interfering with the transmission of movement signals to the striatum
- *Causes*: Combination of genetic and environmental factors. However, it could result from use of illegal drugs contaminated with *MPTP* (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) or *metoclopramide*.
- *Clinical picture*: Main symptoms (five R's):
 1. *Rigidity*: Mostly cogwheel
 2. *Resting tremors*: Disappear with movement
 3. *Hyporeflexia* or *areflexia*
 4. *Bradykinesia*
 5. *Others*: Shuffling gait, mask face, and micrographia
- *Pathology*: *Lewy bodies*, and *degeneration of substantia nigra*
- *Treatment*:
 1. Levodopa (L-dopa) plus carbidopa: It is the mainstay of treatment. L-dopa is preferred over dopamine as it is lipophilic and can easily cross the blood-brain barrier. *Carbidopa* is added to decrease the peripheral effects and metabolism of L-dopa.
 2. Other drugs: Newer dopamine agonists, anticholinergics (to decrease tremors), and monoamine oxidase B (MAO-B) inhibitors

Huntington's Chorea

- *Autosomal dominant* disease on *chromosome 4*
- *Mechanism*: *Atrophy of the caudate nucleus and degeneration of its cholinergic and GABAergic neurons*
- *Clinical picture*: *Dementia, hypotonia, and choreoathetoid movements*, due to *hyperactive N-methyl D-aspartate (NMDA) and glutamate*
- *Diagnosis*: Brain CT or MRI, which shows:
 1. *Atrophy of frontal and temporal gyri and caudate nucleus*
 2. Dilated anterior horns of lateral ventricles
- *Notes*:
 1. Chorea is sudden purposeless movements, while athetosis is slow distal writhing movements.
 2. Huntington's patients usually have *low substance P levels* in the central nervous system (CNS).

3. If you see a case with chorea on the exam, look for these clues:

- If the patient has *rheumatic fever* picture: *Sydenham's chorea*
- If the patient is *pregnant and in her 2nd trimester*: *Chorea gravidarum*
- If the patient has a *strong family history*: *Huntington's chorea*

Tardive Dyskinesia

- **Definition:** It is a movement disorder in patients using *antipsychotics* (neuroleptics) or *metoclopramide* for an extended period of time.
- **Clinical picture:** Repetitive chorea-like movements of the face, tongue, and neck
- **Treatment:** Stop the offending medication.

Wilson's Disease

- **Mechanism:** *Autosomal recessive* disorder causing excessive *tissue copper concentrations*, due to *ceruloplasmin (copper carrier) deficiency*
- **Clinical picture:**
 1. Extrapyramidal manifestations, e.g., wing-beating tremors
 2. Hepatosplenomegaly and renal failure
 3. *Kaiser-Fleischer rings* in the cornea
- **Diagnosis:** Low ceruloplasmin, and high liver and urine copper levels
- **Treatment:** Copper-chelating therapy, e.g., *penicillamine* (causes B6 deficiency)

Hemiballismus

- **Mechanism:** Vascular lesion injuring the *subthalamic nuclei*
- **Clinical picture:** Sudden, aggressive *flinging movements on the contralateral arm*, e.g., “*swinging a baseball bat*” movement

Brainstem

Anatomy

- **Parts:** Midbrain, pons, and medulla oblongata (Figs. 3.12 and 3.13)
- **Blood supply:** Vertebrobasilar system
- **Cranial nerves:** Brainstem is the origin of cranial nerves III to XII.
 1. Midbrain: III and IV

2. Pons: V to VIII
3. Medulla: IX to XII

Midbrain Lesions

- **Parinaud syndrome (dorsal):** Most common cause is *pinealoma*. Lesions may be located in various locations:
 1. Superior colliculi: *Paralysis of upward, downward, and convergent gaze*
 2. Aqueduct of Sylvius: *Noncommunicating hydrocephalus*
- **Benedikt syndrome (paramedian):**
 1. Ipsilateral oculomotor nerve palsy
 2. Contralateral medial lemnisci injury
 3. Contralateral cerebellar ataxia
- **Weber's syndrome (medial):**
 1. Ipsilateral oculomotor nerve palsy
 2. Contralateral corticospinal tract injury
 3. Contralateral paralysis of face, tongue, and palate: patients present with their uvula directed *toward the unaffected side*, plus symptoms of posterior cerebral artery injury.

Pons Lesions

- **Inferior pontine syndrome:**
 1. Medial: Due to injury of *basilar artery*, affecting the corticospinal tract, medial lemniscus, and abducens nerve (VI)
 2. Lateral: Due to injury of the *anterior inferior cerebellar artery*, causing an ipsilateral facial palsy and ipsilateral sensorineural hearing loss
- **Medial longitudinal fascicular (MLF) syndrome:** Also known as internuclear ophthalmoplegia, and is pathognomonic of *multiple sclerosis*. Clinical picture: Injury of the nerve fibers extending *between the abducens and oculomotor nerves*, which leads to palsy of the *medial rectus muscle* along with *nystagmus*.
- **Pontine hemorrhage:** Due to injury of *basilar or cerebellar arteries*. Clinical picture: *Unilateral facial and contralateral body paralysis*. Note: *Pinpoint pupils are observed if bleeding is severe*.

Medulla Oblongata Lesions

- **Medial medullary syndrome:** Due to injury of the *anterior spinal artery*, causing injury to the following structures:

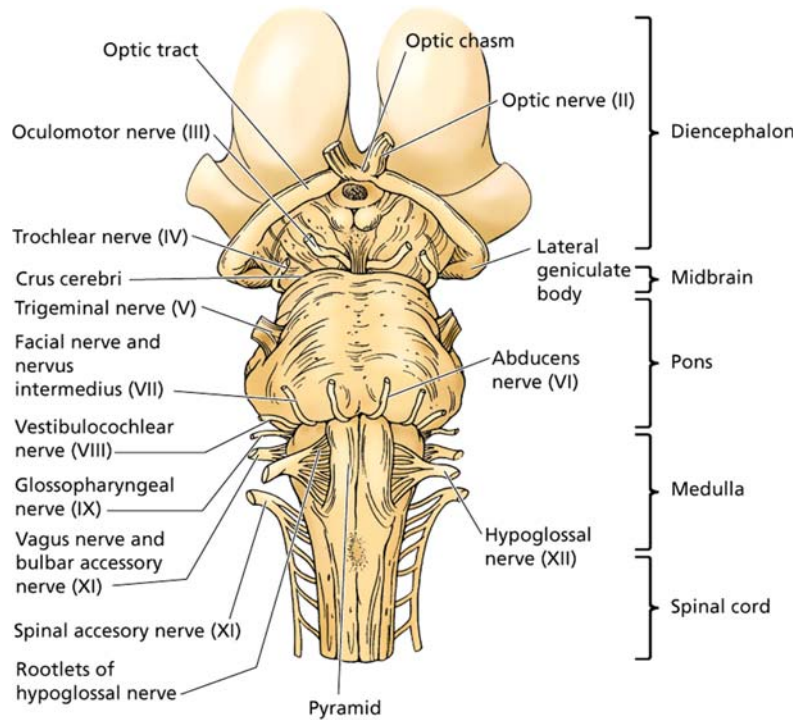


FIG. 3.12 Anatomy of the brainstem (anterior surface)

1. Corticospinal pyramid: Contralateral spastic paresis
2. Medial lemniscus: Contralateral loss of touch and proprioception

3. Hypoglossal nucleus: Ipsilateral flaccid paralysis of the tongue; accordingly, the tongue veers toward the affected side.

- *Wallenberg syndrome (lateral)*: Due to injury of the posterior inferior cerebellar artery, causing injury to the following structures:

1. Nuclei of cranial nerves IX, X, and XI: Dysphagia, dysarthria, dysphonia, and loss of the gag and cough reflexes
2. Sympathetic chain: Causing ipsilateral Horner's syndrome
3. Trigeminothalamic tract: Causing ipsilateral loss of pain and temperature sensations from face
4. Lateral spinothalamic tract: Causing contralateral loss of pain and temperature sensation from the body
5. Vestibular nuclei: Causing vertigo and nystagmus
6. Cerebellar peduncles: Causing ipsilateral cerebellar ataxia

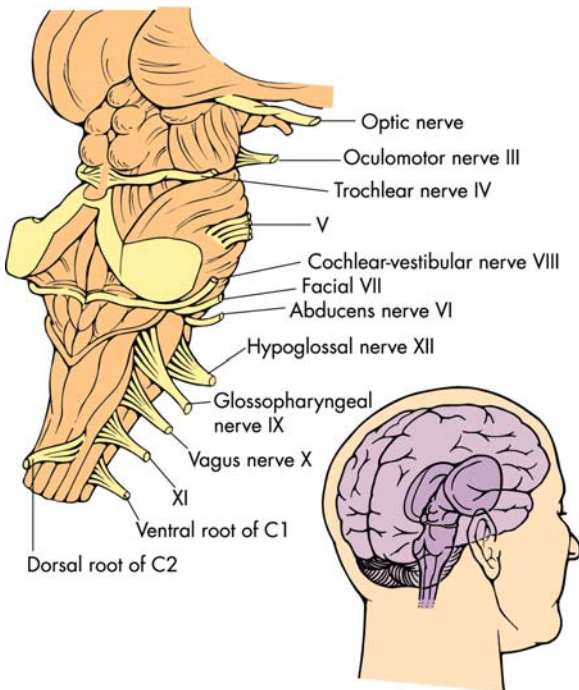


FIG. 3.13 Anatomy of the brainstem (posterior surface)

Spinal Cord

Anatomy

- *Matters:*

1. Grey matter: Formed of neuronal cell bodies, and is found in the horns

2. White matter: Formed of *neuronal fibers*, and is found in the funiculi
- *Extent*: The spinal cord ends at the *conus medullaris (L1)*. It then continues caudally in the form of *cauda equina*; which is formed of the ventral and dorsal roots of *L2 to coccygeal 1*. The subarachnoid space ends at the level of *S2*.
 - *Meninges*:
 1. Pia matter is very “popular” and the other layers like to remain attached to it, so the dura attaches to pia via the *denticulate ligaments*, while the arachnoid attaches to pia via *trabeculations*.
 2. At the end of the cord, the pia matter extends caudally in the form of *filum terminale*, which joins the dura at the level of *S2*.
 - *Spinal cord covers*: Starting from outside in, the layers covering the spinal cord are: Epidural space (contains the *venous plexuses*) → dura matter → subdural space → arachnoid matter → subarachnoid space → pia matter.

Blood Supply

- *Anterior spinal artery*: A branch of *vertebral artery*. It runs in the *ventral median fissure*, supplying the *anterior two thirds of the cord*.
- *Posterior spinal artery*: A branch of *vertebral and posterior inferior cerebellar arteries*. It supplies the *posterior one third of the cord*.
- *Artery of Adamkiewicz*: A branch of *lumbar or left posterior intercostal arteries*. It normally joins the *anterior spinal artery* somewhere in its course and supplies the *lower part of the cord*. Thrombosis or injury of this artery is common in *abdominal aortic aneurysm surgeries*, and leads to *paraplegia, incontinence, and impotence*.
- *Anterior and posterior radicular arteries*

Spinal Nerves

- *31 spinal nerves*: eight cervical, 12 thoracic, five lumbar, five sacral, and one coccygeal. *Remember, there are 33 vertebrae and 31 spinal nerves.*
- *Structure*: Spinal nerves are formed by fusion of the *dorsal afferent roots* with the *ventral efferent roots*. Each spinal nerve divides into a dorsal and ventral ramus:
 1. *Dorsal ramus*: *Supplies the dorsal half of the body*
 2. *Ventral ramus*: *Supplies the ventral half of the body*

Dorsal Column

- It is formed from the *gracile fibers of the lower limbs*, and *cuneate fibers from the upper limbs* (Fig. 3.14).
- *Function*: Transmits *fine touch and proprioception* from the limbs.
- *Course*: The fibers ascend in the dorsal column and *decussate in the medulla* forming the *medial lemniscus*, and they end in *Brodmann areas 1, 2, and 3*.
- *Injury*:
 1. Below decussation: Ipsilateral loss of fine touch and proprioception sensations
 2. Above decussation: Contralateral loss of fine touch and proprioception sensations

Lateral Spinothalamic Tract

- *Function*: Transmits *pain and temperature* sensations from body
- *Receptors*: *Fast A and slow C fibers*
- *Course*: Fibers run in the *Lissauer tract*, then decussate in the *anterior white commissure* at the same level they enter the cord. Fibers then ascend in the *lateral funiculus* and terminate in *Brodmann's area 1, 2, and 3* (Fig. 3.14).
- *Injury*: Contralateral loss of pain and temperature sensations
- *Note*: Anterior spinothalamic tract transmits *deep touch and pressure* sensations from the body. *Injury: Contralateral loss of touch and pressure sensation.*

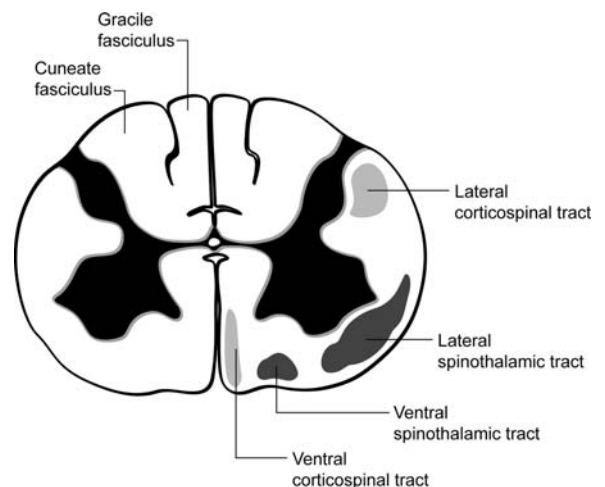


FIG. 3.14 Illustration showing the location of spinal tracts

Lateral Corticospinal Tract

- This tract is characterized by *delayed myelination*, which is *not complete until 2 years of age* (Fig. 3.14).
- *Function*: Transmits *voluntary motor signals*
- *Course*: Fibers arise from the cerebral cortex and *decussate in the medulla*
- *Injury*: *Spastic paresis*

Miscellaneous Tracts

- *Hypothalamospinal tract*: This tract runs from the *hypothalamus* to the *intermediolateral column* of the spinal cord. Injury: *Ipsilateral Horner's syndrome*.
- *Spinocerebellar tract*: Transmits *proprioception from the muscles and joints*
- *Ventral trigeminothalamic tract*: Transmits *pain and temperature from the face*
- *Dorsal trigeminothalamic tract*: Transmits *touch and pressure from the face*

Spinal Cord Lesions

- *Upper motor neuron lesions (UMNLs)*: Causes *hypertonia* and *hyperreflexia*
- *Lower motor neuron lesions (LMNLs)*: Causes *hypotonia*, *hyporeflexia*, and *fasciculations*
- *Spinal cord injury above C3*: May cause *quadriplegia*. Systemic steroids given in the *first 10–12 hours* after spinal cord injury help minimize damage.
- *Spinal cord tumors*: Include *astrocytomas*, *meningiomas*, and *metastatic cancers*
- *Note*: *Dumbbell-shaped spinal cord tumors (schwannomas)* are common in *neurofibromatosis type 2*.

Multiple Sclerosis (MS)

- It is a *demyelinating disease* affecting the brain and spinal cord. It is most common in *women 20–40 years of age*. Refer to Fig. 3.16
- *Clinical picture*: *Nonspecific limb weakness* and *visual deficits due to optic neuritis or internuclear ophthalmoplegia*
- *Diagnosis*:
 1. *MRI of brain*: Shows *periventricular white matter plaques* (Fig. 3.15)
 2. *CSF*: *High immunoglobulin G (IgG) level*
- *Treatment*: *Systemic corticosteroids*
- *Prophylaxis*: *Beta-interferon*

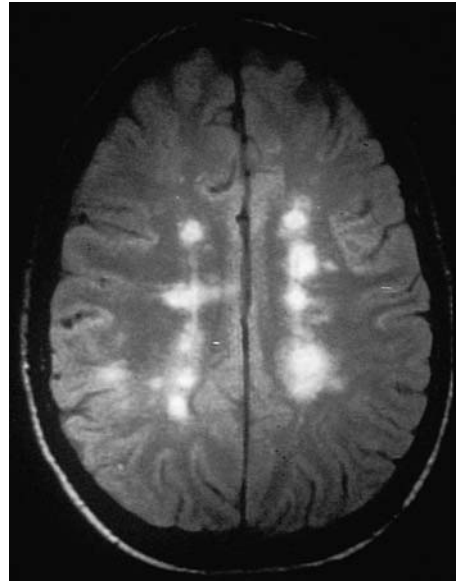


FIG. 3.15 Magnetic resonance imaging showing periventricular plaques in a case of multiple sclerosis

Poliomyelitis (Fig. 3.16)

- *Cause*: Polio virus, transmitted *feco-orally* and replicates in the *oropharynx*
- *Mechanism*: LMNL; due to injury of the *anterior gray horn*
- *Clinical picture*: *Hypotonia*, *hyporeflexia*, *muscle wasting*, and *fasciculations*
- *Diagnosis*:
 1. Isolation of polio virus from *oropharynx* or *stools*
 2. *CSF*: *Lymphocytosis* and elevated protein count
- *Note*: Werdnig-Hoffmann disease is an LMNL that simulates polio, with two exceptions:
 1. Werdnig-Hoffmann's lesions are *symmetrical*, while *polio's are not*.
 2. Werdnig-Hoffmann causes *hypoesthesia*, while *polio is purely motor*.

Amyotrophic Lateral Sclerosis (ALS) (Fig. 3.16)

- *Mechanism*: Also known as *Lou Gehrig disease*. It is combined *UMNL* and *LMNL*, which affects the *anterior gray horn* and the *corticospinal tracts*.
- *Clinical picture*: *Asymmetrical limb weakness* and combination of signs suggesting *UMNL* and *LMNL at the same time*, e.g., *hypertonia* and *fasciculations*

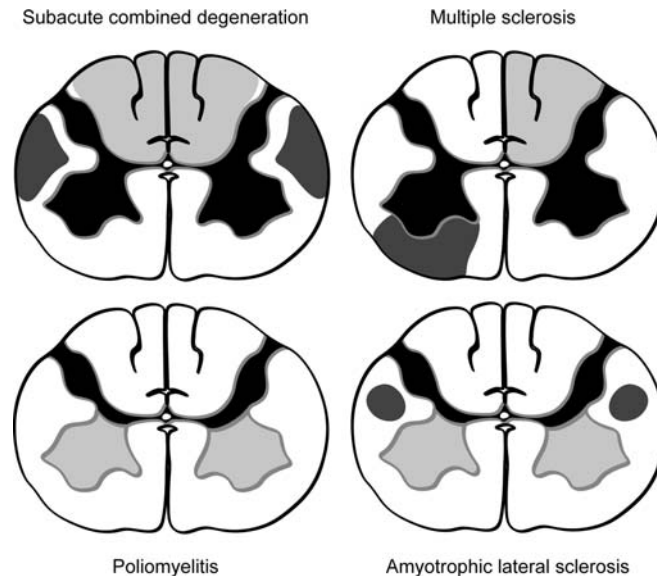


FIG. 3.16 Illustration showing the location of damage in some spinal lesions

Tabes Dorsalis

- *Mechanism: Dorsal column damage due to untreated syphilis*
- *Clinical picture:*
 1. Loss of proprioception and vibration sensations, plus *electric-like pains in the upper and lower extremities*
 2. *Ataxia and positive Romberg sign*, which is difficulty of the patient to stand still and upright with his eyes closed without swaying or even falling over.
- *Note: Tabetic crisis patients present with the above symptoms plus abdominal pain and bladder dysfunction.*

Brown-Séquard Syndrome

- *Mechanism: Hemisection of the spinal cord*
- *Clinical picture:*
 1. *Ipsilateral: Flaccid paralysis and Horner's syndrome*
 2. *Contralateral: Loss of pain and temperature sensations*

Anterior Spinal Artery Occlusion

- Common in abdominal aortic aneurysm surgeries
- *Clinical picture:*

1. Flaccid paralysis and loss of pain and temperature sensations *bilaterally below the level of lesion*
2. *Bilateral Horner's syndrome*

Subacute Combined Degeneration (SCD) (Fig. 3.16)

- *Mechanism: Affects the dorsal and lateral columns, due to vitamin B₁₂ deficiency*
- *Clinical picture: ataxia, loss of proprioception, and vibration sensations in a stocking/glove distribution*
- *Note: When you see a patient on the USMLE with neurologic manifestations in the lower extremity along with high mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), you know what to think!*

Syringomyelia

- *Mechanism: Central cavitation of the cord, which injures the anterior grey horns and the anterior white commissure*
- *Clinical picture: Bilateral hand and arms weakness, along with loss of pain and temperature sensation in both hands*

Guillain-Barré Syndrome

- *Mechanism: An ascending LMNL that affects facial muscles in 50% of cases*

- *Cause:* Usually follows viral infections; however, the most common pathogen associated with this syndrome is *Campylobacter jejuni*.
- *Clinical picture:* Recent flu-like illness, followed by *lower limb weakness* that is *progressing proximally*
- *Diagnosis:* CSF: *Abnormally high protein count with normal cell count*
- *Treatment:* *Plasmapheresis*
- *Argyll Robertson pupil:* It is a pupil that *accommodates to near vision* but *cannot react to light*. Common in patients with *syphilis*.
- *Papilledema:* Occurs with *high intracranial pressure*. Patients present with *blind spots* and a *normal visual acuity*.
- *Uncal herniation:* Causes *bilateral dilated fixed pupils*

Cranial Nerves

I: Olfactory Nerve

- *Course:* Originates from the *olfactory bulb* and ascends through the *cribriform plate of the ethmoid bone* to terminate in the olfactory cortex of *uncus (area 34)*
- *Lesion:* Ipsilateral anosmia
- *Lesion in the uncus:* Olfactory hallucinations

II: Optic Nerve

- *Embryology:* Derived from the *diencephalon*
- *Histology:* Made by the axons of ganglion cells
- *Pupillary light reflex:* Begins with light stimulating the retina → optic nerve → pretectum → Edinger-Westphal nucleus → ciliary ganglion → pupils See Figs. 3.17 and 3.18 for the visual pathway and its injuries.
- *Note:* The pupil *constricts with light* and *dilates in dark*. This process is mediated by the *ciliospinal center of Budge*.

III: Oculomotor Nerve

- *Function:* Supplies all the oculomotor muscles, except:
 1. Superior oblique muscle: Innervated by cranial nerve IV (*SO4*)
 2. Lateral rectus muscle: Innervated by cranial nerve VI (*LR6*)
- *Actions of oculomotor muscles* (Fig. 3.19)

IV: Trochlear Nerve

- *Function:* Innervates the *superior oblique* muscle
- *Injury:* Weak downward gaze and vertical diplopia

V: Trigeminal Nerve

- *Motor:* Supplies the *muscles of mastication* (*masseter, temporalis, pterygoids*)
- *Sensory:* Supplies *face, mouth, and supratentorial dura*.

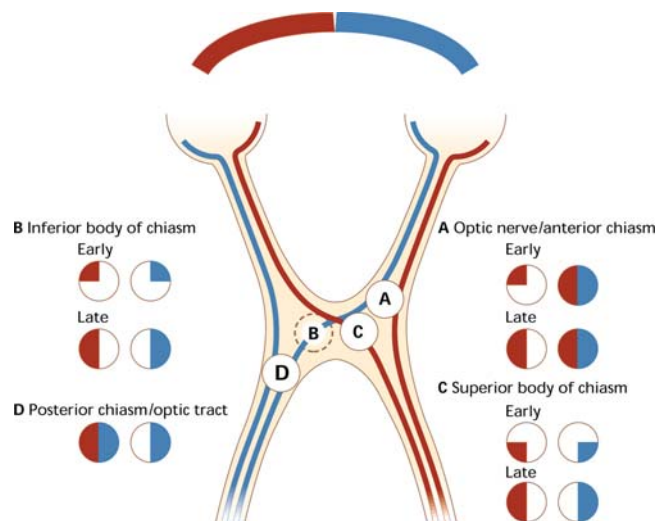


FIG. 3.17 Visual pathway injuries

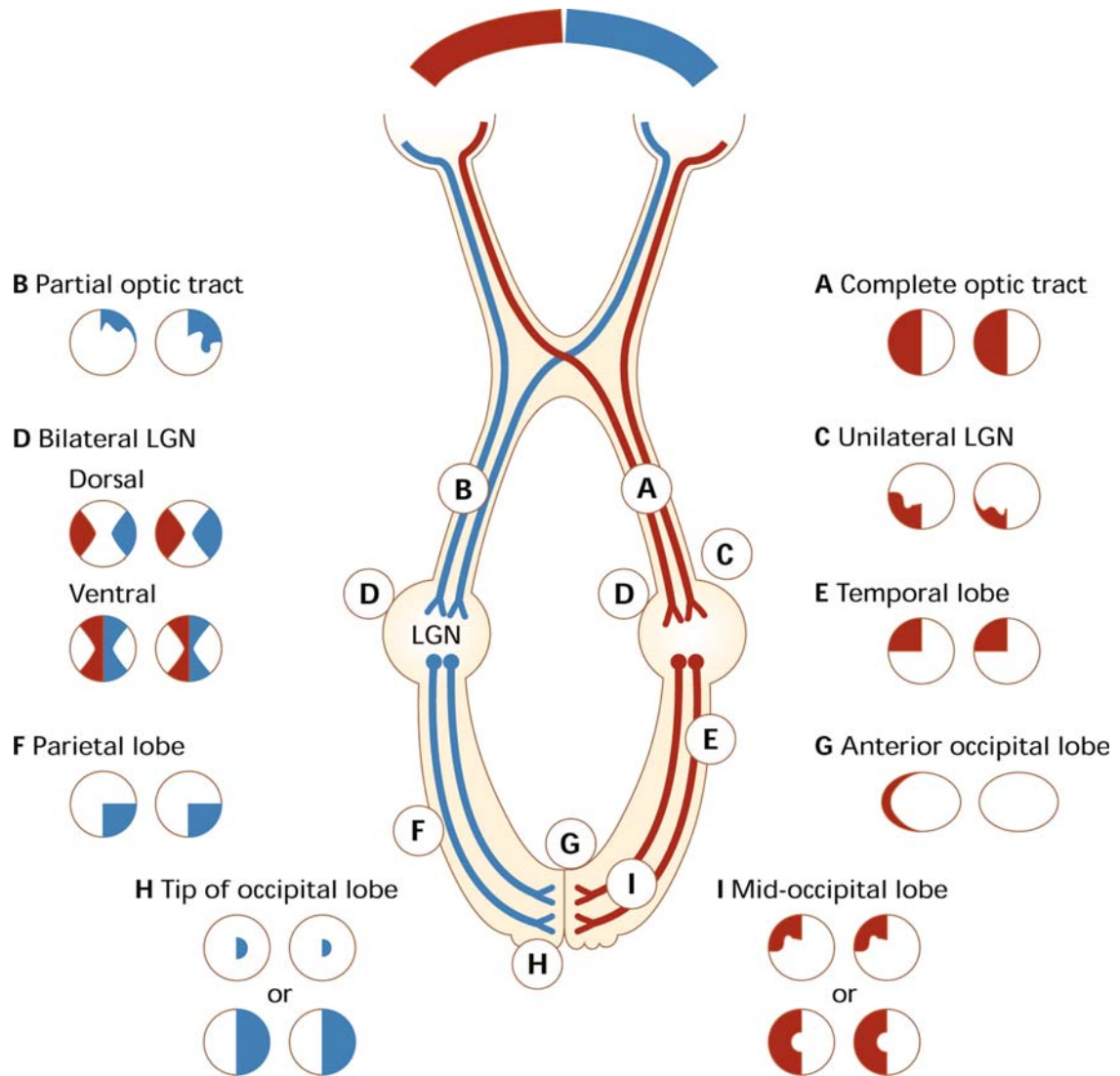


FIG. 3.18 Visual pathway injuries, continued. Lateral geniculate nucleus (LGN)

- **Divisions:** Trigeminal nerve has three divisions:
 1. Ophthalmic (V1): Passes through *superior orbital fissure*
 2. Maxillary (V2): Passes through *foramen rotundum*
 3. Mandibular (V3): Passes through *foramen ovale*
- **Injury:** *Hemianesthesia of the face and weak mastication.* On exam: *The jaw will deviate toward the paralyzed side, due to unopposed action of lateral pterygoid muscle on the healthy side.*
- **Trigeminal neuralgia (Tic douloureux):** Sharp stabbing pain along the distribution of trigeminal nerve. Treatment: *Carbamazepine.*

VI: Abducens Nerve

- **Function:** Innervates the *lateral rectus* muscle
- **Injury:** *Convergent strabismus* and *horizontal diplopia*

VII: Facial Nerve

- **Motor:** Innervates muscles of facial expression (*posterior belly of digastric and stylohyoid*)
- **Taste:** *Anterior two thirds of the tongue*
- **Course:** Relays in the *superior olivary nucleus*, hence it also supplies the *lacrimal and submandibular salivary glands*
- **Clinical picture of facial palsy:**

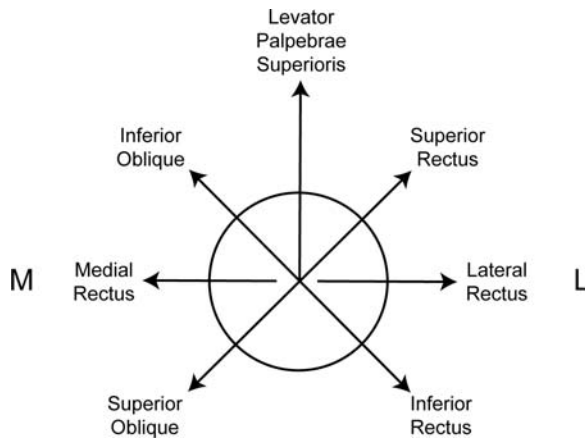


FIG. 3.19 Diagram showing the actions of oculomotor muscles. M: Medial, L: Lateral

1. *Facial droop* and *loss of the nasolabial fold* on the affected side
 2. Inability to *show teeth, blow cheeks, raise eyebrows, or close eyes tightly*
- *Note:* Division of facial nerve to upper face receives bilateral corticobulbar fibers, while the division to the lower face receives only contralateral corticobulbar fibers. This results in the following:
 1. UMNL: Weakness of the *contralateral lower face* (forehead spared)
 2. LMNL (Bell's palsy): Weakness of the *ipsilateral upper and lower face* (forehead affected)

VIII: Vestibulocochlear Nerve

- *Action:* Vestibular portion regulates balance and the cochlear controls hearing.
- *Pathways:*
 1. Hair cells in the inner ear relay signals to the *vestibular ganglion and nuclei*.
 2. Bipolar cells of cochlea relay signals to the *superior olivary nucleus, medial geniculate body (MGB)*, and finally to the *auditory cortex (areas 41, 42)* in the *temporolateral sulcus*.
- *Injury to the vestibular branch:* *Vertigo and nystagmus*
- *Injury to the cochlear branch:* *Tinnitus and sensorineural hearing loss*
- *Horizontal nystagmus:*
 1. Vestibular: *Fast phase is in the same direction*
 2. Post-rotatory: *Fast phase is in the opposite direction*

3. Caloric: Eyes deviate *toward the warm water* and away from cold water in the ear canal

IX: Glossopharyngeal Nerve

- *Functions:*
 1. Sensory: *Taste and sensory to the posterior one third of the tongue*
 2. Innervates the *parotid glands*
 3. Carries input from the carotid sinus (baroreceptor) and the carotid body (chemoreceptor)
- *Injury:*
 1. Loss of taste and sensation from *posterior one third of the tongue*
 2. Loss of gag reflex
 3. Carotid hypersensitivity causing *syncope*
- *Glossopharyngeal neuralgia:* Similar to trigeminal neuralgia. Except that the symptoms right here involve the tongue.

X: Vagus Nerve

- *The main parasympathetic supply to the human body*
- *Injury:* Paralysis of the *soft palate, pharynx, and larynx*; could be fatal
- *Clinical picture:* *Dysphagia, hoarseness of voice, and loss of cough and gag reflexes*
- *On exam:* The *uvula deviates toward the paralyzed side*.

XI: Accessory Nerve

- *Function:* Innervates the *sternocleidomastoid and trapezius muscles*
- *Injury:*
 1. Shoulder drop: Due to a paralyzed *trapezius*
 2. Neck looking toward the side of the lesion: *Due to the unopposed action of the contralateral sternocleidomastoid muscle*

XII: Hypoglossal Nerve

- *Function:* Innervates all the tongue muscles *except the palatoglossus, which is innervated by vagus nerve*
- *Injury:* Tongue deviates toward the paralyzed side *due to unopposed action of the contralateral genioglossus muscle*.

Miscellaneous

Seizures

- *Types:* Seizures can present in different forms, e.g., grand mal, absence, myoclonic, status epilepticus, or febrile convulsions:
 1. Seizures are either *partial*, affecting a localized part of the body, or *generalized*, affecting the whole body at the same time.
 2. Seizures could also be simple or complex. The only and main difference is that complex seizures, unlike simple ones, are associated with *altered or loss of consciousness*.
- *Clinical picture:*
 1. Grand-mal seizures: Start with generalized increased muscle tone (*tonic phase*), followed by generalized convulsions (*clonic phase*) during which loss of control over bowel and bladder, and tongue biting might occur. The last stage is the *postictal phase*, during which the patient is lethargic and confused.
 2. Absence seizures: Patient presents with *episodes of staring spells*, during which he/she continuously performs repeated movement, e.g., smacking lips, mumbling. EEG: Shows *3-Hz spike-and-wave pattern*.
 3. Temporal lobe seizures: Preceded by *olfactory hallucinations, due to uncus stimulation*
 4. Benign rolandic epilepsy: *Manifests as muscle twitching and is common in school-age children*
- *Note:* Seizures are followed by *postictal state (confusion)*, and sometimes *transient paralysis (Todd's paralysis)*
- *Diagnosis:* EEG. MRI of the brain is also needed to rule out organic causes.
- *Most common cause of seizures in children:* Infection (*febrile seizures*)
- *Most common cause of seizures in adults:* Head trauma
- *Most common cause of seizures in elderly:* CVA
- *Treatment:*
 1. Grand mal seizures: Phenytoin or carbamazepine
 2. Absence seizures: Ethosuximide or valproic acid
 3. Myoclonic seizures: Clonazepam
 4. Febrile seizures: Phenobarbitone
 5. Status epilepticus: *Diazepam first*, then fosphenytoin

Deafness

- *Types:*
 1. *Conductive hearing loss:* Caused by obstruction in the auditory canals, e.g., cholesteatoma in middle ear, or atresia of the auditory canal
 2. *Sensorineural hearing loss:* Caused by injury in the auditory pathway, e.g., *congenital rubella infection during the 8th week of pregnancy*
- *On exam:*
 1. Weber test: Place a vibrating tuning fork on the forehead; vibration is louder in the ear with conductive hearing loss and is diminished in the one with sensorineural hearing loss.
 2. Rinne test: On moving a tuning fork from the mastoid process to in front of the external auditory meatus, the sound is louder on the mastoid in conductive cases, and is louder by the meatus in *normal* and *sensorineural hearing loss* cases.
- *Acoustic neuroma:* A benign *Schwann cell tumor* arising from the *vestibulocochlear nerve at the cerebellopontine angle*. It may compress cranial nerves *V* and *VII*. Clinical picture: *Worsening hearing loss* and *tinnitus*. Diagnosis: *MRI*. Treatment: Surgical removal.

Myasthenia Gravis

- *Mechanism:* Antibodies against acetylcholine or its receptors in the muscles, linked to human leukocyte antigen (HLA) *DR3*. Some cases are associated with a *thymus tumor*.
- *Clinical picture:* Muscle weakness and diplopia, worse later in the day
- *Diagnosis:* Edrophonium test (*Tensilon test*) and electromyogram (EMG) are diagnostic.
- *Treatment:* Cholinesterase inhibitors, e.g., pyridostigmine, neostigmine
- *Note:* Eaton-Lambert syndrome is a paraneoplastic syndrome that occurs due to *antibodies against calcium channels*. It stands as the mirror image of myasthenia gravis as patients have similar symptoms, but both the symptoms and the EMG, unlike myasthenia gravis, get *better* by exertion.

Disc Prolapse

- *Cause:* Herniation of the nucleus pulposus, due to trauma or degeneration of annulus fibrosus

- *Clinical picture:*
 1. Radicular back pain shooting down the affected extremity, e.g., neck pain radiating down one arm, or low back pain radiating down one leg
 2. Posterior prolapse of the disc causes spinal stenosis or cauda equina syndrome. The latter is an emergency that presents with *tingling and numbness below level of lesion, saddle hypoesthesia, and bowel/bladder incontinence.*
- *On exam:* Positive *straight leg raising test*, which involves triggering the radicular pain by raising the patient's leg upwards while he lies in supine position.
- *Diagnosis:* MRI of the spine
- *Treatment:* Nonsteroidal antiinflammatory drugs (NSAIDs) and physical therapy. Surgery, e.g., discectomy or laminectomy, is the last resort, especially when there are signs of severe compression, e.g., weakness and muscle atrophy.
- *Note:* When you see a patient with possible disc prolapse, first thing to do is *NSAIDs and physical therapy for 4 weeks.* If no improvement, order MRI.

Carpal Tunnel Syndrome

- *Mechanism:* Median nerve compression under the flexor retinaculum
- *Causes:* Pregnancy, rheumatoid arthritis (RA), or occupational, e.g., *computer work, drilling*
- *Clinical picture:* Hand weakness and numbness, *exacerbated by flexion of the wrist and alleviated by dangling the hand in a dependent position*
- *On exam:*
 1. Atrophy of *thenar muscles*
 2. *Tinel sign:* Tapping of peroneus longus tendon reproduce symptoms
 3. *Phalen test:* Dorsal sides of both wrists are approximated to achieve at least a 90 degrees wrist flexion; this reproduces the symptoms.
- *Diagnosis:* Clinical; however, confirmation is via *nerve conduction studies*
- *Treatment:* *Wrist splints.* Surgery is the last resort (recurrence is common).

Migraine Headache

- *Clinical picture:* *Unilateral throbbing headache* associated with *photosensitivity* and nausea, more common in *females*, and usually preceded with an aura of *light flashes*
- *Physiology:* Serotonin levels are *elevated during the aura*, and they drop as headache worsens.

- *Prophylaxis (chronic cases):* *Beta-blockers*, e.g., propranolol or *methysergide*; however, the latter carries the risk of causing *retroperitoneal fibrosis.*
- *Treatment (acute):* *Sumatriptan (5-hydroxytryptamine-1D [5-HT-1D; serotonin] agonist)* or *ergotamine*
- *Note:* Cluster headache occurs in clusters, each lasting few days at a time. Patients have headache behind a red inflamed eye, lacrimation, and rhinorrhea. Treatment: 100% O₂.

Reflexes

- *Cranial nerve reflexes* (Table 3.1)
- *Deep tendon reflexes (DTRs):*
 1. Biceps reflex: Mediated by *C5 and C6*
 2. Triceps reflex: Mediated by *C7 and C8*
 3. Knee reflex: Mediated by *L2, L3, and L4*
 4. Ankle reflex: Mediated by *S1*
 5. Babinski reflex: Dorsiflexion of big toe and fanning of the toes on stimulation of lateral sole of the foot. *It is a sign of UMNL.*

TABLE 3.1 Cranial nerve reflexes.

Reflex	Afferent	Efferent
Corneal reflex	Ophthalmic nerve (V1)	Facial nerve
Lacrimation reflex	Ophthalmic nerve (V1)	Facial nerve
Oculocardiac reflex	Ophthalmic nerve (V1)	Vagus nerve
Jaw reflex	Mandibular nerve (V3)	Mandibular nerve (V3)

Neurotransmission

- Most neurons in the CNS are *multipolar with Nissl substance* in the cell body and *dendrites.* *Bipolar neurons* are common in the *retinal and vestibulocochlear systems.* *Nissl substance* is rich in *rough endoplasmic reticulum*, hence the rich protein formation.
- *Axonal transport:*
 1. Anterograde: Either slow or fast mediated by *kinesin* proteins
 2. Retrograde: Always fast, mediated by *dynein* proteins
- *Neuronal regeneration:*
 1. CNS: Does not occur
 2. Peripheral nervous system: Occurs by axonal sprouting into an endoneural tube, which is formed of *endoneurium and Schwann cells*

- **Neuronal degeneration:** Anterograde (wallerian), or retrograde (chromatolysis)
- **Neurotransmitters:** Highest concentrations in CNS:
 1. Dopamine: *Ventral tegmentum of the midbrain*
 2. Norepinephrine: *Locus ceruleus of the midbrain and pons*
 3. Serotonin: *Raphe nuclei of the midbrain, pons, and medulla*
- **Dopamine receptors:**
 1. D1: Stimulation is *excitatory*
 2. D2: Stimulation is *inhibitory*; *antipsychotics act on these receptors.*
- **CNS suppressants:**
 1. Brain: *GABA-A*, which acts by opening chloride channels
 2. Spinal cord: *Glycine*
- **CNS stimulators:** *Glutamate*, which acts through *NMDA* receptors
- **Endorphins:** Released from the *hypothalamus*, while *enkephalins* are released from the *globus pallidus*
- **Substance P:** It is a pain mediator released by the *substantia nigra*.
- **Somatostatin:**
 1. Increased: *Huntington chorea*
 2. Decreased: *Alzheimer disease*
- **Sensation transmission:**
 1. Warm sensations and pinprick: *C fibers*
 2. Cold sensation: *A delta fibers*
 3. Proprioception and vibration: *A alpha fibers*

Characteristics and Causes

- **Negri bodies** in the Purkinje cells of the cerebellum: Pathognomonic of *rabies*
- **Hirano rods** and **neurofibrillary tangles:** Pathognomonic of *Alzheimer's disease*
- Degeneration of the **basal nucleus of Meynert:** Pathognomonic of *Alzheimer's disease*
- **Lewy bodies** and **absence of melanin** from **substantia nigra:** Pathognomonic of *Parkinson's disease*
- **Causes of bilateral facial nerve paralysis:**
 1. Bilateral Bell's palsy, e.g., Lyme disease
 2. Sarcoidosis
 3. Guillain-Barré syndrome

Procedures

Lumbar Puncture (Spinal Tap)

- **Location:** L4-L5 space
- **Layers:** Skin → fascia → supraspinous and interspinous ligaments → ligamentum flavum → epidural space → dura → subdural space → arachnoid → subarachnoid space (Fig. 3.20)
- **Side effects:** Headache for up to 48 hours after LP is common, mostly due to *leak of CSF*. It is *alleviated by lying flat* and exacerbated by sitting or standing.
- **Complications:** Post-LP cerebral herniation is a serious complication; hence, CT of the head is *done*

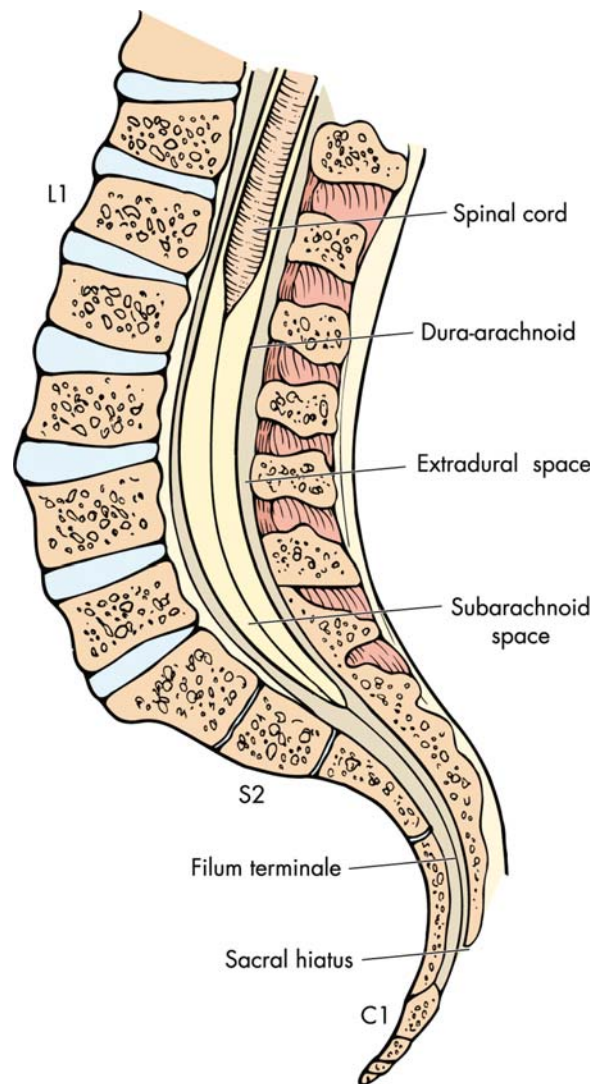


FIG. 3.20 Lateral view of spinal cord

before LP to exclude risk factors for herniation, e.g., mass, edema.

Epidural Anesthesia

- Commonly used in obstetric surgeries and delivery
- *Complications:*
 1. Epidural anesthesia *prolongs the second stage of labor.*
 2. Injection into *vertebral venous plexus: Convulsions and cardiac arrest*

3. Injection into the *subarachnoid space: Respiratory paralysis*

- *Notes:*

1. Postoperative complications, e.g., *deep venous thrombosis (DVT)* and *atelectasis*, are less frequent using epidural compared to general anesthesia.
2. Spinal (saddle) block: It is performed in obstetric anesthesia. *Anesthesia level* desired is *T10* for vaginal deliveries, and *T4* for C-sections.

Chapter 4

Histology

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Skin

- *Epidermis*: Originates from the *ectoderm*. The layers from deep to superficial are arranged as per the mnemonic “*BabeS Love Good Cops*”: Stratum basale, stratum spinosum, stratum lucidum, stratum granulosum, and stratum corneum.
- *Langerhans’ cells*: The skin’s *antigen presenting cells*. They are derived from the *bone marrow* and contain *Birbeck granules*.
- *Melanoblasts*: Responsible for the skin’s *pigmentation*. They are derived from *neural crest* and they contain *melanosomes* (skin pigment).
- *Merkel cells*: Serve as *mechanoreceptors* and are of unknown origin
- *Meissner corpuscles*: Receptors of *light touch*, and are mainly concentrated in the *fingertips* (Fig. 4.1)
- *Pacinian corpuscles*: Deep sensory receptors for *vibration and deep pressure*, and are concentrated in *ligaments and joints* (Fig. 4.2)

Sweat Glands

- *Merocrine*: *Diffuse* distribution. Sweat secretion is by means of *passive diffusion*.
- *Apocrine*: In *axilla* and *groin*; characterized by *decapitation secretion*
- *Sebaceous*: *Around hair follicles*; characterized by *holocrine secretion*

Golgi Apparatus

- *Functions*:
 1. Processes, stores, and packages *proteins* for export to their final destination
 2. Assembles and modifies *proteoglycans* and *oligosaccharides*
- *Structure* (Fig. 4.3)
 1. They contain *matrix granules* on the inner membrane to bind *calcium*.
 2. The Golgi apparatus is often continuous with the *rough endoplasmic reticulum*(RER), which is covered by *ribosomes*, hence the extensive protein synthesis.
- *Note*: The *smooth endoplasmic reticulum*(SER) synthesizes *steroids* and regulates *detoxification*, and is *not* continuous with the Golgi apparatus.

Blood

- *Red blood cell (RBC)*: A *biconcave* cell lacking a *nucleus* (Fig. 4.4)
- *Platelets*: Derived from *megakaryocytes* and like RBCs, *do not have a nucleus*. Function: *Coagulation* and as *antigen recognition cells* (Fig. 4.4)
- *Neutrophils* (Fig. 4.4):

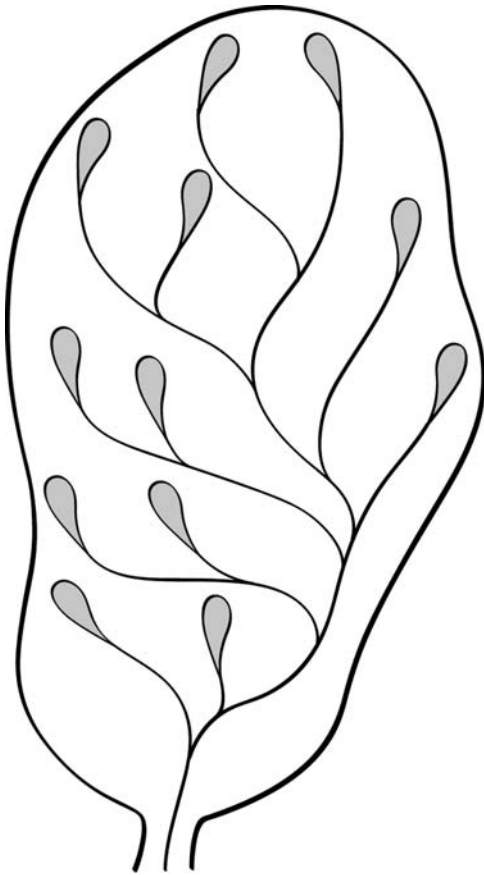


FIG. 4.1 Meissner's corpuscle

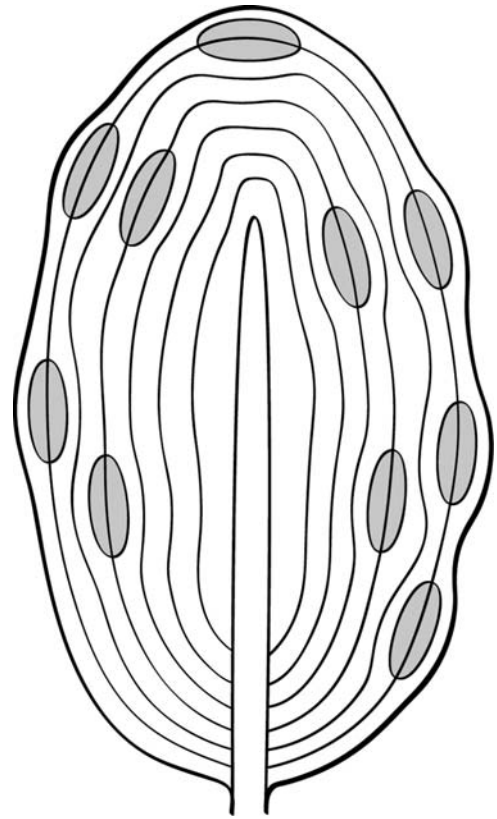


FIG. 4.2 Pacinian corpuscle

1. White blood cells (WBCs) whose nucleus is divided into segments, hence the name *polymorphs*
 2. 70% of WBCs, and perform *phagocytosis* and *chemotaxis*
 3. Contain cytoplasmic lysosomes known as *azurophilic granules*
 4. *Hypersegmented neutrophils* may be seen in *vitamin B₁₂ deficiency*
- *Lymphocytes*: WBCs with a large, round, basophilic nucleus; 20% of WBCs, and are discussed in details in Chapter 8, Immunology (Fig. 4.4)
 - *Eosinophils*: WBCs whose nucleus is characterized by *two connected lobes*; 5% of WBCs, and are increased in *allergies and parasitic infestations* (Fig. 4.5)
 - *Basophils*: WBCs that are filled with multiple *basophilic granules*, e.g., *histamine, heparin*; 2% of WBCs, and are *linked to immunoglobulin E (IgE)*, hence elevated in allergic conditions (Fig. 4.6)
 - *Monocytes*: WBCs that have a *kidney-shaped nucleus* and *frosted glass cytoplasm*; 3% of WBCs, and *convert to macrophages* once they reach any tissue.
 - *Note*: Neutrophils and monocytes exit through vessel walls by a process known as *Diapedesis*, which is usually preceded by sticking to the blood vessel wall (*pavementation*).

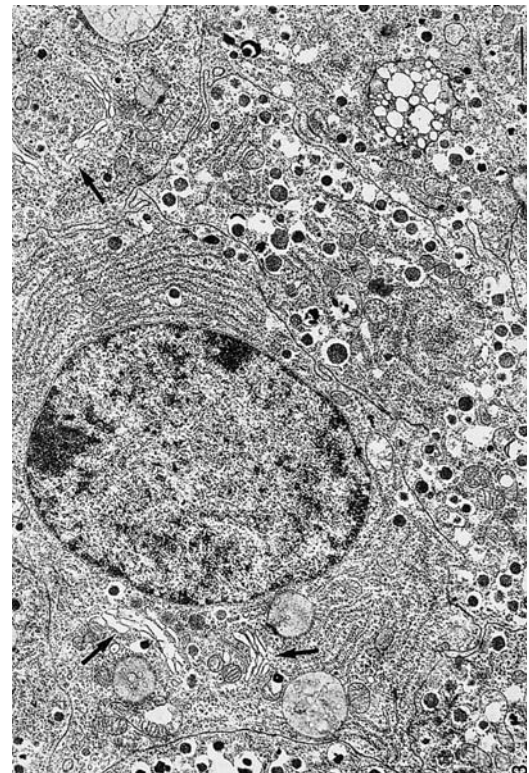


FIG. 4.3 Golgi apparatus (arrows)

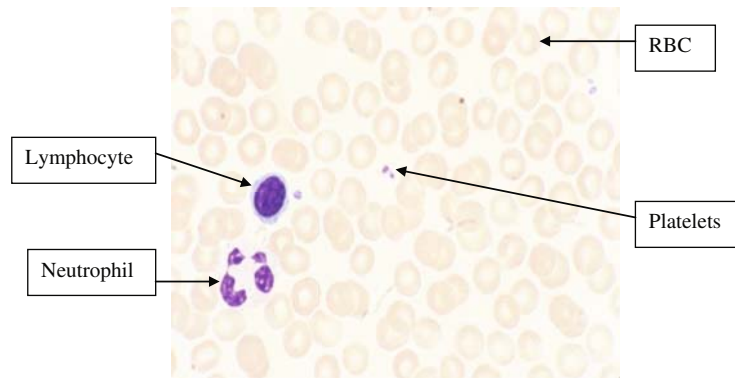


FIG. 4.4 Normal peripheral smear

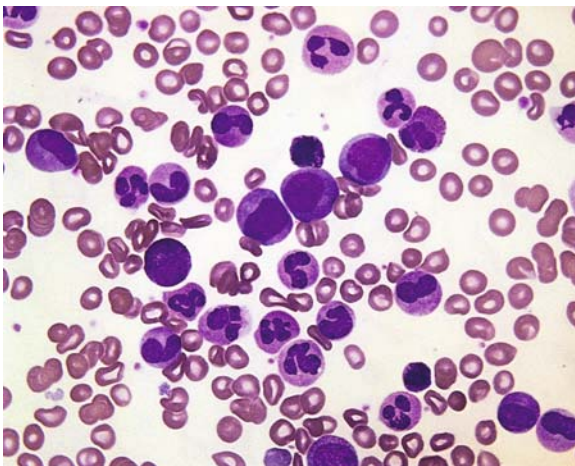


FIG. 4.5 Eosinophils (Multiple in this picture, e.g.: Lower right corner)

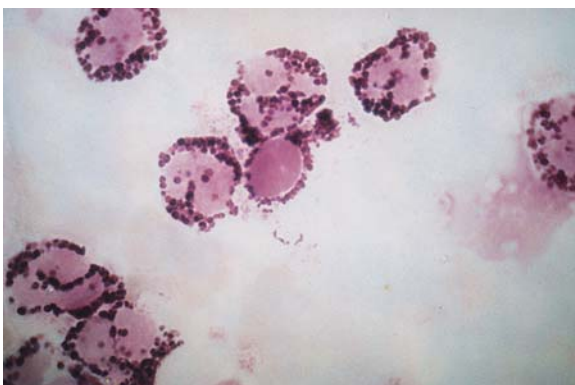


FIG. 4.6 Basophils

Skeletal (Striated) Muscle

- *Cell:* Skeletal muscle cells are *cylindrical*.
- *Nucleus:* *Peripheral*

- *Structure:*

1. Skeletal muscle is formed of *thin actin* and *thick myosin filaments*.
2. Skeletal muscles are arranged in *sarcomeres* giving a *cross-striation* pattern.

- *Type I fibers:* *Dark stained, aerobic*, and responsible for *slow* contractions
- *Type II fibers:* *Light stained, anaerobic*, and responsible for *fast* contractions.
- *Note:* During muscle contraction, *actin filaments shorten*, while myosin does not.

Smooth Muscle

- *Function:* Covers the gastrointestinal (GI) tract as *outer longitudinal* and *inner circular* layers. They are also present in the walls of large arteries.
- *Cells:* Smooth muscle cells are *spindle-shaped* and are arranged in *fasciculi*.
- *Nucleus:* *Centrally located*
- *Cytoplasm:* Smooth muscle cytoplasm is continuous with adjacent cells via *gap junctions*.

Heart

- *Coronary arteries:* Run in the *subpericardial tissue*, which is rich in adipose tissue
- *Pericardium:* Formed of *mesothelial cells*; rich in *microvilli*
- *Myocardium:* Formed of cardiac muscle fibers attached to each other by means of *intercalated disks*, which are further interconnected by *nexus* or *gap junctions*

- *Note:* Cardiac muscle fibers are *cross-striated* and *branched*. Note that skeletal and smooth muscles are *not* branched.
- *Muscular arteries, e.g., radial, femoral, cerebral, and coronary arteries.* The tunica media is composed predominantly of *smooth muscle* plus two elastic layers (lamina):

Vascular System (Fig. 4.7)

- *Layers of blood vessel wall:* From *inside out*:
 1. *Tunica intima:* Endothelium overlying supporting tissue
 2. *Tunica media:* Composed primarily of *smooth muscles* and *elastin*
 3. *Tunica adventitia:* Contains small arteries known as *vasa vasora*, which supply the vessel wall
- *Elastic arteries, e.g., aorta, subclavian, carotid, and brachiocephalic arteries.* The tunica media is composed predominantly of *elastin* and a small amount of smooth muscles.

1. Internal elastic lamina: Situated between the tunica intima and media
2. External elastic lamina: Situated between the tunica media and adventitia

Tracheobronchial Tree (Fig. 4.8)

- *Epithelium:* *Pseudostratified ciliated columnar.* It contains *cilia* and *Kulchitsky cells*, which regulate the airway diameter.
- *Submucosa:* Contains seromucinous glands and goblet cells; responsible for *mucin* production.

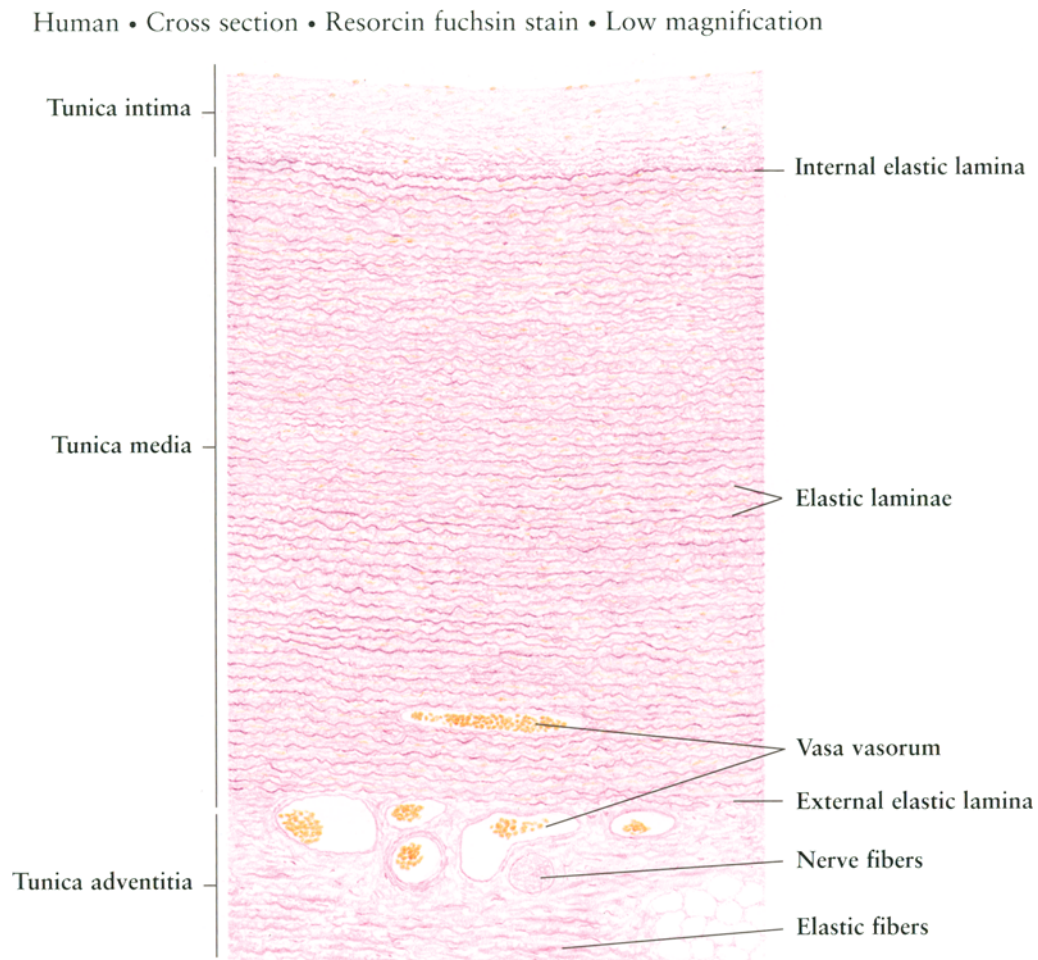


FIG. 4.7 Layers of an elastic blood vessel wall. (From Zhang S-X. Atlas of Histology. New York: Springer-Verlag, 1999:121, with permission of Springer Science and Business Media.)

Human • H.E. stain • Low magnification

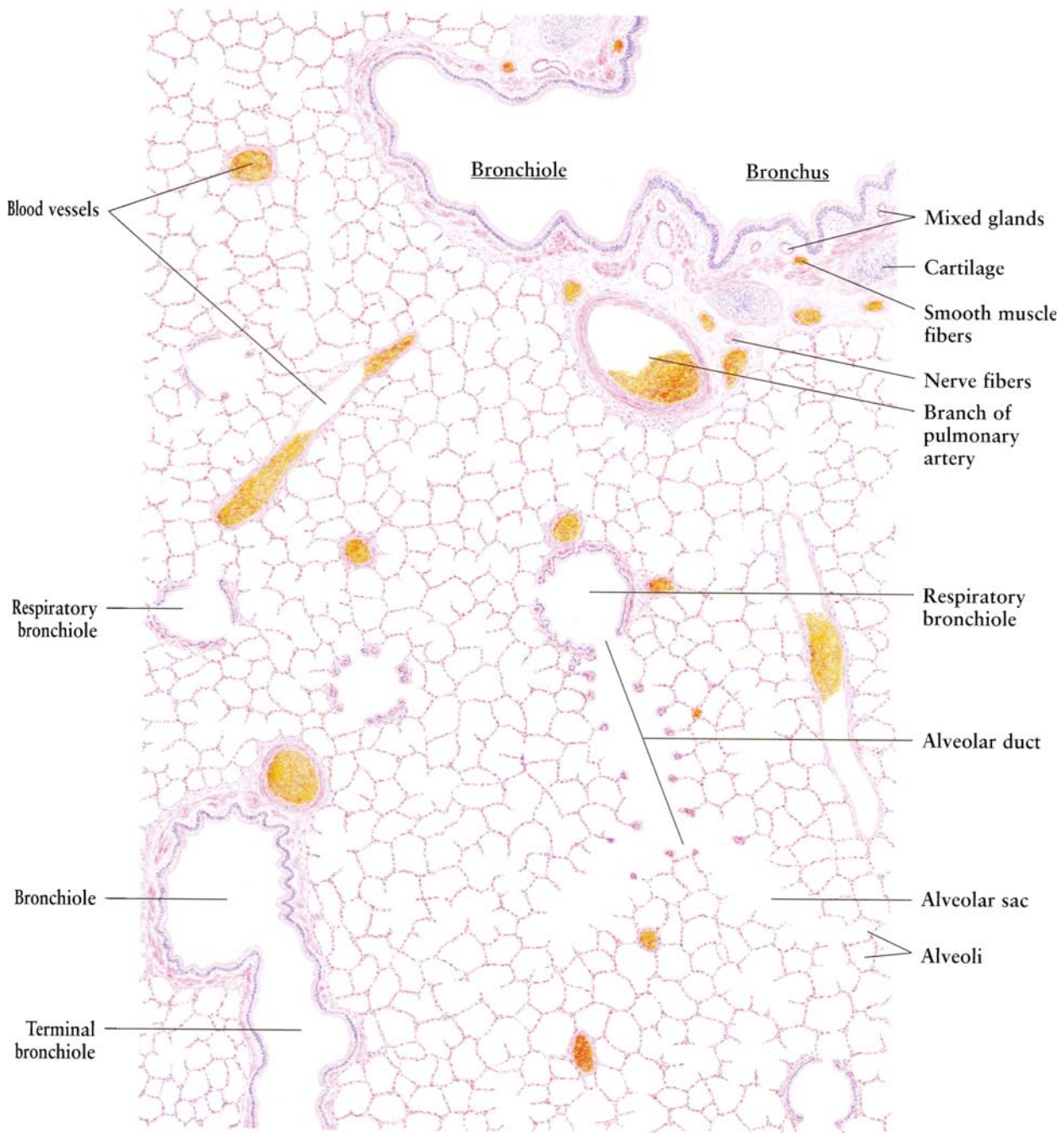


FIG. 4.8 Histology of the bronchial system. (From Zhang S-X. Atlas of Histology. New York: Springer-Verlag, 1999:179, with permission of Springer Science and Business Media.)

Goblet cells are filled with mucin and have a peripheral flat nucleus.

- **Structure:** Chondrocytes. The hyaline cartilage matrix contains type II collagen, hyaluronic acid, and chondroitin sulfate.

Notes:

1. The C-shaped tracheal rings are closed posteriorly by the trachealis muscle.
2. Cartilage of the intervertebral disks is fibrocartilage, not hyaline.

Lungs

- *Type I pneumocytes*: Flat cells that participate in the formation of alveolar-capillary membrane. Other components of the membrane are the *vascular endothelium* and *basement membrane*.
- *Type II pneumocytes*: Cuboidal cells that contain *lamellar bodies*, which secrete *surfactant* (dipalmitoyl-phosphatidylcholine)
- *Clara cells*: Located in the distal bronchioles and they secrete *surfactant*

Salivary Glands

- *Parotid glands*: Strictly *serous glands* that secrete *watery saliva*
- *Sublingual glands*: Strictly *mucinous glands* that secrete *thick mucinous saliva*
- *Submandibular glands*: *Mixed serous and mucinous glands*
- *Note*: Acinar cells of the salivary glands contain *cytokeratin filaments*.

Esophagus

- *Epithelium*: *Nonkeratinized stratified squamous*
- *Submucosa*: Contains *seromucinous glands*
- *Muscular wall*: Formed of smooth muscles, with the exception of the *upper one third*, which is composed predominantly of *skeletal muscles*
- *Barrett's esophagus*: It is a complication of gastroesophageal reflux disease (GERD). Epithelial dysplasia occurs in the lower third of the esophagus, resulting in *columnar epithelium*. *Esophageal adenocarcinoma* is the most serious complication of *Barrett's esophagus*.
- *Note*: The entire gastrointestinal (GI) tract is made of smooth muscles except the *upper third* of esophagus, the *pharynx*, and the *external anal sphincter* (UPS), which are made of *skeletal muscles*.

Stomach (Fig. 4.9)

- *Stem cells*: Present in the *neck* of the gastric glands, and are responsible for *mucosal regeneration*
- *Parietal cells*: Present along the entire length of the gastric glands, and they secrete *HCl* and *intrinsic factor*
- *Peptic cells*: Also known as *chief(zymogenic) cells*, present at the *base* of gastric glands, and they secrete *pepsin*
- *G cells*: Present mainly in the *antrum*, and they secrete *gastrin*

Small Intestine (Fig. 4.10)

- *Epithelium*: *Simple columnar cells*, attached by means of *desmosomes (zona occludens)* and *tight junctions (zona adherens)*. Epithelium is rich in *microvilli*.
- *Brunner glands*: *Alkaline mucus-secreting glands* in the *submucosa of duodenum*. They become *hypertrophied* in cases of *duodenal ulcers*.
- *Muscular layer*: Formed of *outer longitudinal* and *inner circular* layers.
- *Nerve plexuses*: *Submucosal (Meissner's)* and *myenteric (Auerbach's)* nerve plexuses are embedded between the muscular layers. They regulate *intestinal secretion* and *motility*, respectively.
- *Lamina propria*: Contains lymphoid follicles known as *Peyer's patches*. In the Peyer's patches, *M cells* serve as *antigen-presenting cells*.
- *Paneth cells*: They are *pathognomonic of the small intestinal crypts*.
- *Intestinal microvilli*: They move by means of *actin filaments* to perform *absorption*.
- *Notes*:

1. Cilia in the airways and fallopian tubes move via *paired central microtubules* and *nine peripheral doublets*. The cilia are rich in *dynein adenosine triphosphatase (ATPase)*. These cilia perform a *transportive*, rather than *absorptive* function (Fig. 4.11).
2. The colon wall has the same layers as the small intestine, except that the colonic *outer longitudinal* muscle forms three bands known as the *teniae coli*.

Hepatobiliary (Fig. 4.12)

- *Hepatocytes*: They have a high concentration of *glycogen*.
- *Kupffer cells*: Act as *hepatic macrophages*, and are found in the lining of the liver sinusoids
- *Gallbladder*: Lined by *simple columnar epithelium* and its wall is rich in *elastin*

Nervous System

- *Neuroblasts*: Give rise to all the central nervous system (CNS) *neurons*
- *Glioblasts*: Give rise to the following:
 1. *Choroid plexus*: Forms the *blood-brain barrier* and *secretes cerebrospinal fluid (CSF)*
 2. *Ependymocytes*: *Line the ventricles*
 3. *Oligodendrocytes*: *Secrete myelin only in CNS*

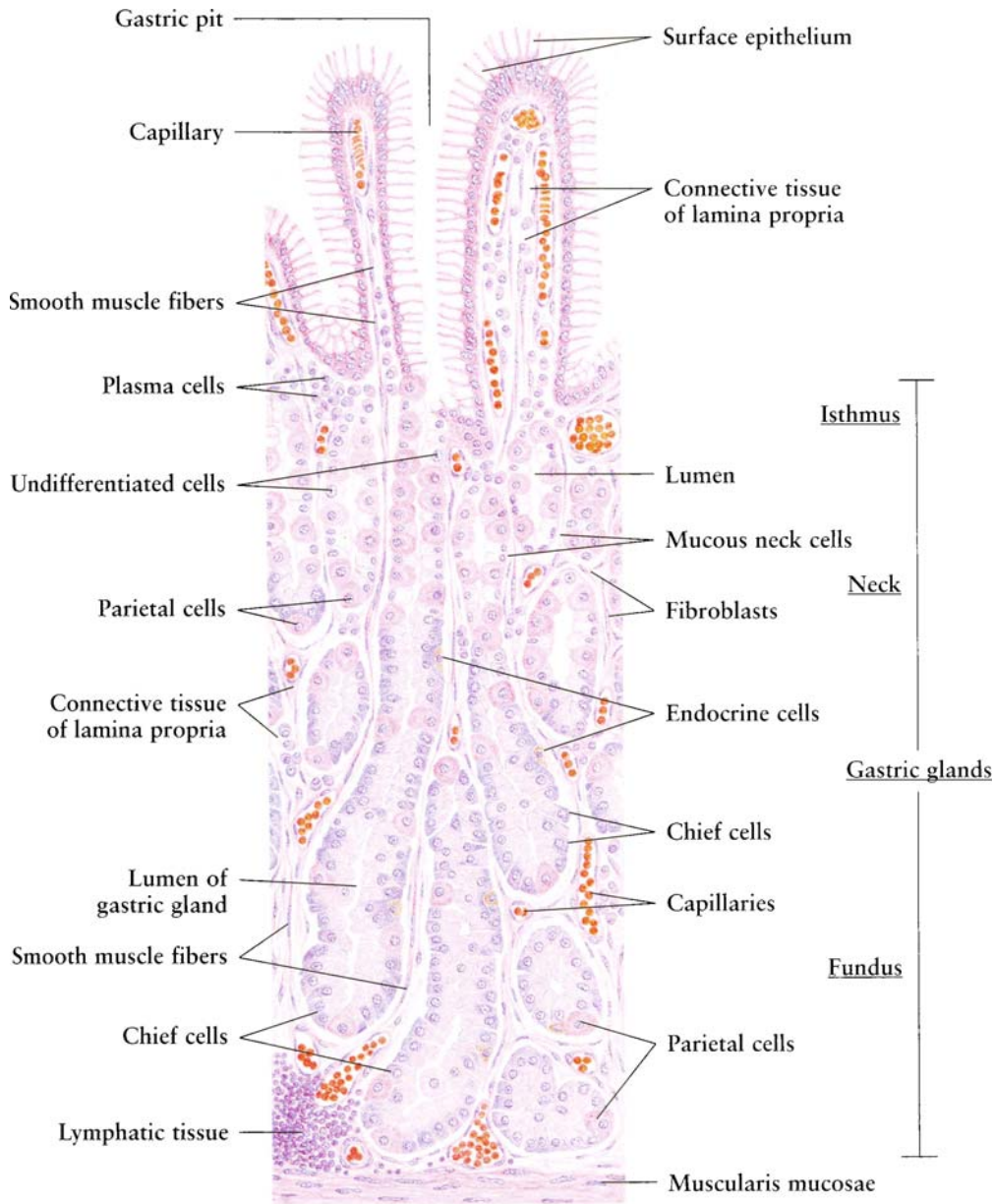


FIG. 4.9 Gastric glands. (From Zhang S-X. Atlas of Histology. New York: Springer-Verlag, 1999:221, with permission of Springer Science and Business Media.)

- 4. Microglia: *CNS macrophages*
- 5. Astrocytes and glial cells: Secrete glial fibrillary acidic protein (GFAP), and serve as the *brain's handyman*, i.e., *support and repair*
- *Notes:*
 - 1. Oligodendrocytes are destroyed in demyelinating disorders, such as multiple sclerosis.
 - 2. Peripheral nervous system's equivalent of oligodendrocytes are the *Schwann cells*. They myelinate the peripheral nervous system.
 - 3. Peripheral nerves are coated from inside out by endoneurium, perineurium, and epineurium.
 - 4. Pineal gland: Formed of pineal *chief cells* and releases *melatonin*, which regulates the circadian rhythm. *Pineal sand* is age-related calcification seen in imaging studies.

Eye

- *Cornea*: Nonkeratinized stratified squamous epithelium. *Membranes*: The corneal substance is

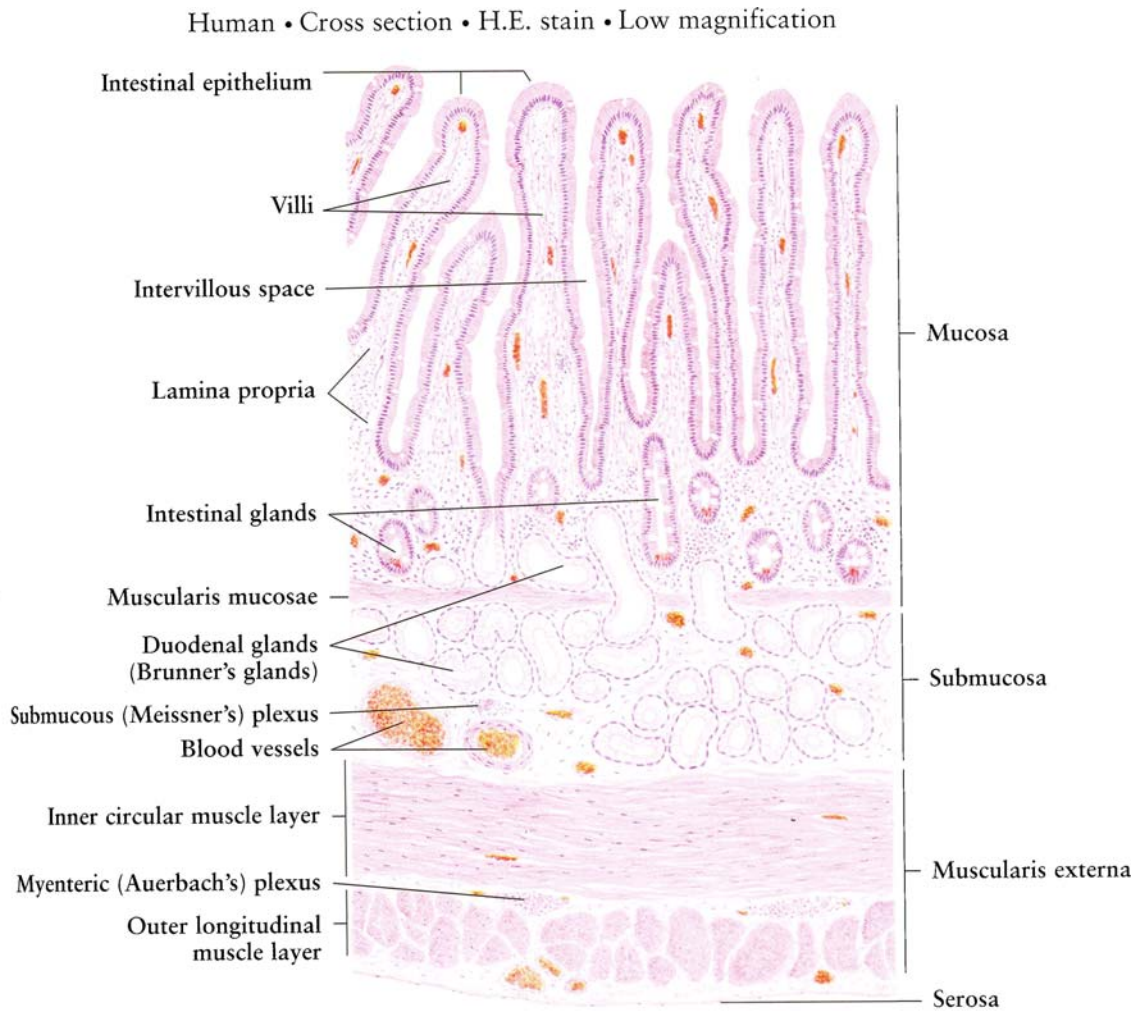


FIG. 4.10 Histology of duodenum. (From Zhang S-X. Atlas of Histology. New York: Springer-Verlag, 1999:225, with permission of Springer Science and Business Media.)

covered anteriorly by Descemet's membrane and posteriorly by Bowman's membrane

- *Retina* (Fig. 4.13)

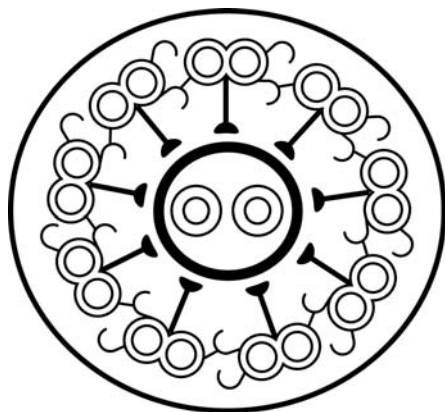


FIG. 4.11 Structure of cilia

Renal System (Fig. 4.14)

- *Juxtaglomerular apparatus:* It regulates the renin-angiotensin system, and is formed of:
 1. Macula densa of distal convoluted tubule (DCT)
 2. Afferent arterioles
 3. Extraglomerular mesangial cells
- *Epithelium:* Transitional epithelium
- *Umbrella cells:* Large cells with scalloped border, which are pathognomonic of the renal system

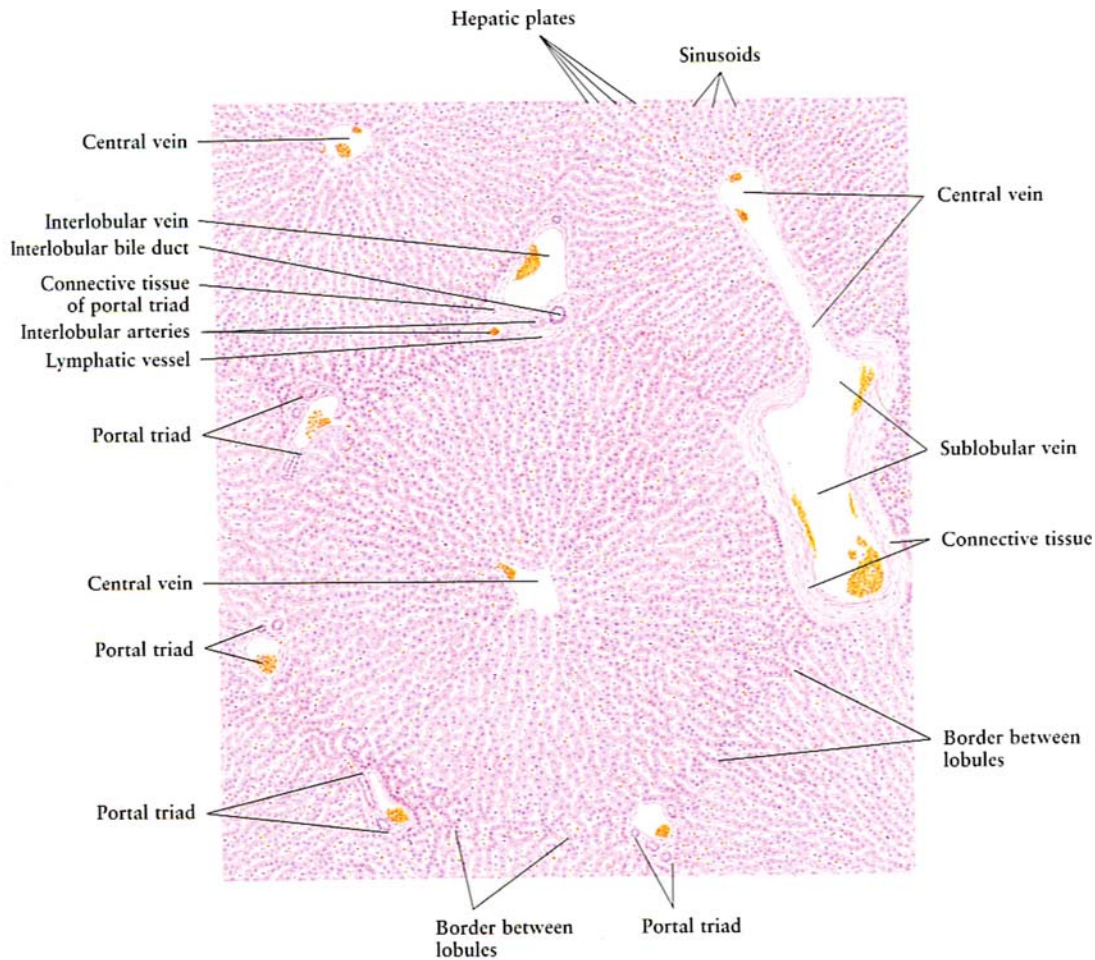


FIG. 4.12 Histology of the liver (From Zhang S-X. Atlas of Histology. Newyork: Springer-Verlag, 1999:241, with permission of Springer Science and Business Media.)

Male Genitalia

- *Prostate*: Formed of *flat basal cells* topped by *tall columnar cells*. The columnar cells contain glycoprotein known as *corpora amylacea*.
- *Seminal vesicles*: Covered by *pseudostratified columnar epithelium*; rich in *lipofuscin*
- *Epididymis*: Lined by *tall pseudostratified columnar epithelium*. It is rich in *microvilli*, incorrectly termed *stereocilia*.
- *Leydig cells*: Scattered in the *testicular interstitium*, and they secrete *testosterone*. They are *polygonal* in shape, and contain *crystals of Reinke* in their cytoplasm
- *Sertoli cells*: *Columnar cells* with *cleft nucleus*, embedded within the *seminiferous tubules*. They secrete *inhibin*, which regulates gonadotrophin secretion and Leydig cell function.

Female Genitalia

- *Endocervix*: Lined by *simple columnar epithelium*
- *Ectocervix*: Lined by *stratified squamous epithelium*
- *Note*: The endocervix and ectocervix are separated by the *squamocolumnar junction (transformation zone)*.

Basement Membrane

- *Structure*: Formed of *type IV collagen* and has three layers:
 1. *Lamina lucida*: Closest to the overlying epithelium
 2. *Lamina densa*: The middle layer

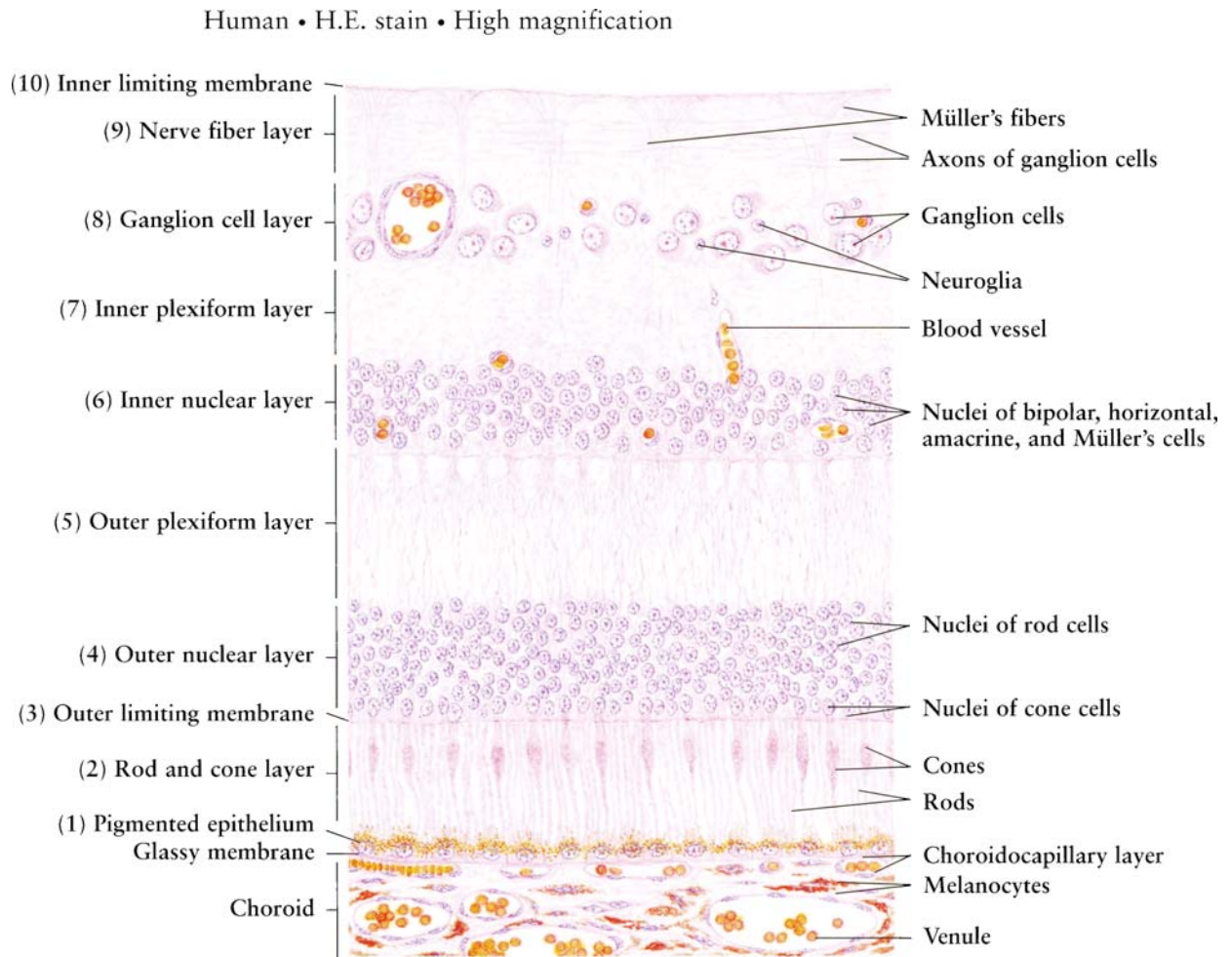


FIG. 4.13 Retina. (From Zhang S-X. Atlas of Histology. New York: Springer-Verlag, 1999:389, with permission of Springer Science and Business Media.)

3. Lamina fibroreticularis: Closest to the surrounding tissues

Collagen

- *Structure: Tropocollagen molecules.* Each tropocollagen molecule is composed of three *alpha chains*, coiled into a *helix*.
- *Type I collagen:* The most abundant, has the greatest tensile strength, and is famous for its *cross-banding* pattern every *64 nm*. It is the collagen of *bone*.
- *Type II collagen:* The collagen of *hyaline cartilage*
- *Type III collagen (reticulin):* A supporting tissue in the *liver, spleen, and lymph nodes*
- *Type IV collagen:* The collagen of *basement membranes*
- *Type V collagen:* The collagen of *epiphyseal growth plates*

Lymph Nodes (Fig. 4.15)

- *Lymphoid follicles:* Two types:
 1. Primary: Contains *mature B lymphocytes*
 2. Secondary: Contains *immature B lymphocytes* in the germinal center, and small mature B lymphocytes in the outer mantle zone
- *Medullary sinuses:* Contain *T and B lymphocytes*
- *Medullary cords:* Contain *plasma cells*

Bone

- *Epiphyseal growth plate:* Found only in long bones, while flat bones grow by deposition of tissue along the edges

Human kidney • H.E. stain • High magnification

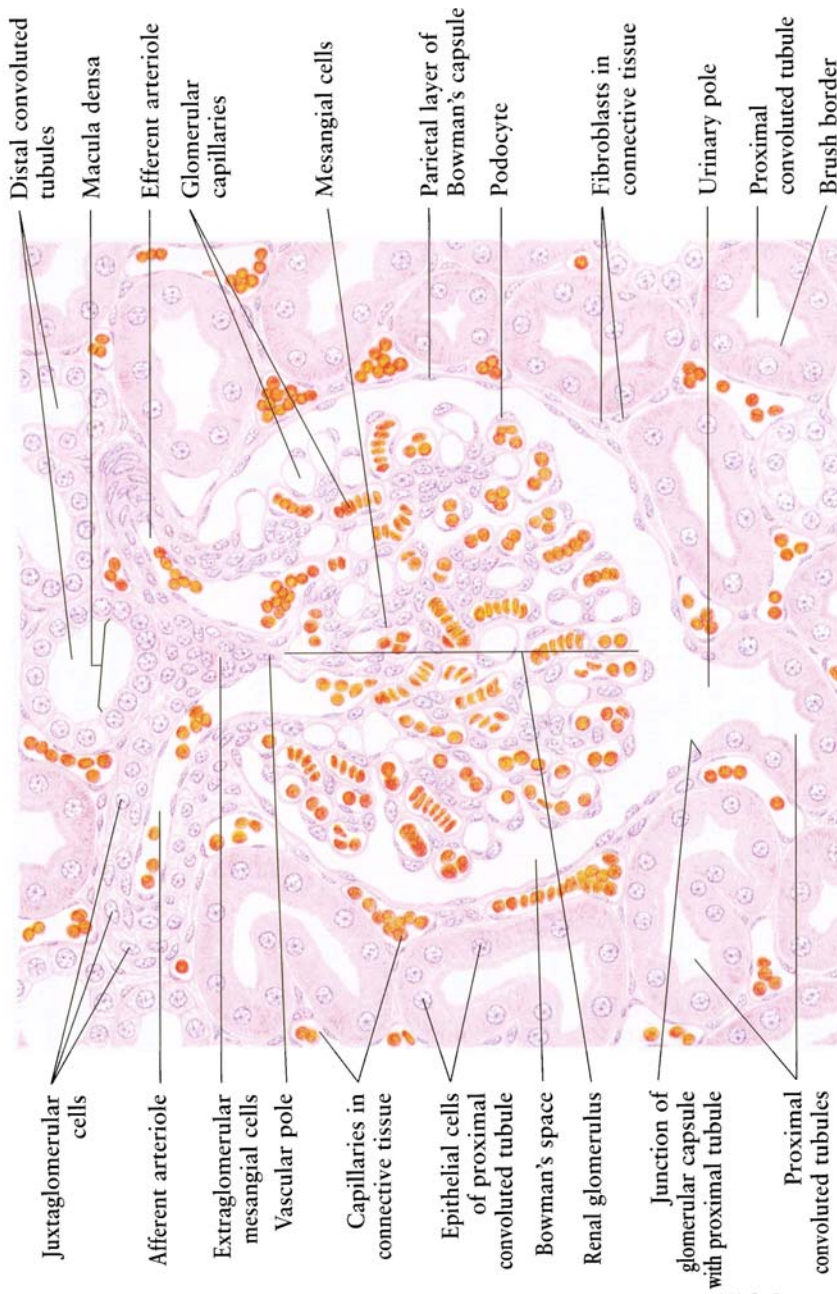


FIG. 4.14 Cortical renal corpuscle. (From Zhang S-X. Atlas of Histology. New York: Springer-Verlag, 1999:257, with permission of Springer Science and Business Media.)

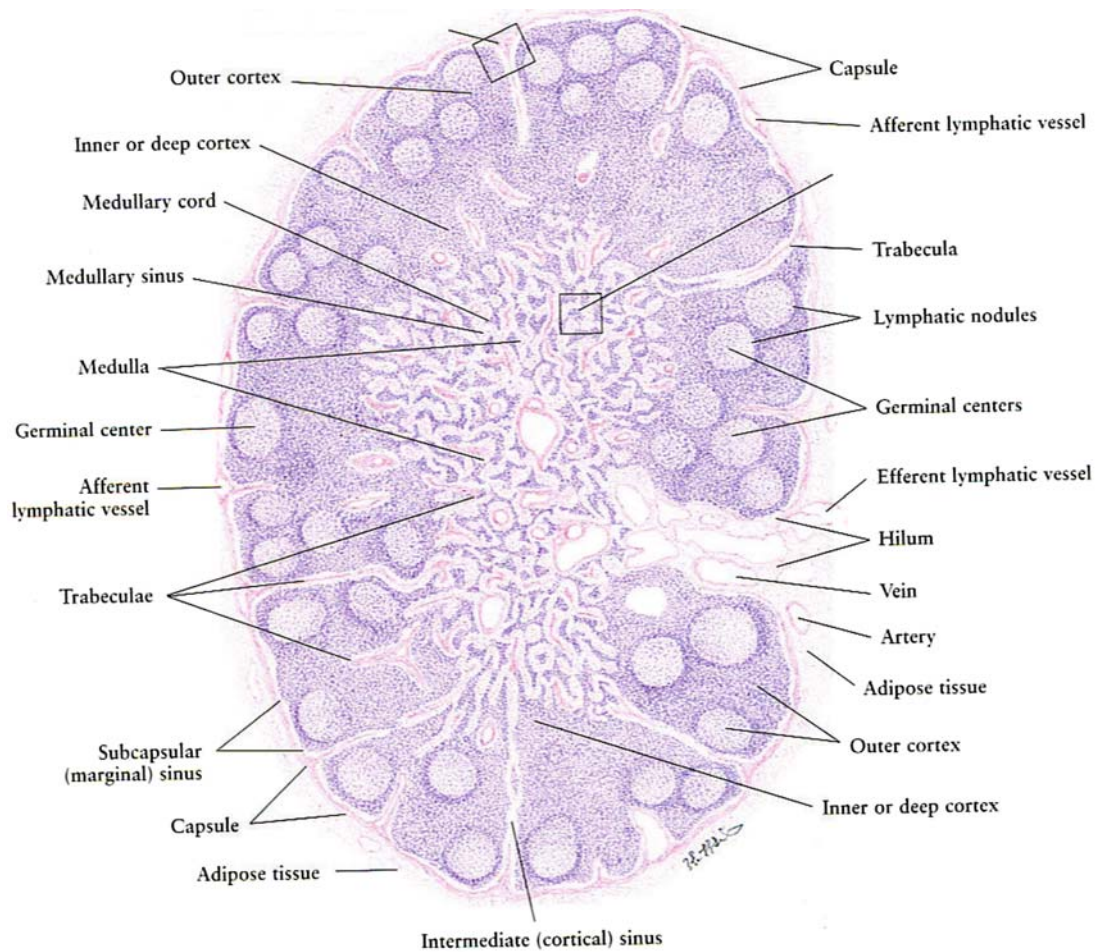


FIG. 4.15 Histology of the lymph node (From Zhang S-X. Atlas of Histology. Newyork: Springer-Verlag, 1999: 145, with permission of Springer Science and Business Media.)

- *Intramembranous ossification*: Takes place in formation of *flat bones*. Conversion of the tissue into bone occurs *directly*.
- *Endochondral ossification*: Takes place in formation of *long bones*. Here, the tissue converts first to cartilage, then to bone.

Chapter 5

Public Health

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Prevention

- *Primary*: Prevent disease occurrence
- *Secondary*: Early detection of the disease
- *Tertiary*: Reduce disability and complications from the disease

Epidemiologic Studies

Cross-Sectional Study

- Used for measuring the *prevalence* of a disease; usually chronic
- *Advantages*: Cheap, easy, and quick
- *Disadvantages*:
 1. Not appropriate for short-term diseases
 2. Chicken-or-egg dilemma

Case-Control Study

- A *retrospective* study
- *Advantages*: Easy, cheap, and simple
- *Disadvantages*: Recall bias, and failure to calculate risk ratio

Cohort Study

- A *prospective* study, e.g., Framingham study
- *Advantages*: Used to measure incidence rates of a disease
- *Disadvantages*: Needs a large sample size; time-consuming and expensive.

Clinical Trial

- Patients are divided into two groups:
 1. Experimental: Take a new medication
 2. Control: Take a placebo

- *Blinding*: May be single blind (patient does not know), double blind (patient and investigator do not know), or triple blind (patient, investigator, and analyzer do not know)
- *Crossover study*: It is a type of clinical trial where both groups 1 and 2 receive both the new medication and the placebo.
- *Disadvantage*: Bias from any of the involved personnel

Preventive Medicine

- *Pap smear*: *Annually* once the female is sexually active until *three normal tests* are obtained; then it is done *every 3 years*
- *Mammogram*: *Annually* starting at age 40
- *Rectal exam and fecal occult blood testing*: *Annually* for both genders starting at age 50
- *Colonoscopy*: *Every 10 years* starting at age 50
- *Prostate exam and prostate-specific antigen (PSA)*: *Annually* starting at age 50
- *Ovarian cancer*: There is no screening for ovarian cancer.

Most Common Causes and Illnesses

- Most common cause of death in:
 1. Children younger than 12 years of age: *Congenital anomalies*
 2. Between the ages of 12 and 24: *Injuries*
- Most common cause of death in the 25 to 64 age group, in order of frequency:
 1. Cancer
 2. Coronary artery disease (CAD)
 3. Cerebrovascular accident (CVA)

- Most common causes of death in elderly, ≥ 65 years, in order of frequency:
 1. Coronary artery disease (CAD)
 2. Cancer
 3. Cerebrovascular accidents (CVA)
- Most common cancer in general: *Skin cancer*
- Most common cancer in males: *Prostate cancer*
- Most common cancer in females: *Breast cancer*
- Most common cancer-related fatality in both genders: *Lung cancer*
- Most common malignancy in children: *Acute lymphoblastic leukemia*
- Most common benign tumor in children: *Hemangioma*
- Most common cause of pneumonia in children: *Foreign-body aspiration*
- Most common cause of arthritis:
 1. Males: *Gout*
 2. Females: *Rheumatoid arthritis*
- Most common nosocomial infections, in order of frequency:
 1. Urinary tract infection (UTI)
 2. Wound infection
 3. Pneumonia
- Most fatal occupation in the U.S.: *Mining*
- Most common allergic skin reaction: *Exanthemas*
- Most common allergic skin reaction in females: *Nickel allergy*
- Most common cause of acute cholecystitis: *Cystic duct stone*
- Most common cause of blindness:
 1. White race: *Cataract*
 2. Black race: *Glaucoma*
- *Panic attacks*: More common in females in their midteens to thirties; show a familial pattern
- *Domestic violence*: More common in females, especially in the pregnant
- *More common in the black race than whites*: Infant death, hypertension, prostate cancer, and fatality from CVAs

Cancer Statistics

- First-degree relatives of breast cancer patients have a *2 to 3 times greater risk* of developing breast cancer.
- Skin cancer has *no* genetic predisposition.
- Most important prognostic factor in cancer: *Staging*
- Exposure to ultraviolet (UV) rays may cause *skin cancer*.
- The incidence of lung cancer is decreasing in males, due to decreased rates of smoking.
- Most *common* asbestos-related malignancy: *Bronchogenic carcinoma*
- Most *specific* asbestos-related malignancy: *Mesothelioma*
- Stomach cancer incidence rates are *decreasing* worldwide.
- The most fatal gynecologic cancer: *Ovarian cancer*
- The most common gynecologic cancer: *Endometrial cancer*
- There are *no* hereditary factors responsible for testicular cancer.
- There is *no human leukocyte antigen (HLA) association* with Hodgkin's lymphoma.
- There is *strong HLA association* with Non-Hodgkin's lymphoma.

Racial and Gender Differences

- *Crohn's disease*: More common in those of *Jewish descent*
- *Testicular cancer*: Rates are higher in *single men* compared to married men
- *Cystic fibrosis*: More common in the *Amish population*
- *Barbiturate abuse*: More common among middle-aged women
- *Ischemic heart disease*: Women present more commonly with *angina*, while men present more commonly with *acute infarction*.
- *Rheumatoid arthritis*: The incidence in females is *three times* that of males.

Infectious Diseases

- The case fatality rate of meningococemia is *5% to 15%*.
- The best prevention of water-borne cryptosporidiosis outbreaks in the U.S.: *Filtering drinking water*
- Bacterial vaginosis is associated with *preterm labor*.
- Chronic chlamydial infection is associated with infertility, *due to tubal scarring*.
- *Ascaris lumbricoides* worm matures in patients' lungs, and may cause protein deficiency.
- Paragonimiasis is contracted from *crabs*, cysticercosis from *swine*, nocardiosis from *soil*, and hantavirus from *fleas feeding on rodents*.
- The nosocomial infection rate in the U.S. is *5% to 10%*, commonly *due to lack of hand washing*.

- Herpes simplex virus (HSV) types I and II have different antibodies, and there is *no cross-immunity*.
 - *Clostridium perfringens* food poisoning begins 12 hours after ingestion and resolves within 24 hours.
 - Pneumococcal vaccine is not effective if given to children younger than 2 years of age.
 - Diphtheria toxoid provides the body with antitoxins that last for 10 years.
 - Rotavirus causes watery diarrhea, and is more common during the winter months in the upper latitudes.
 - An infant with a viral infection, e.g., chicken pox, may experience Reye's syndrome if given aspirin. Reye's syndrome manifests as microvesicular hepatomegaly, jaundice, hypoglycemia, and hyperammonemia.
 - Asplenic patients are prone to infections by encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. The most aggressive is *Streptococcus pneumoniae*.
 - The only drug approved to treat syphilis during pregnancy is *penicillin*.
 - Major factor determining the magnitude of risk of HIV transmission after a needle stick injury: *Depth of the injury*
 - *Zidovudine (AZT)* has been proven to decrease HIV transmission from infected mother to fetus during pregnancy.
 - First symptom of botulism: *Sore throat and blurry vision*
 - Death in botulism cases is due to *paralysis of respiratory muscles*.
 - Diseases that are required to be reported to the Centers for Disease Control and Prevention (CDC) include AIDS, gonorrhea, hepatitis B virus (HBV), and pertussis.
 - Summertime outbreaks of fever, pharyngitis, and conjunctivitis in children is commonly due to *adenovirus infection* contracted from *swimming pools*.
- old) divided by the total of fetal deaths and live births combined
2. $Perinatal\ death\ rate = \frac{Deaths\ during\ perinatal\ period}{(Fetal\ deaths + live\ births)}$
- *Neonatal death rate:*
 1. The number of deaths in neonatal period (the first 28 days of life) divided by the number of live births; deaths during this period are most commonly due to *prematurity*.
 2. $Neonatal\ death\ rate = \frac{Deaths\ in\ neonatal\ period}{Live\ births}$
 - *Infant mortality rate:*
 1. The number of deaths during the first year of life divided by the number of live births
 2. *It is the best index of health status of a community.*
 3. In the U.S., the infant mortality rate is approximately 10/1000 live births.
 4. The death rate of black infants in the U.S. is *twice as high* as that of white infants.
 5. This rate is improved by *family planning and contraception awareness*.
 6. $Infant\ mortality\ rate = \frac{Deaths\ during\ first\ year\ of\ life}{Live\ births}$
 7. From the above entries, note that the infant mortality rate is equal to the neonatal + post-neonatal death rates.
 - *Maternal mortality rate:*
 1. The number of deaths in women during pregnancy and the puerperium divided by 1000 live births
 2. Death during this period is most commonly due to *postpartum hemorrhage*.
 3. $Maternal\ mortality\ rate = \frac{Deaths}{1000}$
 - *Note:* Mortality rates are much higher in the neonatal period and elderly age groups than in any other age.

Mortality Rates

- *Fetal stillbirth rate:*
 1. The number of stillbirths divided by the total of still and live births combined
 2. Fetal deaths are most commonly due to congenital malformations. The fetal death rate is usually underestimated.
 3. $Fetal\ still\ birth\ rate = \frac{Still}{(Still + live)}$
- *Perinatal death rate:*
 1. The number of deaths in the perinatal period (from the point of fetal viability until 7 days

Risk Factors

- Multiple sclerosis (MS) risk factors include: *Female gender, white race, middle latitudes, and positive family history*
- The most important risk factor for breast cancer: *Age*
- The most important risk factor for cataract: *Age*
- Isolated systolic hypertension, i.e., systolic BP >160, is a risk factor for *CVAs*.
- Obesity is a risk factor for non-insulin-dependent diabetes mellitus (*NIDDM*).

- Hypertension is *not* a risk factor for thromboembolism; however, it is a risk factor for atherosclerosis.
- Hypercholesterolemia is *not* a risk factor for cholesterol gallstones; the determining factor is the *cholesterol/bile salt ratio* in the bile.

Metals

- *Zinc deficiency*: Causes altered mental status and poor wound healing
- *Benzene exposure*: Causes aplastic anemia, testicular atrophy, and leukemia. Screened for by measuring the *urinary phenol level*
- *Arsenic*: Affects the liver and kidneys, and may cause warts
- *Manganese*: Causes *mask face deformity*
- *Polyvinyl chloride (PVC)*: Used in water pipes, and may affect the skin, lungs, and liver
- *Inorganic mercury overexposure*: Causes gingivitis
- *Lead*:
 1. The major environmental source of lead: *Air*
 2. The most effective prevention of lead poisoning: *Environmental elimination*
 3. The best way to measure blood lead levels: *Venipuncture*
 4. The best way to *screen* lead exposed workers for toxicity: *urinary aminolevulinic acid (ALA)*
 5. Chelation by *ethylenediaminetetraacetic acid (EDTA)* is only needed if the serum lead level exceeds *45 µg/dL*.
- *Cement*: Contains carbon monoxide (CO), which may affect the oxygen carrying capacity of red blood cells (RBCs)
- *Petroleum*: Contains hydrogen sulfide (H₂S), which causes *central nervous system (CNS) toxicity*
- *Cyanide*: Acts by inhibiting cellular O₂ uptake by *competing with cytochrome oxidase*
- *Benzene exposure*: Screened for by measuring the *urinary phenol level*

Dietary

- Pinto beans and the treponemal disease *yaws* cause false-positive FTA tests.
- An extra *3500 calories* leads to *one pound* increase in weight.
- The most effective method of determining alcoholism in primary care: *CAGE questionnaire*:
 1. C: Have you felt you need to Cut down on your drinking?
 2. A: Have you ever been Annoyed by people criticizing your drinking behavior?

3. G: Have you ever felt Guilty about drinking?
4. E: Have you ever felt you needed an Eye-opener first thing in the morning?

- Legal alcohol level during driving: *Less than 0.08%*
- Iron: Molasses is the richest source of *iron*. Iron absorption is inhibited by *wheat*. Iron deficiency anemia is *more common in lactating* than pregnant women.
- Patients having vitamin B₁₂ deficiency are at risk of *protein deficiency*.
- Eggs are a rich source of *niacin*.

Health Insurance

- About *35 million* Americans have no health insurance; most of them have jobs.
- Diagnosis-related groups (DRGs) are covered by Medicare part A, and have a fixed cost. Any increase in this cost is known as *creep*.
- The DRG system main goal is to overcome rising hospital costs.
- Medicare is entitled to cover the elderly (helpful to remember: “-Care for the elderly”), while Medicaid is entitled to cover the poor (“-Aid for the poor”).
- Components of Medicare:
 1. Medicare part A: Covers hospital costs
 2. Medicare part B: Covers physicians' bills
- Medicare is handled by the federal government, while Medicaid is handled by the state governments separately.
- End-stage renal disease (ESRD) patients are covered by *Medicare*.

Miscellaneous

- Interference in a patient's case without his/her consent is considered *battery*.
- Radiation effects:
 1. 100 to 800 rad: Bone marrow depression
 2. 800 to 3000 rad: GI injury
 3. More than 3000 rad: cardiovascular system (CVS) and CNS injury
- Estimation of the incidence of hypertension requires a *fixed cohort study*.
- Earliest manifestation of decompression sickness: *Joint pains*
- Children of alcoholic parents have *higher tolerance* for alcohol.

- Anorexia nervosa is more common in the *high social class* than lower classes.
- Hormonal replacement therapy (HRT) *increases* incidence of ischemic heart diseases, CVAs, and thromboembolism.
- Only 25% of smokers respond to nicotine patches.
- The four components of medical ethics include:
 1. Beneficence: Help the patient.
 2. Nonmaleficance: Do no harm.
 3. Justice
 4. Autonomy: Respect the patient's wishes.
- Supererogatory refers to individuals doing unusual effort to save a life, e.g., carrying a patient into the emergency room, donating an organ to a patient.
- Noise-induced hearing loss occurs at 4000 Hz.
- Legal allowance for noise: 90 decibels
- Five percent of the elderly population reside in *extended care facilities*.

Statistics

- *Standard deviation and distribution* (Fig. 5.1)
- *Hawthorne effect*: Occurs when patients involved in a study change their behavior during the study time, simply because of their awareness of being involved in that study
- *Validity (accuracy) = Right results*. Validity of a test could be measured by sensitivity and specificity. When you specify a single point on the curve, this is *accuracy*.
- *Reliability (precision) = Test-retest reliability*. When the curve is narrower, it is more *precise*.
- *Important equations* (Table 5.1)

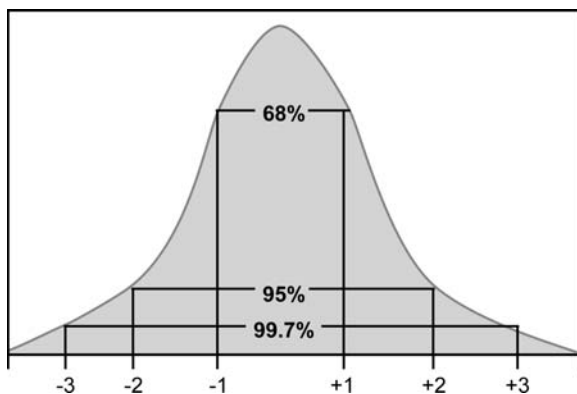


FIG. 5.1 Standard deviation curve

TABLE 5.1 Sensitivity and specificity.

Test	Diseased	Not diseased
Positive	A	C • False-positive result (type 2 error)
Negative	B • False-negative result (type 1 error)	D

1. $Sensitivity = (A)/(A + B) \times 100$. Sensitivity is a *screening test* entitled to detect *diseased individuals*.
 2. $Specificity = (D)/(D + C) \times 100$. Specificity is a *confirmatory test* entitled to detect *healthy individuals*.
 3. $Positive\ predictive\ value = (A)/(A + C)$
 4. $Negative\ predictive\ value = (D)/(D + B)$
- *Rates and ratios*:
 1. $Prevalence\ rate = \text{Number of existing cases}/\text{Patients at risk per unit of time}$
 2. $Incidence\ rate\ (absolute\ risk) = \text{Number of new cases}/\text{Patients at risk per unit of time}$
 3. $Mortality\ rate = \text{Number of deaths}/\text{Patients at risk per unit of time}$
 4. $Case\ fatality\ rate = \text{Number of deaths per episode}/\text{Number of episodes} \times 100$
 5. $Relative\ risk\ ratio\ (morbidity\ ratio)\ (mortality\ ratio) = \text{Incidence rate in exposed}/\text{Incidence rate in nonexposed} = (A)/(A + C)\ \text{divided by}\ (B)/(B + D)$
 6. $Attributable\ risk\ (risk\ difference) = \text{Incidence rate in exposed} - \text{Incidence rate in nonexposed} = (A)/(A + C) - (B)/(B + D)$
 7. $Odds\ ratio\ (estimated\ relative\ risk) = \text{Odds that case was exposed}/\text{Odds that control was exposed} = (A) \times (D)/(B) \times (C)$
 - *Mode, median, and mean*:
 1. *Mode*: The value that occurs with the highest frequency
 2. *Median*: The value that divides the other values equally.
 3. *Mean*: The *average* of values
 4. *Example*: For the following values (4, 6, 2, 2, 4, 3, 2, 1, 6), the mode is 2, because it has the highest frequency. The mean is 3.33 (Total of values/Number of values = 30/9 = 3.33). The median here is 3, because if you arrange the digits in order, 3 will be the digit dividing them into two equal sets, i.e., 1, 2, 2, 2, 3, 4, 4, 6, 6.

Chapter 6

Genetics

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Chromosomes and Genes

- **Chromosome:** Each chromosome is formed of two parallel chromatids attached to each other by the *centromere*. Each chromatid is formed of a short and a long segment.
- **Diploid:** Each human *somatic* cell contains 46 chromosomes (*diploid cells*), divided into 44 *autosomal* chromosomes and 2 *sex* chromosomes.
- **Haploid:** Each human *gamete* cell contains only 23 chromosomes (*haploid cells*).
- **Gene:** It is a segment in the chromatid. Its mirror image on the other chromatid of the same chromosome is known as *allele*.

Karyotyping

- It is a method used to visualize and evaluate the chromosomes and their disorders.
- **Technique:** *Lymphocytes* are taken from the blood and are cultured in a cell excitatory medium. The cell cycle is arrested artificially at the *metaphase of mitosis*, where chromosomes are extracted and examined.

Barr Body

- It is an *inactivated X chromosome*. Any cell in the human body should contain *no more than one functioning X chromosome* at a time. Any *extra X chromosome* is referred to as a *Barr body*.
- **Diagnosis:** By performing a *buccal smear*
- **Example:** Male cells carry XY chromosomes, so the number of Barr bodies in a healthy male cell is zero. Female cells carry XX chromosomes, so each healthy female cell has one Barr body.

Important Definitions

- **Anticipation:** A phenomenon in which a disease gets more aggressive upon its inheritance to future generations
- **Incomplete penetrance:** A phenomenon in which a disease skips some generations during its inheritance
- **Imprinting:** Phenotypic differences between patients depend on the source of the inherited gene, i.e., maternal vs. paternal

- *Variable expression*: Phenotype of the same disease varies from one patient to another

Chromosomal Disorders

Structural

Translocation

- *Mechanism*: An injury to the chromosome leads to *exchange of genetic material* between nonhomologous chromosomes.
- *Robertsonian translocation*: Fusion of the long arms of two different chromosomes. Total chromosomal cell count is 45, and the patient is phenotypically normal. This is the most common form of translocation, and it could cause recurrent first trimester abortions.
- *Non-Robertsonian translocation*: Total chromosomal cell count is 46, but the patient is phenotypically abnormal.

Breakage

- *Mechanism*: It occurs due to toxins or radiation, e.g., ultraviolet (UV) rays.
- *Location*: The breaks could be on the same side of the centromere (paracentric) or on either side of the centromere (pericentric).

Others

- *Isochromosome*: Occurs due to division of the centromere *transversally* rather than vertically. The outcome is two chromosome segments, one with two short arms and the other with two long arms.
- *Duplication*: It is the presence of two copies of the same chromosomal segment. It occurs due to error in the *crossing over* of chromosomes.
- *Inversion*: It occurs when a chromosomal segment is broken, and reinserts itself in the wrong direction.
- *Deletion*: It is loss of part of the chromosome.
- *Ring chromosome*: Two chromosomes with deleted ends fuse together forming a ring.

Numerical

Polyploidy

- The cell chromosomal count is 46 *plus one or more extra sets of haploid chromosomes (23)*.
- *Triploidy*: It is three multiples of the 23 chromosomes, and it occurs due to one or more of the following mechanisms:

1. *Nondisjunction of chromosomes during the first meiotic division*
2. *Fertilization of a diploid ovum by a haploid sperm*
3. *Fertilization of a haploid ovum by two haploid sperms*

- *Tetraploidy*: It is four multiples of the 23 chromosomes, and it occurs due to *failure to complete the first zygotic division*.

Aneuploidy

- The cell chromosomal count is abnormal, *but not in multiples of 23, as in polyploidy*.
- *Mechanism*: *Nondisjunction during the anaphase of meiosis*
- *Examples*:
 1. Extra autosomal chromosome, e.g., trisomies
 2. Extra sex chromosome, e.g., Klinefelter's syndrome
 3. Deleted sex chromosome, e.g., Turner's syndrome

Mosaicism

- It is having cells with *variable* chromosomal counts, e.g., normal, monosomy, trisomy all at the same time.

Genetic Disorders

Autosomal Dominant (AD)

- A dominant trait manifests in both heterozygous and homozygous states.
- There is *no carrier state*; if you have the gene, you have the disease.
- Incidence is equal in both genders.
- If one parent is carrying the gene, children have a 50% chance of inheriting it.
- In the pedigree of inheritance, it is *vertical and involving both genders* (Fig. 6.1).
- Most common AD disease: *von Willebrand's disease*
- Other AD diseases: Osteogenesis imperfecta type I and spherocytosis

Autosomal Recessive (AR)

- A recessive trait manifests *only in homozygous states*.
- There is a carrier state; the heterozygote got the gene but did not get the disease.
- Incidence is equal in both genders.
- *Most AR disorders occur due to enzyme deficiency*.

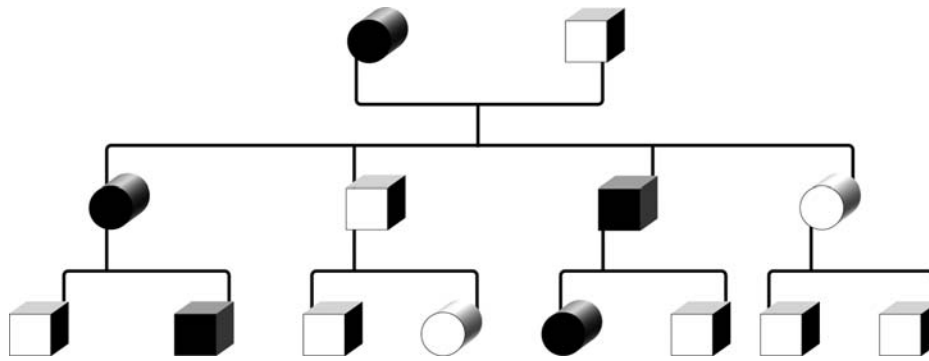


FIG. 6.1 Autosomal dominant pedigree. Note the vertical inheritance. Black = case, white = healthy, square = male, circle = female

- If both parents are heterozygous, 50% of the children will be the same, and 25% will be homozygous for the trait and get the disease.
- In the pedigree of inheritance, it is *horizontal and involving both genders* (Fig. 6.2).
- Most common AR disease in whites: *Cystic fibrosis*
- Most common AR disease in African-Americans: *Sickle cell anemia*
- Other AR diseases: Osteogenesis imperfecta types II and III and thalassemia

- There is a carrier state; only in females. *Males are always cases, never carriers.*
- Unique to all X-linked diseases is the gene inheritance system:
 1. Fathers pass their genes to their daughters.
 2. Mothers pass their genes to *both* sons and daughters.
- Diseased father and healthy mother: Leads to carrier daughters and normal sons
- Healthy father and carrier mother: Leads to carrier state in 50% of daughters and a disease in 50% of the sons
- In the pedigree of inheritance, it is *vertical and involving males only* (Fig. 6.3).
- Examples: Hemophilia, Duchenne muscular dystrophy, glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, fragile X syndrome

X-Linked Recessive (XLR)

- An X-linked trait manifests *only in males*, never in females.

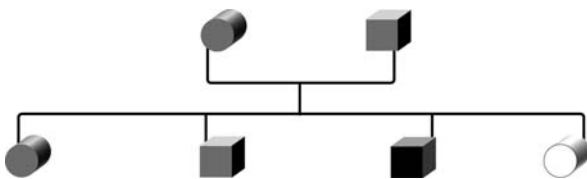


FIG. 6.2 Autosomal recessive pedigree. Note the horizontal inheritance. Gray = carrier; black = case

Others

- *X-linked dominant (XLD)*: It is a rare disorder with more incidence in *females*. The mode of inheritance is the same as in XLR; father passes his genes to his daughters, and mother passes her genes to both sons and daughters. Example: *Alport syndrome*.

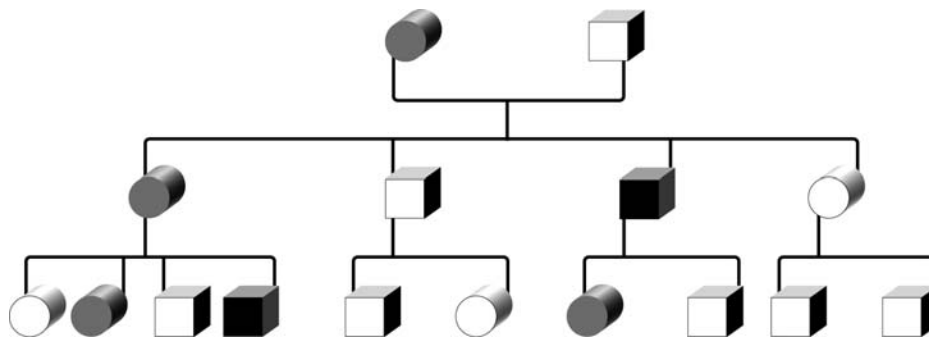


FIG. 6.3 X-linked recessive pedigree

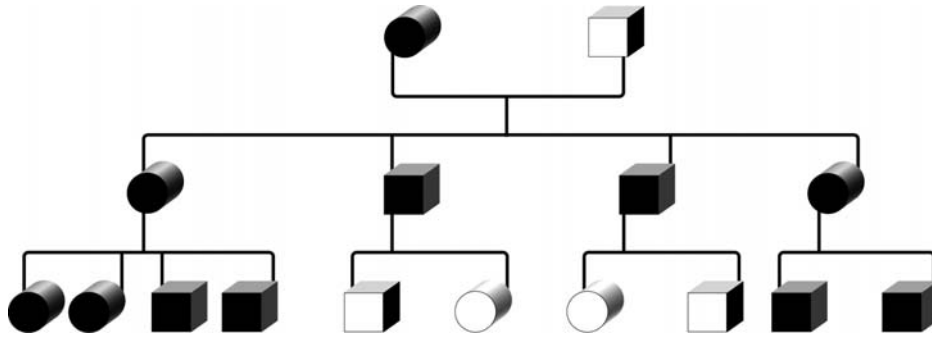


FIG. 6.4 Mitochondrial inheritance

- *Y-linked*: Traits are carried only on Y chromosome through which the father passes the genes to his sons. Incidence is *entirely in males*, as it is Y-linked. Example: Excessive hair on the chest, hair on the back of the neck.
- *Mitochondrial*: This mode of inheritance is always passed from *mother* to children; *it is never paternal*. In the pedigree of inheritance, it is *vertical showing maternal inheritance to both genders*, and *absence of paternal inheritance* (Fig. 6.4).

Spotlight on Famous Disorders

Down Syndrome (Fig. 6.5)

- *Trisomy of chromosome 21*
- *Mechanism: Nondisjunction*, and less commonly translocation (*t14:21*) and mosaicism



FIG. 6.5 A patient with Down syndrome

- *Clinical picture*:
 1. Head: Microcephaly with flat occiput and flat nasal bridge
 2. Eyes: *Medial epicanthal folds* and *speckled iris* (Brushfield spots)
 3. Mouth: Small mandible (micrognathia) and microstomia
 4. Upper limbs: Short broad hands (*brachydactyly*) with a *simian crease*
 5. Genital: Cryptorchidism and infertility
 6. Lower limbs: Gapping between toes (*sandal gap toe*)
 7. Congenital anomalies: *The most common (in descending order)*:
 - *Endocardial cushion defects* = ventricular septal defect (VSD) + atrial septal defect (ASD) + common atrioventricular (AV) canal
 - *Annular pancreas* and *duodenal atresia*
- *Antenatal diagnosis*:
 1. Suspected during ultrasound (US) in the first trimester by presence of *nuchal translucency*
 2. Diagnostic criteria for Down syndrome through amniocentesis:
 - *Low amniotic alpha-fetoprotein (AFP) level* or *maternal serum AFP (MSAFP)*; below 0.4 mOsm
 - *Low estrogen (E3) level*
 - *Elevated human chorionic gonadotropin (β -HCG) level*
- *Notes*:
 1. Down syndrome is the *most common cause of congenital mental retardation*.
 2. Patients with Down syndrome have frequent recurrent infections, due to an *impaired phagocytic system*.

- Down syndrome patients have high risk of developing *acute lymphoblastic leukemia (ALL)* and *Alzheimer's dementia in an early age*.

Edward's Syndrome

- *Trisomy of chromosome 18*
- *Mechanism: Nondisjunction*
- *Clinical picture:*
 1. Mental and growth retardation, and multiple congenital anomalies
 2. *Hypertonia, prominent occiput, clenched hands, and rocker-bottom feet*
 3. *Choroid plexus cysts*
 4. Intrauterine: *Single umbilical artery*
- *Antenatal diagnosis:* Diagnostic criteria for Edward's syndrome:
 1. *Low amniotic alpha-fetoprotein level or MSAFP; below 0.4 mOsm*
 2. *Low estrogen (E3) level*
 3. *Low B-HCG level*

Patau's Syndrome

- *Trisomy of chromosome 13*
- *Mechanism: Nondisjunction*
- *Clinical picture:*
 1. Mental and growth retardation, and multiple congenital anomalies
 2. *Colobomas: Erosions in the iris*
 3. *Cleft lip or cleft palate, and polydactyly*

Turner Syndrome

- *Mechanism: Monosomy (45X) or isochromosome of long arm of X chromosome*
- *Clinical picture:* A female patient with:
 1. *Short stature: A red flag that you should never miss*
 2. *Head: Low posterior hair line and low-set ears*
 3. *Mouth: Straight lower lip and curved upper one ("shark mouth")*
 4. *Neck: Webbing*
 5. *Chest: Underdeveloped breasts with widely spaced nipples ("shield chest")*
 6. *Extremities: Cubitus valgus and short metacarpal bones.*
 7. *Congenital anomalies:*
 - Cardiovascular system (CVS): *Coarctation of the aorta*
 - Genitourinary (GU) system: *Fibrosed ovaries and horseshoe kidneys*
 - Gastrointestinal (GI) system: *Colonic telangiectasia*

- *Notes:*

1. Spontaneous abortion might occur when the fetus has Turner syndrome, as she might develop *hydrops fetalis* or *cystic hygroma*.
2. Buccal smear in these patients shows *no Barr body*.
3. Patients with Turner syndrome should receive screening for all the congenital anomalies, and receive hormone replacement therapy.

Klinefelter's Syndrome

- *Mechanism: Extra X chromosome causing trisomy (47XXY)*
- *Clinical picture:* A male patient with:
 1. Tall stature with *euchooid* features
 2. *GU: Small penis, scrotum, and testicles*
 3. *Infertility: Due to occluded genital ductal system*
- *Notes:*
 1. Buccal smear in these patients shows *at least one Barr body*.
 2. Patients with Klinefelter's syndrome should receive testosterone replacement therapy

Duchenne Muscular Dystrophy (DMD)

- *X-linked disease* as the DMD gene is located on the short arm (p) of X chromosome at position 21(Xp21)
- *Mechanism:* It lies in the *lack of:*
 1. *Dystrophin protein:* Regulates calcium channels of muscles
 2. *Actin:* Anchors the extracellular matrix
- *Clinical picture:*
 1. *Calf muscle pseudohypertrophy:* Calves appear enlarged, but are weak due to deposition of *connective and fibrous tissue*.
 2. *Muscle weakness and hyporeflexia, proximal more than distal*
 3. *Gower sign's:* Patient uses the arms to rise from the floor.
 4. *Skeletal deformities:* It is the most common cause of *thoracolumbar scoliosis* in children.

5. Cardiomyopathy, and early death

- **Diagnosis:** High serum levels of the isoenzyme of creatine kinase with muscle subunits (CK-MM), aldolase, and lactate dehydrogenase (LDH). *Electromyogram (EMG) and muscle biopsy are diagnostic.*
- **Note:** Becker muscular dystrophy is similar to DMD, except for the fact that *dystrophin is present but in small amounts.* The disease is milder and slower in progression.

Alport Syndrome

- *X-linked dominant*; however, in a minority of cases AR or AD
- **Mechanism:** Defect in *type IV collagen*, a component of basement membranes.
- **Clinical picture:** *Painless hematuria, cataract, and sensorineural hearing loss.* So when you see a child on the USMLE who is deaf and having hematuria, you know what to think!
- **Complication:** Chronic kidney disease, and end-stage renal disease (ESRD)

Fragile X Syndrome

- *X-linked recessive* disease
- **Mechanism:** *Fragile site on the long arm of the X chromosome.* The fragile site is due to an abnormal number of *CGG repeats*. This leads to decreased expression of the *FMR1* gene, which normally produces a protein needed for brain functioning.
- **Clinical picture:** Key word here is *Big*:
 1. Head: Long face, big ears, and big jaw
 2. GU: *Big* testicles
 3. Development: Autism and mental retardation

Cri du Chat Syndrome

- **Mechanism:** *Deletion of the short arm of chromosome 5 (5p-)*
- **Clinical picture:**
 1. Mental and growth retardation, and multiple congenital anomalies
 2. *Moon face* and *cat-like cry*: Due to *laryngeal hypoplasia*

Von Hippel–Lindau (VHL)

- **Mechanism:** *Deletion of VHL* gene on chromosome 3
- **Clinical picture:** Hemangioblastomas everywhere, e.g., cerebellum, retina

- **Complication:** Malignancy; *VHL* is normally a tumor suppressor, so these patients are at increased risk of developing *renal cell cancer*.

Wolf-Hirschhorn Syndrome

- **Mechanism:** *Partial deletion of the short arm of chromosome 4 (4p-)*
- **Clinical picture:**
 1. Prominent forehead and nose, *frequently compared to a warrior's helmet*
 2. Short philtrum of the upper lip

Prader-Willi Syndrome

- **Mechanism:** *Deletion of the long arm of chromosome 15 (15q-).* Deletion here occurs by *paternal imprinting due to methylation of cytosine during gametogenesis.*
- **Clinical picture:**
 1. Short, obese patient with *small hands and feet, and almond-shaped eyes*
 2. Prader-Willi patients have *hyperphagia* and *hypogonadism*

Angelman Syndrome

- Also known as *happy puppet syndrome*
- **Mechanism:** *Deletion of the long arm of chromosome 15 (15q-).* The differentiating point from Prader-Willi is that the imprinting in Angelman is *maternal*.
- **Clinical picture:** Mental retardation, and the patient is continuously laughing and smiling (*like a happy puppet*)

DiGeorge Syndrome

- **Mechanism:** *Deletion of long arm of chromosome 21 (21q-)*
- **Pathology:** This leads to defective development of the *third and fourth pharyngeal pouches*; accordingly, *parathyroid glands and thymus are absent.*
- **Clinical picture** (helpful to remember: “George always shows TLC”):
 1. Tetany: Due to *hypocalcemia, due to absent parathyroid hormone (PTH)*
 2. Lack of a *thymus*: Leads to recurrent infections
 3. Cardiovascular anomalies

Cystic Fibrosis

- *AR* disease, due to *3 base deletion of phenylalanine.*

- *Mechanism:* Mutation of *CFTR* gene on the long arm of chromosome 7, which controls chloride channels
- *Clinical picture:*
 1. Recurrent respiratory infections: Mainly *Pseudomonas cepacia* and *Staphylococcus*
 2. Malabsorption and steatorrhea: Deficiency of vitamins *A, D, E, and K*
 3. Infertility and meconium ileus: Due to viscid secretions
 4. *Clubbing:* In almost all patients with cystic fibrosis
- *Diagnosis:* Sweat chloride test; level of more than 60 mEq is diagnostic
- *Treatment:* Chest physiotherapy, antibiotics, and pancreatic enzymes

Phenylketonuria (PKU)

- *Autosomal recessive* disease
- *Mechanism:* Absence of *phenylalanine hydroxylase* enzyme, which normally converts phenylalanine to tyrosine
- *Clinical picture:*
 1. Fair skin and blue eyes: Due to decreased *melanin* synthesis
 2. Microcephaly and mental retardation: Due to accumulation of phenyl-pyruvate, -lactate, and -acetate
 3. Hypertonia and seizures: Due to accumulation of *serotonin*
 4. Musty odor: Due to accumulation of *phenylacetate*
- *Diagnosis:*
 1. Measuring the activity of phenylalanine hydroxylase enzyme
 2. Elevated serum levels of phenylalanine >20%
 3. Elevated urine levels of phenylpyruvate, -lactate, and -acetate
- *Treatment:* Dietary restriction of phenylalanine and aspartame (which releases phenylalanine when digested)
- *Note:* Do not confuse PKU with homocystinuria, as the latter also presents with congenital fair skin and blue eyes plus thromboembolic phenomena.

Galactosemia

- *Autosomal recessive* disease
- *Type I:*

1. *Mechanism:* Absence of *galactokinase* enzyme, which normally converts galactose to galactose-1-phosphate
 2. *Clinical picture:* Cataracts and galactosuria
- *Type II:*
 1. *Mechanism:* Absence of *galactose-1-phosphate uridylyltransferase* enzyme, which normally converts galactose-1-phosphate to glucose-1-phosphate
 2. *Clinical picture:* *Cataracts, galactosuria* and:
 - CNS: Microcephaly and mental retardation
 - GI: Hepatosplenomegaly and liver cirrhosis
 - GU: Fanconi's syndrome = Glucosuria, phosphaturia, and aminoaciduria
 - Metabolic: Hypoglycemia, due to inhibited *glycogenolysis* enzymes
 - *Treatment:* Restricting galactose in the diet

Albinism

- *AR*, but can also be inherited as AD or X-linked recessive
- *Mechanism:* Absence of *tyrosinase* enzyme, which normally converts tyrosine to melanin
- *Clinical picture:* Depigmented skin, hair, iris and retina
- *Complications:* High risk of *blindness* and *skin cancer*

Apert Syndrome

- *Autosomal dominant* syndrome
- *Mechanism:* Mutation in the gene of *fibroblast growth factor (FGF-2)*
- *Clinical picture:*
 1. *Craniosynostosis:* Premature ossification of the skull sutures
 2. *Fused digits*

Neurofibromatosis

- *Autosomal dominant* syndrome
- *Type I* (Von Recklinghausen's):
 1. Inherited on *chromosome 17*
 2. Cutaneous *café-au-lait* patches (Fig. 6.6)
 3. Lisch nodules: *Pigmented iris nodules*
- *Type II* (Central neurofibromatosis):
 1. Inherited on *chromosome 22*
 2. Bilateral *acoustic neuroma* and astrocytoma. Note that acoustic neuroma is a *schwannoma* with *Antoni A* and *Antoni B* bodies.



FIG. 6.6 Café-au-lait patches of neurofibromatosis

Tuberous Sclerosis

- Autosomal dominant syndrome
- Clinical picture:
 1. Diffuse hamartomas
 2. Ash leaf spots: Flat, hypopigmented skin lesions
 3. Shagreen patches: Areas of increased skin thickness
 4. Subungual fibroma
 5. Periventricular tubers: Causing mental retardation and seizures

Xeroderma Pigmentosum

- It is an example of breakage disorder.
- Mechanism: Ultraviolet light causes failure of the DNA repair mechanism, namely the ultraviolet endonuclease. This leads to accumulation of pyrimidine dimers.
- Clinical picture: Skin lesions and cancer

Hereditary Nonpolyposis Colon Cancer (HNPCC)

- Mechanism: Mismatch repair secondary to microsatellites. *MSH2* gene is blamed in most HNPCC cases.
- Clinical picture: HNPCC (Lynch syndrome) is a familial form of colon cancer. It involves the following diagnostic criteria (helpful to remember: 3,2,1):
 - 3: Colon cancer in at least 3 first-degree relatives
 - 2: These cancers occur over a period of at least 2 generations.
 - 1: At least one of these three relatives is less than 50 years of age.
- Note: Women in families with HNPCC are at high risk of endometrial and ovarian cancer as well.

Leber Optic Neuropathy

- It is an example of mitochondrial inheritance.
- Mechanism: Mutation of *ND4* gene, which normally functions as follows:
 1. Regulates the conversion of arginine to histidine
 2. Encodes reduced nicotinamide adenine dinucleotide (*NADH*) dehydrogenase, which regulates adenosine triphosphate (ATP) and electron transport
- Clinical picture: Loss of central vision, and maintaining a peripheral tubular field
- Complication: Optic nerve degeneration and blindness

Spotlight on Famous Oncogenes

- Oncogenes: They are the genes regulating tumors and malignancies.
- *BRCA*: Mutation leads to breast and ovarian cancer.
- *p53*: Mutation of this tumor suppressor gene on chromosome 17 leads to cancer.
- *Rb1*: Mutation of this gene leads to retinoblastoma.
- *APC*: Mutation of this gene (on chromosome 5) leads to familial adenomatous polyposis (FAP).
- *ras*: Associated with colon cancer
- *c-myc, t8:14*: Associated with Burkitt's lymphoma
- *Bcl-2, t14:18*: Associated with follicular lymphoma
- *Bcr/abl*: Associated with chronic myeloid leukemia (CML)

- *Philadelphia chromosome, t9:22*: This translocation is pathognomonic for *CML*, and its presence is associated with a *good prognosis*.
- *t15:17*: This translocation is pathognomonic for *acute myeloid leukemia (AML)*, and its presence is associated with a good prognosis.
- *Human herpes virus (HHV-8)*: Kaposi sarcoma
- *Human papilloma virus (HPV)*: Cervical cancer
- *Epstein-Barr virus (EBV)*: Burkitt's lymphoma and nasopharyngeal cancer
- *Hepatitis viruses B and C*: Hepatocellular cancer
- *Note*: DNA mutations can be diagnosed using single-stranded conformational polymorphism (*SSCP*), which shows *two bands for homozygous mutations and four for heterozygous ones*.

Chapter 7

Microbiology

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Bacteria

- All bacteria are *haploid* structures; they can trap iron using *siderophores*, and can also perform fermentation processes.
- Gram-positive bacteria appear violet because they absorb *cresyl violet stain*.
- Gram-negative bacteria appear red because they absorb *safranin stain*.
- Cell wall of bacteria is mainly made up of *peptidoglycan*:
 1. Gram positive: It is *thick* with *extensive cross-linking*.
 2. Gram negative: It is *thin* with *minimal cross-linking*.

Structure

Gram-Positive Bacteria

- Cell envelope from *inside out* is formed of *two layers*:
 1. *Cytoplasmic membrane*: A lipid bilayer spanned by proteins. This layer, unlike animals' membranes, contains *no sterols*.
 2. *Cell wall*: Formed of 3 P's—Peptidoglycan, Polysaccharides, Proteins—and an antigenic determinant known as *teichoic acid*.

Gram-Negative Bacteria

- Cell envelope from *inside out* is formed of *three layers*:
 1. *Cytoplasmic membrane*: Lipid bilayer spanned by proteins
 2. *Cell wall*: Very thin peptidoglycan layer with *no teichoic acid*; however, it is rich in *murein lipoprotein*. Cytoplasmic membrane and cell wall are separated by the *periplasmic space*, which is rich in enzymes and proteins.
 3. *Outer layer*: Lipid bilayer containing *porin* channels and *lipopolysaccharides (LPSs)*. LPS is differentiated into:
 - O antigen: Toward the outside
 - Polysaccharides: Forms the core
 - Lipid A: An *endotoxin* situated toward the inside
- *Notes*:
 1. The only gram-positive bacterium that contains endotoxins is *Listeria monocytogenes*.
 2. Mycoplasma only has a cytoplasmic membrane and *no cell wall*.

3. Lipid bilayer is arranged as follows:

- *Hydrophobic tails* pointing toward the *center*
- *Hydrophilic heads* pointing toward the *outside*

Toxins

- *Exotoxins*
 1. Neurotoxins: e.g., tetanus and botulism
 2. Enterotoxins: e.g., *Escherichia coli*. *Composition*: Action and binding regions. *Mechanism*: Increases the NaCl content inside the intestine, which causes diarrhea.
- *Endotoxins*: A component of the gram-negative bacterial cell membrane
- *Septic shock*: Treating gram-negative bacteria with antibiotics can lead to bacterial destruction and release of huge amounts of endotoxins, causing septic shock. This process is regulated by *interleukin-1 (IL-1)* and *tumor necrosis factor (TNF)*.

Cocci and Bacilli

- *Gram-positive cocci*: Staphylococci (*clusters*), streptococci (*chains*) or pneumococci (*pairs*)
- *Gram-negative cocci*: Meningococci and gonococci (*kidney-shaped pairs*)
- *Gram-positive bacilli*: *Corynebacterium diphtheriae* (*Chinese letters appearance*), *Clostridium tetani* (*terminal spores*), and *Clostridium welchii* (*subterminal spores*)
- *Gram-negative bacilli*: *E. coli*, *Klebsiella*, and *Vibrio cholera* (*short curved comma shaped*)

Metabolism

- Bacterial DNA is a double-stranded circle, while smaller circles might exist, and are known as plasmids. *Plasmids have the ability to resist antibiotics*.
- Bacteria release catalase and peroxidase to protect themselves from the destructive effect of hydrogen peroxide (H₂O₂). They also release superoxide dismutase to break down the oxygen free radicals.
- *Metabolic types of bacteria*:
 1. Obligate aerobe: Needs the *presence* of oxygen
 2. Obligate anaerobe: Needs the *absence* of oxygen. They are *malodorous*. Suspect in cases of aspiration pneumonia, e.g., *alcoholics*, syncope
 3. Facultative aerobe: Aerobic, but can also work in anaerobic conditions

4. Microaerophilic: Works only in the presence of small amounts of oxygen. These bacteria are deficient in catalase and peroxidase enzymes.
 5. Heterotrophs: Bacteria using organic carbons for metabolism
 6. Autotrophs: Bacteria using inorganic ammonium and sulfide for metabolism
- **Notes:**
 1. Aminoglycosides and Tetracyclines work AT 30S subunit of ribosomes; all other protein synthesis inhibitors work on 50S.
 2. Facultative intracellular organisms, e.g., *Salmonella*, *Listeria*: They can live and metabolize normally inside macrophages after being phagocytosed.

Flagella

- They bind to the cell membrane by means of a *basal body*, and are the means of *motility*. Bacteria could have no flagella (e.g., *Shigella*), single flagellum (e.g., *Vibrio*), or multiple flagellae (e.g., *E. coli*).
- *Pili (fimbriae)*: They are *short* and *not motile*, so they are used by the bacteria as means of *adhesion* to other structures. *E. coli*, *Campylobacter jejuni*, and *Neisseria gonorrhoeae* contain large number of pili.

Capsule

- **Composition:** Capsules are made of *polysaccharides*. The only exception is *Bacillus anthracis*, which is made of *amino acids*, e.g., *glutamate*, etc.
- **Colonies:** Capsulated *Streptococcus pneumoniae* form smooth colonies, and vice versa.
- **India ink:** It makes the capsule look like a halo around the capsulated bacteria, thus used to diagnose infection with capsulated organisms, e.g., *Cryptococcus neoformans*.
- **Quellung reaction:** Depends on *antibody-induced swelling of the capsule*
- **Opsonization:** Depends on binding of the *Fc portions* of antibodies to the capsule, which in turn allows macrophages to eat the bacteria
- **Spores:** Composed of *three membranes, keratin*, and *exosporium layer*.

Multiplication

- **Transformation:** Naked DNA of one cell attaches itself into another cell of close species. This is followed by entrance of the DNA into the cell and

attaching to its genome, resulting in the transformation of the genetic characters of the recipient cell.

- **Conjugation:** A sex pilus builds up between two cells like a bridge, to facilitate the transport of *fertility (F) plasmid* and *antibiotic resistance genes*.
- **Transduction:** Bacteriophage (*a virus that infects bacteria*) transmits a piece of DNA from one bacterial cell into another. A bacteriophage holds on to the cell by its tail fibers and injects the DNA from its head all the way down into the cell. Types of bacteriophages are listed in Table 7.1.
- **Transposons:** Walking DNA strands that pass from one cell to another

Streptococci

- **Characteristics:** Arranged in *chains*, and have *no catalase enzyme*.
- **Hemolytic activity:**
 1. Beta-hemolytic: Complete hemolysis
 2. Alpha-hemolytic: Partial hemolysis
 3. Gamma-hemolytic: No hemolysis
- **Lancefield classification:** Streptococci are classified based on the (*C*) of the carbohydrate in the cell wall into types A to S.

Group A Beta-Hemolytic Streptococcus pyogenes Virulence Factors

- C of the carbohydrate component (CHO)
- *M protein:* Virulence factor, which stimulates antibody production
- Streptolysin O: *Oxygen labile* toxin, which mediates hemolysis. Streptococci carrying this toxin are inhibited by oxygen.
- Streptolysin S: *Oxygen stable* toxin, which mediates hemolysis. Streptococci carrying this toxin are not inhibited by oxygen. *Streptolysin S is not antigenic*.

TABLE 7.1 Types of bacteriophages.

	Virulent	Temperate (prophage)
Mechanism	When DNA converts to messenger RNA (mRNA), it ruptures the cell	It acts on lysogenization of bacteria Lysogenic immunity: a prophage blocks subsequent infection with a similar phage
Transduction Errors	Generalized Incorporation errors	Specialized Splicing errors

- Erythrogenic toxin: Mediates scarlet fever and toxic shock syndrome (TSS)
- Others: Streptokinase, DNAase, anti-C5a peptidase

Diseases Caused by *Streptococcus pyogenes*

- *Streptococcus* pharyngitis: *Clinical picture*: Sore throat, fever, cervical lymphadenopathy, exudates and pus on tonsils, and lack of cough. Treatment: Penicillin.
- *Streptococcus* skin infection: Folliculitis, cellulitis and impetigo, which can also be caused by staphylococci. Treatment: Penicillinase-resistant penicillin, e.g., dicloxacillin.
- Necrotizing fasciitis: It is a flesh-eating infection caused by *Streptococcus* entering through a break in the skin and causing *myositis*, *redness*, and *bullae*. Treatment: Penicillin G plus clindamycin (*used to block toxins*).
- Scarlet fever: *Scarlet rash* (sandpaper erythematous rash sparing the face), fever, *circumoral pallor*, and *strawberry tongue* accompanied by erythematous tonsils covered by pus and exudates. Treatment: Penicillin.
- Toxic shock syndrome: Also caused by *Staphylococcus*. *Clinical picture*: Vomiting and diarrhea followed by rash. Common with use of cervical contraception, e.g., sponges. Treatment: Penicillin G plus clindamycin.
- Rheumatic fever: Following *Streptococcus* pharyngitis. Discussed in Chapter 10, Pathophysiology.
- Post-*Streptococcus* glomerulonephritis: Following *Streptococcus* pharyngitis or skin infection. Discussed in pathophysiology.

Alpha-Hemolytic *Streptococcus* (*Streptococcus viridans*)

- *Streptococcus salivarius*: *Most common cause of sub-acute bacterial endocarditis*. Staphylococci are the most common cause of *acute bacterial endocarditis*.
- *Streptococcus intermedius*: Causes *abscesses*. If *Streptococcus* *intermedius* is isolated in the blood, next best step is *computed tomography (CT) with contrast of the abdomen and pelvis to locate any abscesses*.
- *Streptococcus mutans*: Causes *dental caries*.

Group D *Streptococcus* (Alpha-Hemolytic)

- Enterococci: Most common is *Enterococcus faecalis*, which is a cause of nosocomial infections. Treatment: *Pristinomycins*. It resists penicillin and vancomycin.
- Non-enterococci: Most common is *Streptococcus bovis*, a risk factor for *colon cancer*

Group B *Streptococcus* (*Streptococcus agalactiae*)

- It is a commensal flora of the vagina, and is the *most common cause of neonatal meningitis*, followed by *E. coli* and *Listeria monocytogenes*

Streptococcus pneumoniae

- Morphology: *Alpha-hemolytic lancet-shaped diplococci* with a *thick capsule*
- Diagnosis:
 1. Culture: *Streptococcus pneumoniae* is *Optochin sensitive*, i.e., cannot grow in the presence of Optochin. Note: *Streptococcus viridans* is Optochin resistant, and *Streptococcus pyogenes* is bacitracin sensitive.
 2. Positive Quellung reaction
- Prevention: Vaccine (*Pneumovax*) is formed of 23 *polysaccharide capsular antigens*.
- Clinical picture and treatment: It is the most common cause of:
 1. Community-acquired pneumonia: Treatment: macrolides (e.g., azithromycin) plus a third-generation cephalosporin
 2. Otitis media and mastoiditis in children: Treatment: amoxicillin
 3. Meningitis in the elderly: Treatment: penicillin

Staphylococci

- *Characteristics*: Arranged in *clusters*; release *catalase enzyme*
- *Staphylococcus aureus*: It releases the following:
 1. Coagulase: Works on *fibrin*
 2. Protein A: Binds *Fc portion of immunoglobulin*
 3. Penicillinase: Destroys *penicillin*
 4. Hemolysin: Against red blood cells (*RBCs*) and *neutrophils*
 5. Leukocidin: Against white blood cells (*WBCs*)
 6. Hyaluronidase: A *spreading factor*
 7. Exfoliatin: *Exotoxin* causing *scalded skin syndrome*
 8. Enterotoxin: *Heat stable exotoxin* causing *food poisoning*
 9. TSST-1: Exotoxin causing *toxic shock syndrome*, by binding to *class II major histocompatibility complex (MHC)*
- *S. aureus* is the most common cause of *postinfluenza pneumonia*. Pneumonia caused by *S. aureus* is characterized by *lung cavitation*, *hemoptysis*, *empyema*, and *pneumatoceles*.

- *S. aureus* is the most common cause of *septic arthritis* and *osteomyelitis*. *Salmonella* is a common cause of osteomyelitis in patients with sickle cell disease; however, *S. aureus* is still the most common cause.
- Food poisoning due to *S. aureus* is contracted through ingestion of dairy products, e.g., yoghurt, pudding. It starts 1–2 hours after ingestion and resolves quickly without complications.
- Methicillin-resistant *S. aureus* (MRSA) is treated with *vancomycin*. Recently, new strains exist that are resistant to vancomycin, such as vancomycin-Indeterminate *S. aureus* (VISA).
- *Staphylococcus epidermidis*: Normal skin flora that can contaminate *prosthetic devices*. So, when you see a patient on the USMLE with sepsis or endocarditis that developed shortly after insertion of any mechanical object into the body, e.g., valve or catheter, you know what to think!
- *Staphylococcus saprophyticus*: The *second most common cause of urinary tract infection (UTI)* in sexually active women after *E. coli*.

Bacillus anthracis

- *Spore-forming, gram-positive* bacillus. It is the only capsulated bacteria with a *protein capsule*.
- *Mechanism*: *Bacillus anthracis* exotoxin is formed of three parts:
 1. *Edema factor*: An extracellular adenylate cyclase
 2. *Lethal factor*: Can cause pulmonary edema
 3. *Protective antigen*: Facilitates invasion of edema factor into the cells
- *Clinical picture*: *Anthrax*, which has different forms:
 1. *Respiratory*: Exotoxins released in the lungs, causing pneumonia known as *wool sorter's disease*
 2. *Cutaneous*: Black round lesion, also called a *malignant pustule*
 3. *Gastrointestinal (GI) tract*: Intestinal necrosis
- *Prevention*: Vaccine, made from the *protective antigen* portion of the exotoxin
- *Treatment*: Penicillin

Bacillus cereus

- *Spore-forming, gram-positive* bacillus
- *Mechanism*: Heat stable or labile toxin in *undercooked rice*
- *Clinical picture*: *Diarrhea, mostly after ingestion of undercooked rice*
- *Treatment*: Self-resolving without treatment

Clostridium tetani

- *Spore-forming, gram-positive anaerobic* bacillus with *terminal spores* (*C. tetani* has *terminal spores*)
- *Mechanism*: *Tetanospasmin* toxin causes tetany by inhibiting the release of gamma-aminobutyric acid (GABA) from cerebellum, and glycine from Renshaw cells of spinal cord.
- *Clinical picture*: Muscle spasms, lockjaw, and risus sardonicus. The latter is a fixed smile due to muscle spasm, and is a sign of advanced disease.
- *Prevention*: Vaccination, and tetanus toxoid is given every 10 years.
- *After exposure*: Example: patient injured his foot by stepping on a rusty nail:
 1. If last toxoid dose was within the last 5 years, no toxoid is needed.
 2. If last toxoid dose was more than 5 years ago, give a new dose of toxoid.
 3. If patient has never been immunized, give tetanus toxoid and immunoglobulin.
- *Treatment of tetanus*:
 1. Airway protection, and clean wound
 2. Medications: Vaccine, immunoglobulin, and muscle relaxants

Clostridium botulinum

- *Spore-forming, gram-positive anaerobic* bacillus
- *Mechanism*: The toxin prevents acetylcholine release at the level of the *neuromuscular junction*.
- *Source*: Canned foods and *honey*. A typical case on the USMLE is for an infant whose parents put honey in his milk bottle.
- *Clinical picture*: Botulism:
 1. Flaccid paralysis: *Descending march from head to toe* (“floppy baby”)
 2. Five D’s: Dilated pupils, diplopia, dysphagia, dysarthria, and diminished gag reflex
- *Diagnosis*: Detection of toxins in *stools* (*Best specimen*) or serum
- *Treatment*:
 1. First step is to *secure an airway* by intubating the patient
 2. Botulinum antitoxin: Even before confirming the diagnosis

Clostridium difficile

- *Spore-forming, gram-positive anaerobic* bacillus
- *Mechanism*: Exotoxins. Toxin A causes diarrhea. Toxin B is cytotoxic.

- *Clinical picture: Pseudo-membranous colitis.* Usually follows the use of broad-spectrum antibiotics, e.g., ampicillin, clindamycin. Patient presents with severe watery malodorous diarrhea and abdominal pain.
- *Diagnosis:* Detecting *C. difficile* toxins in the stools
- *Treatment:* Oral metronidazole or vancomycin. They have to be given orally as they act *locally* inside the intestine.

Clostridium perfringens

- *Spore-forming, gram-positive anaerobic bacillus*
- *Clinical picture: Gas gangrene;* presents as severe cellulites and myonecrosis
- *On exam:*
 1. *Crepitus* on palpation of the lesions, indicating the presence of gas
 2. *Black fluid* oozing from the lesion upon pressure
- *Treatment: Hyperbaric O₂* and antibiotics, e.g., penicillin G plus clindamycin

Corynebacterium diphtheria

- Non-spore-forming, gram-positive bacillus, with a unique *Chinese letter appearance*
- *Mechanism:* Colonizes in *pharynx*, and releases *exotoxins* targeting the cardiovascular system (CVS) and the central nervous system (CNS).
- *Clinical picture:* Fever, chills, sore throat, and barking cough; often confused with croup
- *On exam: Grayish pseudomembrane* on pharynx. Histologically, it is formed of *C. diphtheria*, necrotic tissue, WBCs, and fibrin.
- *Diagnosis:* Culture on *Loeffler* or *Tellurite* media
- *Complications:* Respiratory failure, myocarditis, bulbar palsy, or even lower motor neuron lesion (LMNL) (combined motor and sensory loss)
- *Treatment:* Helpful to remember: “Treat diphtheria with *DAD*”:
 1. Diphtheria antitoxin
 2. Antibiotics: Penicillin (PCN) is the drug of choice. If PCN allergy exists, erythromycin is a good alternative.
 3. DPT (diphtheria, pertussis, tetanus) vaccination: As there is no postinfectious immunity
- *Notes:*
 1. Diphtheria toxins can only be produced in patients with *iron deficiency*.
 2. Exotoxin of diphtheria works through its A portion by inhibiting *elongation factor 2 (EF2)* and

protein synthesis. This is achieved by adenosine diphosphate (*ADP*) *ribosylation*.

Listeria monocytogenes

- *Non-spore-forming, gram-positive bacillus, with unique features:*
 1. It is a *facultative intracellular* organism.
 2. It is the only gram-positive organism capable of releasing *endotoxins*.
 3. *End-over-end motility* (“tumbling”)
- *Clinical picture:* Meningitis and sepsis. It is the third most common cause of meningitis in neonates (after *Streptococcus agalactiae* and *E. coli*). It also causes meningitis in immunocompromised patients (also see Chapter 3, Neuroanatomy).
- *Treatment: Ampicillin + sulbactam* or sulfamethoxazole/trimethoprim (SMX/TMP)

***Neisseria meningitidis* (Meningococci)**

- *Kidney-shaped, gram-negative diplococci;* 5% of the population are carriers for this bacterium; occurs in the *nasopharynx*
- *Virulence factors:*
 1. Endotoxin: Can cause adrenal hemorrhage and petechiae
 2. Capsule, immunoglobulin A (IgA) protease, the ability to extract iron from human blood
- *Risk groups: Army recruits* and children younger than 2 years of age
- *Clinical picture:*
 1. Meningitis: Discussed in Chapter 3, Neuroanatomy
 2. Disseminated meningococemia: Fever, rash, arthritis, and petechial rash
 3. Fulminant meningococemia (*Waterhouse-Friderichsen syndrome*): Bilateral adrenal hemorrhage, and purpura fulminans. So when you see a patient on the USMLE with meningitis, hypotension, hypoglycemia, and purpura, you know what to think!
- *Diagnosis:*
 1. Culture: Grows on Thayer Martin medium
 2. Meningococci can ferment maltose and glucose into acid (*Note: Gonococci can ferment glucose only, but not maltose*).
- *Treatment:* Third-generation cephalosporin
- *Prophylaxis for contacts:* Rifampicin.

- *Note*: Adrenal hemorrhage gives *shell-like calcifications* pattern on x-ray
- *Meningitis*: The second most common cause of neonatal meningitis.

Neisseria gonorrhoea (Gonococci)

- *Kidney-shaped, gram-negative diplococci*
- *Virulence factors (2 P's)*: Pili and Protein II
- *Clinical picture*:
 1. *Greenish penile or vaginal discharge*
 2. Newborns: *Ophthalmia neonatorum*. That's why all newborns receive prophylactic erythromycin eyedrops after birth.
- *Complications*:
 1. Disseminated gonococemia: *Pustular rash*, arthritis, *tenosynovitis*, and fever
 2. Urethritis, prostatitis, epididymitis, pelvic inflammatory disease, and even ectopic pregnancy (*due to adhesions*)
 3. *Fitz-Hugh–Curtis syndrome*: Perihepatitis, which is also caused by *Chlamydia*. Patient presents with right upper quadrant (RUQ) abdominal pain and elevated transaminases.
- *Treatment*: Drug of choice is *third-generation cephalosporins*. If patient is allergic to cephalosporin, the drug of choice is *ciprofloxacin*.
- *Note*: *Neisseria (Branhamella) catarrhalis* is a respiratory tract flora that *resists penicillin*.

Escherichia coli

- *Gram-negative bacillus*
- *Mechanism*: Acts by means of pili, endo-, and exotoxins. Also has flagellar (H) antigen, capsular (K) antigen, and O antigen (LPS).
- *Diarrhea*:
 1. Traveler's diarrhea ("Montezuma's revenge"), a severe diarrhea causing dehydration. Treatment: Ciprofloxacin or SMX/TMP. Prophylaxis: Norfloxacin.
 2. *Enterotoxigenic E. coli*: It causes watery diarrhea
 3. *Enterohemorrhagic E. coli (E. coli 0157-H7)*: Bloody diarrhea due to hemorrhagic colitis, caused by *Shiga-like toxin*, also called *verotoxin*. Complication: Hemolytic uremic syndrome (HUS) (see Chapter 10, Pathophysiology).
 4. *Enteroinvasive E. coli*: Bloody diarrhea high in WBC content
- *UTI*: *E. coli* is the most common cause of UTI in sexually active women. Treatment: Ciprofloxacin or SMX/TMP

Klebsiella pneumoniae

- *Gram-negative bacillus*
- *Mechanism*: It has *no Flagella*, hence no flagellar (H) antigen.
- *Clinical picture*:
 1. Apical (*Friedlander*) pneumonia: *Red current jelly sputum*
 2. Sepsis and UTI
- *Treatment*: *Third-generation cephalosporin*

Salmonella

- A motile *H₂S-releasing* bacterium, with *Vi antigen*
- *Source*: Food or water contaminated with animal feces. A famous source is *undercooked eggs*. *Salmonella typhi* is carried only by humans in the gallbladder; it is not carried by animals.
- *S. typhi*: A facultative intracellular organism, causing *typhoid (enteric) fever*, where patient presents with *step-ladder fever*, *rosy spots on the abdomen*, and right lower quadrant (RLQ) abdominal pain often confused with appendicitis. Treatment: *ciprofloxacin* or *ceftriaxone*.
- *S. cholerae-suis*: Causes bacteremia, which targets lungs, liver, or even the brain
- *S. enteritidis*: Causes mucous or watery diarrhea. Treatment: Self-resolving. *Antibiotics will prolong bacterial shedding*.

Pseudomonas aeruginosa

- *Gram-negative bacillus*, which produces green pigment (*fluorescin*) and blue pigment (*pyocyanin*) and *exotoxin A*
- *Mechanism*: Exotoxin A functions just like diphtheria's toxin (*inhibits EF2*)
- *Clinical picture*:
 1. Pneumonia: Mainly in immunocompromised and *cystic fibrosis patients*
 2. Endocarditis: Mainly in *IV drug abusers*, targeting the *tricuspid valve*. However, *S. aureus* is still the most common cause of acute bacterial endocarditis in IV drug abusers.
 3. Skin ulcers and osteomyelitis: Mainly in *diabetics* and *IV drug abusers*
 4. Corneal infections: Mainly in patients using *contact lenses*

- 5. Malignant otitis externa, *swimmer's ear*, and *hot-tub folliculitis*
- *Treatment: Anti-Pseudomonas penicillin*, e.g., carbenicillin, ticarcillin, or piperacillin.

Vibrio cholera

- Gram-negative, *short, curved, fast-darting bacilli*
- *Mechanism: Cholera toxin (cholera toxin) acts by ribosylation of adenyl cyclase via activating Gs protein.*
- *Clinical picture: Rice water diarrhea*
- *Treatment:*
 1. Supportive for dehydration and electrolyte imbalance
 2. Doxycycline: *It only shortens the duration of illness.*
- *Notes:*
 1. *Vibrio parahaemolyticus*: Fever, abdominal colic, and watery diarrhea in a *healthy person*, 12–48 hours after ingestion of a *seafood meal*. *Treatment: Supportive.*
 2. *Vibrio vulnificus*: Fever, abdominal colic, watery diarrhea and *vesiculobullous skin eruption* in a patient with *chronic liver disease*, 12–48 hours after ingestion of a *seafood meal*. *Treatment: Doxycycline or tetracycline.*

Miscellaneous Enterics

- *Proteus mirabilis*: Three strains exist, with cross-reacting antigens, namely *OX-2*, *OX-19*, and *OX-K*. This bacterium can split urea to produce *ammonia*, which leads to *UTI with alkaline urine*. Association: *Magnesium-ammonium-phosphate (MAP) (struvite) nephrolithiasis*.
- *Helicobacter pylori*: A *urea-splitting, gram-negative bacillus*. A common cause of *duodenal ulcers*. Diagnosis: Clo test (A medium changes its color when urease from *H. Pylori* converts urea to ammonia), urease breath test, and checking for stool antigens. *Treatment:*
 1. *Amoxicillin + clarithromycin + proton pump inhibitor* for 2 weeks
 2. If allergic to penicillin: *Metronidazole + tetracycline + bismuth* for 2 weeks
- *Enterobacter*: It is a normal GI tract flora.
- *Serratia*: An enteric that produces *bright red pigment*.
- *Shigella*: A pathogen transmitted by contaminated hands and water. Releases *verotoxin*, which causes *bloody diarrhea; rich in WBC count*.
- *Campylobacter jejuni*: It causes *bloody loose diarrhea*. *Treatment: Erythromycin*. Association: *Guilain-Barré syndrome*.

- *Yersinia enterocolitica*: Causes *appendicitis-like pain*, mucosal ulceration, and diarrhea. Mechanism: Release of enterotoxins and direct intestinal cells invasion.
- *Bacteroides fragilis*: An intestinal flora that causes *abscesses*
- *Bacteroides melaninogenicus*: Releases a black pigment, and is famous for causing necrotizing pneumonia and periodontal diseases

Haemophilus influenzae

- *Polymorphic gram-negative bacillus*
- *Requirements: nicotinamide adenine dinucleotide (NAD) and heme of blood (factors V and X)*
- *Classification: It is classified according to the type of capsule from A to F.*
- *Clinical picture: H. influenzae B (HiB) is the most pathogenic type and it causes the following:*
 1. *Meningitis*: Common in children between 6 months and 3 years of age. Antibiotics cause lysis of bacteria and release of antigens, inducing an immune reaction. This could be prevented by giving steroids 15 minutes prior to starting the antibiotics.
 2. *Epiglottitis*: Fever, hyperextended neck (*dog-sniffing position*), copious drooling of saliva and stridor. Do not attempt to examine pharynx (might cause *laryngeal spasm*). Diagnosis: Neck x-ray shows swollen epiglottis, also called *thumbs-up sign*. Examine airway in the *operation room* using a direct laryngoscope, to visualize the swollen cherry red epiglottis.
 3. *Septic arthritis*: Mostly in children and usually affects a single joint
- *Prevention: HiB capsule vaccine (2, 4, 6, and 12 months) given in combination with DPT. The mechanism depends on stimulation of the T cells by the diphtheria toxin against the HiB capsule.*
- *Treatment: Third-generation cephalosporins (cefotaxime or ceftriaxone). HiB is resistant to penicillin.*

Haemophilus ducreyi

- Gram-negative bacillus
- *Clinical picture: A painful ulcer known as chancroid, which differs from chancre by being painful, and associated with painful lymphadenopathy*
- *Treatment: Erythromycin or SMX/TMP*

Haemophilus (Gardnerella) vaginalis

- Also called *bacterial vaginosis (BV)*; a gram-negative bacillus
- *Clinical picture*: Vulvar itching and vaginal whitish discharge with a *fishy odor*
- *Diagnosis*:
 1. *Whiff test*: Adding KOH increases intensity of fishy odor
 2. *Clue cells*, which are squamous cells with smudged borders.
 3. *Vaginal pH* >4.5
- *Treatment*: Metronidazole

Legionella pneumophila

- Gram-negative bacillus
- *Source*: Shower heads and air conditioners
- *Clinical picture*:
 1. Pontiac fever: Fever and headache that resolve in a week
 2. Legionnaire pneumonia: *Atypical pneumonia*, where the x-ray looks much worse than how the patient presents; usually associated with diarrhea and altered mental status
- *Diagnosis*:
 1. Direct immunofluorescent testing (*DIF*): Test of choice
 2. Culture: Grows on charcoal agar, rich in iron and cysteine
 3. Legionella antigens in the urine
- *Treatment*: Erythromycin

Bordetella pertussis

- Gram-negative bacillus
- *Virulence factors*:
 1. Bordetella toxin: Activates cyclic adenosine monophosphate (*cAMP*) through ADP ribosylation, by inhibiting Gi protein. This stimulates the release of histamine and insulin, and inhibits phagocytosis.
 2. Adenyl cyclase granules, tracheal cytotoxin, and filamentous hemagglutinin
- *Clinical picture*:
 1. *Catarrhal phase* (1–2 weeks): Fever, cough, and expectoration
 2. *Paroxysmal phase* (4–8 weeks): Paroxysms of cough followed by inspiratory whoop. The pathognomonic feature is vomiting immediately following these paroxysms.

3. *Convalescent phase* (months): Mild cough that resolves gradually

- *Complication*:
 1. Bronchopneumonia: It is the most common complication.
 2. Bronchiectasis: It is the second most common; however, it is very specific.
- *Diagnosis*: Unique presentation, plus:
 1. Leukocytosis: Namely *atypical lymphocytosis*
 2. Sputum culture: Bordetella pertussis grows on Bordet Gengou agar
 3. Normal erythrocyte sedimentation rate (ESR)
- *Treatment*: Erythromycin for 14 days
- *Notes*:
 1. There is *no transplacental immunity* against pertussis. Immunity against pertussis is only cell mediated, while the transplacental immunity is humoral.
 2. There is *no postinfectious immunity* against pertussis.
 3. *B. pertussis* and *C. diphtheria* are both extracellular organisms releasing exotoxins.

Facultative Intracellular Organisms

- *Yersinia pestis (plague)*
 1. Virulence factors: *FI* (antiphagocytic), V and W antigens
 2. Transmitted from rats via flea bites
 3. *Clinical picture*:
 - Bubonic plague: Inguinal lymphadenopathy and subcutaneous bleeding
 - Pneumonic plague: Pneumonia
 - Septicemic plague: Septicemia
 4. Prevention: Isolation of rats, and DDT for fleas
 5. Note: *Y. pestis's ends stain darker than its center.*
- *Francisella tularensis (tularemia)*
 1. Transmitted by rabbits and ticks
 2. *Clinical picture*: Black ulcerating nodule in the skin with enlarged lymph nodes (L.N), plus fever and chills of sudden onset
- *Brucellosis*: Undulant fever (peaks up only at night) and noncaseating granulomas in the liver, due to ingestion or contact with infected meat or milk products
- *Treatment of facultative intracellular organisms*: Aminoglycosides or doxycycline

Chlamydia

- Gram-negative, intracellular organism with ATP/ADP translocator
- Chlamydia cycle:
 1. Elementary body (infectious stage) is endocytosed inside the infected cell to be converted into an initial reticulate body.
 2. Reticulate body then divides into multiple reticulate bodies.
 3. The reticulate bodies undergo a process of conversion into multiple elementary bodies.
 4. Elementary bodies leave the cell to infect other cells.
- Types and clinical picture:
 1. A, B, C: Trachoma: Scarring and traction of eyelid inwards, which leads to irritation of the conjunctiva by the rubbing lashes, and eventually chronic conjunctivitis.
 2. L1, L2, L3: Lymphogranuloma venereum: Genital ulcers, lymphadenitis, lymphangitis, and proctocolitis
 3. D-K:
 - Urethritis: Chlamydia is the most common sexually transmitted disease.
 - Inclusion conjunctivitis: In newborns 3–4 days after birth. Prophylactic erythromycin eyedrops just after birth is now a standard of care.
 - Reiter syndrome: Conjunctivitis, urethritis, and circinate ulcer on glans penis, and big joint migrating arthritis. Associations: Plantar fasciitis, Achilles tendonitis, aortic regurgitation, and lung fibrosis.
 - Fitz-Hugh–Curtis syndrome
 - Infant and atypical pneumonia
- Treatment: Drug of choice is azithromycin
- Notes:
 1. Chlamydia pneumoniae is cultured on HeLa cells of sputum.
 2. Chlamydia Taiwan acute respiratory agent (TWAR) pneumoniae causes mild pneumonia plus cardiac diseases.
 3. Chlamydia psittaci is transmitted from birds, and causes atypical pneumonia as a part of systemic disease, also called psittacosis.

Rickettsia

- Gram-negative, intracellular organism with ATP/ADP translocator

- Characteristics: Same antigens as Proteus mirabilis (OX-2, OX-19, OX-K), which can be distinguished and diagnosed by Weil-Felix test.
- Clinical picture:
 1. Rocky Mountain spotted fever: Caused by Rickettsia rickettsii, transmitted by ticks (Dermacentor) Clinical picture: Fever, and petechial rash that starts in the palms and soles and creeps toward the trunk
 2. Epidemic typhus: Caused by Rickettsia prowazekii, transmitted by ticks. Clinical picture: Fever, and rash that involves the whole body except palms and soles
 3. Endemic typhus: Caused by Rickettsia typhi, transmitted by rats. Clinical picture: Fever, and rash that starts on the fifth day of fever.
 4. Q fever: Caused by Coxiella burnetii, transmitted through contact with animals and animal products. Clinical picture: Fever and pneumonia, due to inhalation of endospores. It is the only rickettsia that does not cause rash.
 5. Bartonella henselae: Causes cat-scratch disease. Clinical picture: Cat scratch, followed by fever, rash, and swollen tender pustular lymphadenopathy. Complication: Bacillary angiomatosis, which is proliferation of blood vessels, common in AIDS patients.
 6. Ehrlichia canis: From dog licks, causing fever and rash. Peripheral smear shows numerous morulae inside the monocytes.
- Diagnosis: Complement fixation test (CFT)
- Treatment: Doxycycline plus chloramphenicol.

Treponema pallidum

- A gram-negative organism, also called spirochete
- Incubation period: 6 weeks
- Clinical picture: Syphilis. Congenital syphilis transmits to fetus after the 4th month of gestation.
- At birth:
 1. Atrophied dried nasal mucosa (snuffles)
 2. Hepatosplenomegaly
 3. Maculopapular rash and severe periostitis
- Childhood form: Characterized by multiple pathognomonic findings:
 1. Ear, nose, and throat (ENT): Saddle nose (destroyed nasal bridge), Hutchinson teeth (separated and notched upper central incisors), Mulberry molars (molars with too many cusps), and rhagades.

2. Bone: *Sabre shins* (inflamed bowed tibiae), *Clutton joints* (painless effusion), and destruction of medial proximal tibial metaphysis (*Wimberger sign*)

Adulthood Syphilis

- **Primary (6 weeks):** Characterized by *painless chancre* and *painless lymphadenopathy*. Chancre is a *well-demarcated ulcer with indurated base*, and it resolves spontaneously *without scar formation*.
- **Secondary:**
 1. Rash: All forms *except vesicular*, i.e., macular, papular, pustular, mixed, but *never vesicular*. Rash is more prominent *in palms and soles*.
 2. Condyloma lata: Wart-like lesions on moist surfaces. *They are highly contagious lesions*.
- **Latent:** 25% of patients have relapse during that period
- **Tertiary:**
 1. **Gummas:** They occur in skin (painless) or bones (painful).
 2. **CVS:** Injury to Vasa vasora, of aorta, leading to *aortic aneurysm* and *aortic dissection*. Also causes coronary obstruction and aortic regurgitation.
 3. **Neurosyphilis:**
 - Multiple forms ranging from asymptomatic, to meningitis or even infarction
 - *Tabes dorsalis:* As explained in Chapter 3, Neuroanatomy, it targets the *dorsal column* (causing ataxia), and *dorsal roots* (causing loss of reflexes, pain, and temperature sensation)
 - **General paresis of insane:** Aphasia, confusion, and seizures
 - *Argyll-Robertson pupil:* Pupil that *accommodates but never reacts to light*
- **Diagnosis:**
 1. Darkfield microscopy: *Corkscrew movement*
 2. Serology: Venereal Disease Research Laboratory (VDRL) test, rapid plasma reagent (RPR), *Treponema pallidum immobilization (TPI) test*, or *the most specific test, which is the florescent treponemal antibody test (FTA)*
- **Treatment:** *Penicillin* is the drug of choice for all patients, as follows:
 1. Congenital syphilis: Benzathine penicillin G for 10 days

2. Primary, secondary, and early latent syphilis: Benzathine penicillin G 2.4 million units, *only once*
3. Late latent syphilis: Benzathine penicillin G 2.4 million units *weekly for 3 weeks*
4. Neurosyphilis: Procaine penicillin G 2.4 million units daily + probenecid for *14 days*

- **Notes:**

1. Patients with penicillin allergy must undergo penicillin desensitization.
2. *Jarisch-Herxheimer's reaction:* A few days after starting treatment, patients develop sudden spike in temperature and worsening symptoms. This occurs *due to release of pyrogenes from killed bacteria*. Treatment: Supportive, and continue treatment.
3. *Indication of cure from syphilis:* Fourfold decrease in titers
4. *Treponema endemicum:* Causes endemic syphilis, contracted from shared utensils
5. *Treponema pertenue:* Causes *yaws*, which is *disfiguring facial ulcers*
6. *Treponema carateum:* Causes *pinta*, which is *colored skin lesions*

Borrelia burgdorferi

- A gram-negative organism, also called a spirochete, causing *Lyme disease*
- **Transmission:** *Ixodes tick*
- **Clinical picture:**
 1. Stage 1: *Erythema chronicum migrans* (ECM). It is a ring-shaped lesion with central clearing (Fig. 7.1).
 2. Stage 2:
 - Arthralgias and arthritis
 - CVS injury, e.g., myocarditis, AV block
 - CNS injury, e.g., meningitis, *bilateral Bell's palsy*
 3. Stage 3: Chronic arthritis and encephalopathy
- **Prevention:** Vaccination, e.g., *Lymerix* or *Immu-lyme*, before going to infested areas, i.e., *northeast, midwest, and West Coast*
- **Diagnosis:** *Clinical*, as antibodies against *Borrelia burgdorferi* cross-react with other organisms
- **Treatment:**
 1. Less than 8 years of age: *Oral amoxicillin for 21 days*
 2. 8 years of age or older: *Oral doxycycline for 21 days*



FIG. 7.1 Erythema chronicum migrans of Lyme disease

- 3. If CNS or CVS injury: *Parenteral ceftriaxone or penicillin G for 21 days*
- *Note:* Do not confuse this with *Borrelia recurrentis*, another spirochete transmitted by ticks and body lice. *Clinical picture:* Relapsing fever. *Diagnosis:* Darkfield microscopy after staining with Wright or Giemsa stain. *Treatment:* Erythromycin or tetracycline.

Leptospira interrogans

- A gram-negative organism, also called a spirochete, causing *leptospirosis*
- *Transmission:* Swimming in water contaminated with urine of infected animals
- *Clinical picture:*
 1. *Early stage:* Fever, headache, conjunctivitis, and photophobia

2. *Late stage:* Meningitis, muscle aches, and rash
- *Complication: Weil disease:* Vasculitis, jaundice, renal failure, and rash
 - *Treatment: Penicillin*

Mycobacterium leprae

- An *acid-fast* bacterium, stains *red*, lives in *cold temperature*, and causes leprosy (Hansen's disease)
- *Reservoir: Armadillo*
- *Clinical picture:* Table 7.2 lists types and presentation
- *Diagnosis:* Biopsy of *skin or nerve* lesions shows *acid-fast bacilli*. *This bacterium cannot be cultured on artificial media.*
- *Treatment: Rifampicin, dapsone, and clofazimine.* *Note that clofazimine can cause erythema nodosum leprosum, which is treated with thalidomide.*
- *Note:* Leprosy can cause *chronic pneumonitis*.

TABLE 7.2 Types and clinical picture of leprosy.

	Lepromatous leprosy	Tuberculoid leprosy
Skin and mucous membranes	<ul style="list-style-type: none"> • Leonine faces: thick skin, saddle nose, no eyebrows • Nasal mucous membrane involvement, e.g., rhinitis 	<ul style="list-style-type: none"> • Hypopigmented painless skin lesions, with loss of sensations • No mucous membrane involvement
Eyes	Keratitis and iridocyclitis	Unaffected
Testes	Atrophy	Unaffected
Peripheral nerves	Late and bilateral	Early and unilateral
Lepromin test	Negative (cell-mediated immunity is destroyed)	Positive (cell-mediated immunity is intact)
Prognosis	Bad (contagious)	Good (not contagious)

- *Notes on other acid-fast bacteria:*
 1. *Mycobacterium tuberculosis*: Causes tuberculosis
 2. *Mycobacterium avium* complex (MAC): Causes severe systemic illness in AIDS patients (see below)
 3. *Mycobacterium scrofulaceum*: Causes cervical lymphadenopathy in children
 4. All acid-fast bacteria have *cord factor*, which inhibits WBC migration.

Mycoplasma

- The only bacteria *without a cell wall*. It is a very small bacterium, and is covered by a cytoplasmic membrane *rich in sterols*
- Mycoplasma grows on *Eaton agar*.
- *Types and clinical picture:*
 1. *Mycoplasma pneumoniae*
 - Clinical picture: *Atypical pneumonia* (chest x-ray [CXR] looks much worse than the patient's presentation, along with diarrhea and altered mental status)
 - CXR shows streaky infiltrate.
 - Diagnosis: High serum *IgM* levels against *Mycoplasma*
 - Treatment: *Erythromycin* (penicillin-resistant because of absent cell wall)
 2. *Ureaplasma urealyticum* (*T. mycoplasma*)
 - Mechanism: Lyses urea into ammonia and CO₂ (remember *Proteus*?)
 - Clinical picture: *UTI with alkaline urine*, and magnesium ammonium phosphate (*struvite*) *nephrolithiasis*.
 - Treatment: *Erythromycin*
- *Note: Autoimmune hemolytic anemia is common with mycoplasma infections.*

Pasteurella multocida

- *Source:* Cat and dog bites
- *Management:* Clean the wound (*do not stitch it tight*) + antibiotics, e.g., penicillin

Viruses

- Similarly to bacteria, all viruses are *haploid*. The only exception is *retroviruses*.
- The genetic material of viruses is either DNA or RNA (*never both*).
 1. All DNA viruses are double stranded (ds-DNA), except *parvovirus*.

2. All RNA viruses are single stranded (ss-RNA), except *reoviruses*, e.g., rotavirus.

- Viruses with *positive-strand RNA* may form proteins.
- Viruses with a negative-strand RNA must convert it first into a positive strand using *RNA polymerase*, then protein synthesis may occur.
- Viruses with DNA undergo *transcription* to positive strand RNA, then protein synthesis.

Orthomyxovirus

- Single-stranded (ss) *negative RNA* virus with an *envelope*
- *Characteristics:* Two proteins: neuraminidase (NA) and hemagglutinin (HA). They both get attached to cells by means of the M protein to carry on the following missions:
 1. *NA destroys the host cell's mucin.*
 2. *HA attacks the sialic acid of RBCs.*
- *Influenza:* Orthomyxovirus with three serotypes (A, B, C). Influenza A infects humans, causing the flu (fever, rhinitis, tracheobronchitis).
- *Antigenic drift:* During replication, *minor changes* in the antigenic structure of NA and HA of influenza virus takes place. This allows the virus to escape a sensitized host's immune system.
- *Antigenic shift:* Major viral genome rearrangement, leading to a *major change* in NA and HA, causing worldwide pandemics. Common with *influenza A*.
- *Treatment:*
 1. *Amantadine* (mechanism: inhibits uncoating of influenza A)
 2. *Zanamivir:* *Inhibits neuraminidase; used for both influenza A and B*
- *Note:* Influenza virus is cultured on *monkey kidney cells agar*.

Paramyxovirus

- *Single-stranded negative RNA* virus, *without an envelope*
- *Characteristics:* *Fusion proteins*, allowing infected cells to fuse forming giant cells
- *Parainfluenza*
 1. *Clinical picture:* Croup (laryngotracheobronchitis) in children, manifested by hoarseness of voice, retrosternal soreness, a *pathognomonic barking cough*, fever, and stridor
 2. *Diagnosis:* X-ray of the neck; showing subglottic narrowing (*steeple sign*), (Fig. 7.2)
 3. *Treatment:* *Racemic epinephrine inhalation*

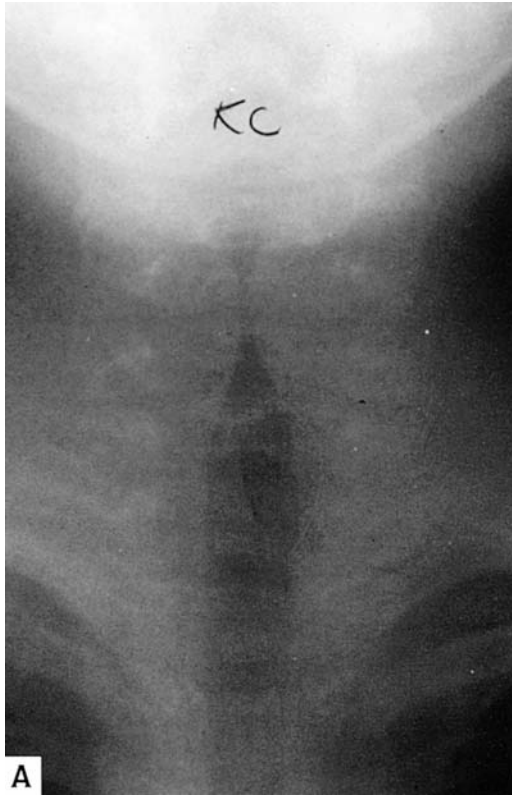


FIG. 7.2 Steeple sign. Note the subglottic narrowing

- *Respiratory syncytial virus (RSV)*
 1. *Clinical picture*: Bronchiolitis in children (4–18 months of age), who present with cough, expectoration, lung wheezes, and crackles
 2. *CXR*: Hyperinflated chest
 3. *Treatment*: Ribavirin
 - *Measles*
 1. *Clinical picture*: Starts with cough, coryza, conjunctivitis (CCC), and *Koplik spots* (red lesions with white/blue center on buccal mucosa), followed by a rash
 2. *Rash*: *Maculopapular* and *confluent*, starts *behind the ears* and descend downwards. It heals with branny desquamation also from the top downward.
 3. *Complications*:
 - *Most common*: *Pneumonia*. Early due to measles, or late due to secondary bacterial infection
 - *Most specific*: Subacute sclerosing panencephalitis (*SSPE*)
 4. Note: Measles is a predisposing factor for *vitamin A deficiency*
 - *Mumps*
 1. *Clinical picture*: Swollen salivary glands, mainly the *parotids*
 2. *Complications*:
 - *Most common*: *Pancreatitis*
 - *Most dangerous*: *Endocardial fibroelastosis*
 - *Orchitis*: Might cause testicular atrophy
 - *Sensorineural* hearing loss
- ### Human Immunodeficiency Virus (HIV)
- *Enveloped ds-RNA* virus with multiple functional enzymes including reverse transcriptase, protease, and integrase
 - The outer shell is formed of capsid protein, gp41 and gp120 capsid proteins, and p24 (*early marker*)
 - Reverse transcriptase (*RNA-dependent DNA polymerase*) converts the virus's RNA to DNA
 - *HIV genome*: It has long terminal repeat sequences (*LTRs*) which include:
 1. Sticky ends: Recognized by integrase
 2. Promotor/enhancer region: DNA transcription
 3. gag (group antigens): Code for viral antigenic proteins
 4. pol (protease, integrase, and reverse transcriptase): *Protease is the agent that makes HIV contagious.*
 5. tat (transactivator): Activates transcription
 6. env (envelope proteins)
 - *Transmission*: Infection is mainly through blood or sexual intercourse; *more in females and those who engage in anal intercourse*
 - *Pathology*: HIV targets the following cells:
 1. T lymphocytes: Mainly *CD4*. *If CD4 count drops below 200, the patient requires treatment, even if he does not have any obvious infection.*
 2. B lymphocytes: This can trigger other immunologic disease.
 3. Monocytes and macrophages: They act as *reservoir* for the virus. They can also transport it to the CNS, causing aseptic meningitis and neuropathy.
 - *Clinical picture*
 1. Initial viremia followed by a latent period of 5–10 years
 2. AIDS-related complex (ARC): Weight loss, fever, and night sweats
 - *Diagnosis*:
 1. Positive enzyme-linked immunosorbent assay (ELISA) test is the first step.
 2. If positive, confirm diagnosis by doing *Western blot* test.

- *Follow-up:* Best done through the viral RNA load, and CD4 count. They are used for prognostic purposes, early detection of progression of HIV to AIDS, and to assess response to treatment.
- *Complications:*
 1. Kaposi sarcoma (**PURPLE skin nodules**): By human herpes virus-8 (HHV-8). Kaposi sarcoma occurs due to vascular proliferation and hemosiderin deposition.
 2. Oral hairy leukoplakia: By Epstein-Barr virus (EBV). Can be seen on the lateral borders of the tongue.
 3. Chorioretinitis: By cytomegalovirus (CMV)
 4. Esophagitis: By *Candida albicans*
 5. Diarrhea: By *Cryptosporidium parvum*. Treatment: *Azithromycin*.
 6. Meningitis: By *Cryptococcus neoformans*
 7. Seizures: By *Toxoplasma gondii*. They have diffuse intracranial calcifications, and contrast enhancing mass. Treatment: *Sulfadiazine + pyrimethamine*. Drug of choice to treat toxoplasmosis during pregnancy is *spiramycin*.
 8. Leukemia: *Human T-cell leukemia virus 1 (HTLV-1)* causes hairy cell leukemia, while *HTLV-2* causes T-cell leukemia.
 9. Pneumonia:
 - *Pneumocystis jiroveci* (formerly *P. carinii*, which caused *P. carinii pneumonia [PCP]*). Suspect when CD4 count is less than 200.

Diagnosis: Bronchoalveolar lavage or lung biopsy. *Culture:* Does not grow in vitro, but stains with methenamine silver. *Treatment:* SMX/TMP and/or pentamidine.

- *Mycobacterium-avium Complex (MAC):* An acid-fast bacillus. Suspect when CD4 count is less than 100. *Clinical picture:* Pneumonia. *Diagnosis:* Lung biopsy. *Treatment:* Clarithromycin, ethambutol, and rifabutin.

- *Treatment of HIV:* Discussed in Chapter 9, Pharmacology.

- *Notes:*

1. Prophylaxis against HIV after a contaminated needle stick injury is a 1-month course of LIZ (*Lamivudine, Indinavir, Zidovudine*). The main factor deciding the probability of transmission is the depth of the injury.
2. Risk of maternofetal transmission of HIV is significantly reduced by treating the mother during pregnancy with *zidovudine*.

Hepatitis Viruses

- These viruses cause inflammation of the hepatic tissue.
- *Causes:* Hepatitis viruses A, B, C, D, E, F, G, CMV, EBV, alcohol
- Table 7.3 lists hepatitis A, B, and C viruses. Note that hepatitis D and E are weak viruses. Hepatitis D can cause superinfection in a patient already

TABLE 7.3 Hepatitis A, B, and C.

	Hepatitis A (HA)	Hepatitis B (HB)	Hepatitis C (HC)
Type	RNA picornavirus	DNA hepadnavirus	RNA flavivirus
Incubation period	2–6 weeks	2–6 months	Variable
Transmission	Feco-orally	Parenterally	Parenterally
Carrier state	No	Yes	Yes
Chronicity	No	Yes	Yes
Malignancy	No	Yes	Yes
Serology	<ul style="list-style-type: none"> • HA IgM: recent infection • HA IgG: old infection 	<ul style="list-style-type: none"> • HBs antigen: active infection • HBs antibodies: old infection or vaccination (patient is immune) • HBc antigen: present only in hepatocytes; not serum • HBc IgM: active infection (patient is in window gap) • HBc IgG: old infection • HBe antigen: active viral replication and high contagiousness • HBe antibody: old infection 	<ul style="list-style-type: none"> • HC antibodies: not measurable in the serum consistently, even during an active infection • Polymerase chain reaction (PCR): the best measure to detect hepatitis C
Prevention	<ul style="list-style-type: none"> • Vaccine available • Immunoglobulin can be given within 72 hours after exposure 	<ul style="list-style-type: none"> • Vaccine (inactivated HBs antigens) is available (given at 0, 1, and 6 months) • Immunoglobulin can be given within 7 days after exposure 	No vaccine or immunoglobulin

infected with hepatitis B. Hepatitis E can cause fulminant infection *only during pregnancy*.

- *Clinical picture:*
 1. Fever, headache, and generalized fatigue
 2. Right upper quadrant pain: Mild tender hepatomegaly on exam
 3. Jaundice: Best seen in *sclera* and *palate*. Sclera stays jaundiced for a while after disease resolution, *the reason being the high affinity of collagen fibers of the sclera to bilirubin*.
- *Complications:*
 1. Chronicity, fulmination, or relapse
 2. Immune mediated due to hepatitis B surface (HBs) antigens: Glomerulonephritis and vasculitis. e.g., polyarteritis nodosa
- *Pathology: Lymphocytic infiltration* of the liver (centrizonal and portal tract)
- *Treatment:*
 1. Hepatitis A: Supportive and bed rest
 2. Hepatitis B: *Interferon* and *lamivudine*
 3. Hepatitis C: *Interferon* and *ribavirin*
- *Notes on treatment:*
 1. Interferon acts by *inhibiting the transcription and translation of the virus*. Side effects: Flu-like symptoms and immune disorders, e.g., thyroiditis, bone marrow depression, hemolytic anemia, and Guillain-Barré syndrome.
 2. Sudden rise of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) after starting treatment is a sign of successful therapy. *This occurs due to destruction of the virally infected hepatocytes. (Doesn't that remind you of the Jarisch-Herxheimer reaction?)*
- *Other forms of hepatitis:*
 1. Chronic active hepatitis: Pathology shows *piecemeal* and *bridging necrosis*, and *rosette formation* in the hepatocytes
 2. Autoimmune hepatitis: Diagnosed by positive ANA and *anti-smooth muscle antibodies*. Treatment: *Steroids*; if they fail, *add azathioprine*.
 3. Alcoholic hepatitis: Pathology shows *perivenular ballooning* and *necrosis* along with *Mallory bodies*. Labs shows *AST/ALT ratio of more than 2*, *elevated IgA*, and *elevated gamma-glutamyltransferase (GGT)*.
 4. Acute fatty liver of pregnancy: Severe hepatitis and liver failure during pregnancy, could be caused by hepatitis E virus infection

5. Cholestasis of pregnancy: Benign condition presenting with *pruritus* during the *third trimester* and it resolves spontaneously after delivery. There is high alkaline phosphatase and direct bilirubin.
6. HELLP: A pregnancy-associated disease. H: Microangiopathic hemolysis. EL: Elevated liver enzymes. LP: Low platelets.

Herpes Viruses

- It migrates up the nerves to establish a latent infection in the sensory ganglia.
- It has a *cytopathic* effect.
- *Types and clinical picture:*
 1. Herpes simplex virus
 - Type I: Keratitis (*branching dendritic ulcer*), and gingivostomatitis
 - Type II: Painful genital vesicles, itching, discharge, and dysuria
 2. Varicella zoster virus
 1. Initial infection: Chicken pox: multiple crops of lesions, *in all stages of development, all at the same time*, i.e., macules, papules, pustules, vesicles, crusted, and healing lesions
 2. Latent stage: Virus dormant in the sensory ganglia and dorsal roots
 3. Shingles: Painful vesicular rash following a *dermatomal distribution* (Fig. 7.3). Reactivation of the virus to cause shingles is common in *immunocompromised* patients, e.g., diabetes mellitus (DM), malignancy, on chemotherapy.



FIG. 7.3 Shingles

- *Diagnosis: Tzanck smear showing intranuclear inclusions (Cowdry A bodies) and multinucleated giant cells*
- *Treatment: It is helpful only if used within the first 48 hours of rash onset. Treatment does not cure the disease; it only shortens duration of the rash, and decreases risk of complications, e.g., postherpetic neuralgia*
 1. Herpes simplex: *Acyclovir*
 2. Varicella zoster: *Famciclovir*
- *Note:*
 1. Acyclovir may cause reversible renal toxicity, due to *crystalluria*. Accordingly, you must advise your patient to increase fluid intake while taking acyclovir.
 2. Exposure to sunlight and major emotional disturbance may lead to multiple herpes recurrences.
 3. Herpetic lesions ulcerate easily, giving an easy access to more potent infections, e.g., HIV.
- *CBC: Atypical lymphocytosis, and anemia due to antibodies against the Li antigen of RBCs*
- *Diagnosis: Monospot test: Positive heterophil antibodies against sheep RBCs*
- *Contraindication: Penicillin causes rash in these patients*
- *Complication: Splenic rupture. So when you see a patient on the USMLE with features of mononucleosis who engages in wrestling, and then comes to the emergency room with excruciating abdominal pain, you know what to think!*
- *Treatment: Self-resolving*
- *Note: Cytomegalovirus (CMV) is an important virus, so try to remember:*
 1. It lives in the *buffy coat* of WBCs.
 2. It causes *cytomegaly (swollen cells)*.
 3. Clinical picture: Asymptomatic or infectious mononucleosis, chorioretinitis in AIDS patients, and *pneumonitis after bone marrow transplantation*.
 4. Treatment: *Ganciclovir*. If patient is ganciclovir-resistant, use *foscarnet*.

Human Herpes Virus-6 (HHV-6)

- It causes *Roseola infantum (Exanthem subitum)*.
- *Clinical picture: High-grade fever, followed by rash on the trunk, which spreads outward to the extremities as it fades away*
- *Note: Do not confuse this with Erythema infectiosum (fifth disease) caused by parvovirus B19, where the patient presents with a slapped-cheeks appearance and maculopapular rash that starts on the arms and spreads to the trunk and lower extremities. Complication: Aplastic anemia.*

Epstein-Barr Virus (EBV)

- It targets *B lymphocytes*, causing *Burkitt's lymphoma*, nasopharyngeal carcinoma, and *infectious mononucleosis (IM)*. IM is discussed in detail below.
- *Transmission: Mostly through saliva, hence the name kissing disease*
- *Clinical picture: Fever, chills, fatigue, sore throat due to pharyngitis, and abdominal pain due to splenomegaly*
- *On exam:*
 1. *Petechiae* on hard and soft palate
 2. Multiple enlarged and tender cervical lymphadenopathy
 3. *Splenomegaly*: Lower edge is felt just below the costal margin

Rabies

- A *rhabdovirus* that replicates *locally in a wound*, and may travel up neuronal axons into the CNS to cause encephalitis
- *Source: Multiple, most famous are dogs, cats, bats, and raccoons*
- *Pathology: Brain tissue shows virions, also called Negri bodies*
- *Clinical picture: Fever, headache, and hydrophobia due to pharyngeal muscles spasm. This may lead to foaming at the mouth, a classic symptom of rabies.*
- *Treatment: Immunoglobulins and active immunization, using five injections of a killed virus vaccine*
- *Note: Washing the wound with soap and water dissolves the lipid envelope of the virus, which leads to prolongation of its incubation period.*

Other Viruses

- *Rubella (German measles; 3-day measles): Just like measles, it starts with cough, coryza, and conjunctivitis. The key differences are:*
 1. Measles is characterized by Koplik spots, while rubella is characterized by *posterior auricular and posterior cervical lymphadenopathy*.

2. Rash of measles is confluent, while that of rubella is not.
- *Coxsackie virus*: Two types:
 1. *Coxsackie A*: Causes the following:
 - Painful mouth and pharynx vesicles, fever, and sore throat, also called *herpangina*. If these lesions spread to involve the hands and feet, it is known as *hand-foot-mouth syndrome*.
 - Acute hemorrhagic conjunctivitis.
 2. *Coxsackie B*: Causes pleurisy, myocarditis (*Coxsackie B4*), and pericarditis.
 - *Poxvirus*: Replicates in the *cytoplasm*. Clinical picture: Small pox and molluscum contagiosum. The latter are *umbilicated, pearly white, hemispherical papules* (Fig. 7.4).
 - *Papilloma virus*: It causes *warts*. HPV strains 16, 18, and 31 may cause *cervical cancer*.
 - *Adenovirus*: Cause rhinitis, sinusitis, and conjunctivitis. It is commonly transmitted by *swimming pool water in the summer months*.
 - *Rhinovirus and coronavirus*: Cause common cold (rhinitis, conjunctivitis, and fatigue). Transmitted mainly by *fomites*.
 - *Rotavirus*: Double-stranded RNA virus with double capsid. It is the most common cause of diarrhea in children. Rotavirus cannot be cultured from the stools.
 - *Hantavirus*: It causes fever, hemorrhage, and renal failure. Source: *Rats*. Treatment: *Ribavirin*.
 - *Yellow fever virus*: It causes fever, hepatitis, and jaundice.



FIG. 7.4 Molluscum contagiosum

- *Poliovirus*: Causes poliomyelitis. Discussed in Chapter 3, Neuroanatomy.

Fungi

- The cell membrane of fungi is rich in ergosterol, and is surrounded by a capsule.
- Antifungal medications are discussed in detail in Chapter 9, Pharmacology.

Tinea Capitis (Fig. 7.5)

- *Ringworm of the scalp*
- *Cause: Dermatophyte, microsporum, or trichophyton*
- *Clinical picture*: Lesions are well circumscribed, usually multiple in the scalp, oval in shape, of variable sizes, and contain *hair stumps*. Lesions heal *without scar* formation.
- *Treatment: Oral antifungal*, such as terbinafine, itraconazole, or griseofulvin for 4–6 weeks
- *Notes*:

1. Kerion: A subtype of tinea capitis infection. Clinical picture: A painful swelling on the scalp with pustular discharge, often confused with an abscess. Treatment: No incision and drainage is needed, antifungals usually suffice.
2. Favus: A subtype of tinea capitis infection. Clinical picture: *Saucer-shaped*, crusty yellow lesions in the scalp, known as *scatula*. Unlike usual tinea infections, this one heals *with a scar*, and could cause alopecia.

Tinea Corporis (Fig. 7.6)

- *Ringworm of the trunk*
- *Cause: Dermatophyte, microsporum, or trichophyton*
- *Clinical picture*: Lesions are oval or rounded, with red elevated *circinate* margins and *central clearing*, hence called *tinea circinata*.
- *Treatment*: Local antifungal, plus oral antifungal for 3 weeks in severe cases

Tinea Cruris

- *Jock itch*
- *Location of lesions*: Groin and buttocks area
- *Clinical picture*: Lesions are *bilateral and symmetrical*, reddish with raised *festooned* edges
- *Treatment*: Local antifungal, plus oral antifungal for 3 weeks in severe cases



FIG. 7.5 Tinea capitis



FIG. 7.6 Tinea corporis

Tinea Pedis

- *Athlete's foot*
- *Location: Interdigital spaces of the foot, but can occur anywhere in the foot*
- *Clinical picture: Skin maceration*
- *Treatment: Local antifungal, plus oral antifungal for 3 months in severe cases*

Tinea Unguium

- *Onychomycosis*
- *Clinical picture: White, brittle, and discolored nails*
- *Treatment: Oral terbinafine; 6 weeks for fingernails, and 12 weeks for toenails, plus local antifungal in severe cases*

Tinea Versicolor (Fig. 7.7)

- *Pityriasis versicolor*
- *Cause: Malassezia furfur; a subtype of Pityrosporum orbiculare*
- *Location: Trunk, usually the upper chest, neck, and back*
- *Clinical picture: Lesions are small, well-defined, scaling macules, of various colors*
- *Diagnosis:*
 1. Examination of the lesions under Wood's light shows *yellow color*.



FIG. 7.7 Tinea versicolor

2. KOH skin scraping shows the hyphae and yeast in *spaghetti and meatballs appearance*.
- *Treatment: Local with imidazole cream, plus oral ketoconazole in severe cases*
 - *Note: Some lesions are hypopigmented due to azelaic acid production by the fungus, which inhibits the melanocytes.*

Candidiasis

- *Candida albicans* exists in two forms:
 1. Yeast: It serves as flora.
 2. Mycelia: Pathogenic form
- *Predisposing factors: Obesity, hyperhidrosis, and DM*
- *Clinical picture:*
 1. *Cutaneous candidiasis:* Common in skin folds, e.g., diaper rash. Lesions are red and moist with festooned edges, and are surrounded by papules known as *satellite lesions* (Fig. 7.8).
 2. *Oral candidiasis (thrush):* Common in patients using inhaled steroids, and it could involve the tongue and the esophagus. Lesions are multiple white painful plaques. Prevention: *Washing the mouth* after using the steroid inhalers (Fig. 7.9)
 3. *Genital candidiasis:* It is the most common genital infection in females worldwide. Clinical picture: Whitish, milky vaginal discharge and curd-like patches.
- *Diagnosis: Pseudohyphae* under microscopy (Fig. 7.10)



FIG. 7.9 Oral thrush



FIG. 7.10 Hyphae and spores of *Candida albicans*

- *Treatment:*
 1. Cutaneous and oral candidiasis: Mainly local, with nystatins or imidazole
 2. Genital candidiasis: Single dose of oral fluconazole



FIG. 7.8 Diaper candidiasis

- *Notes:*
 1. Most fungal infections could be easily treated with a topical antifungal, like imidazole cream or ointment, except for two infections that require systemic therapy: tinea capitis and tinea unguium.
 2. Griseofulvin attacks only dermatophytes and it causes GI upset.
 3. Ketoconazole and terbinafine are hepatotoxic.

Cryptococcus neoformans

- *Polysaccharide encapsulated yeast*
- *Transmission:* Pigeon droppings
- *Clinical picture:* Meningitis in immunocompromised patients, e.g., AIDS
- *Diagnosis:*
 1. *India ink* staining of cerebrospinal fluid (CSF) shows a *halo around the yeast cells*.
 2. Culture: Grows on *Sabouraud's agar*
- *Treatment:* Combination of *amphotericin B* and *flucytosine*
- *Notes:*
 1. Amphotericin B: Causes phlebitis, nephrotoxicity and febrile reaction. Prevention: Give aspirin or acetaminophen before amphotericin treatment.
 2. Flucytosine: Causes bone marrow depression and GI upset

Coccidioides immitis

- *Thick-walled spherules, causing coccidioidomycosis (San Joaquin valley fever)*
- *Location:* Common in the *southwestern United States (desert areas)*
- *Clinical picture:* Atypical pneumonia and *erythema nodosum* (tender red nodules on tibia)
- *Diagnosis:* Positive complement fixation test
- *Treatment:* Fluconazole or itraconazole. Amphotericin B is used only in severe cases.
- *Note:* So when you see a patient on the USMLE who has been to a desert area in the southwestern U.S. recently, and now has pneumonia and bumps on his legs, you know what to think!

Miscellaneous Fungal Infections

- *Sporothrix schenckii:* Cigar-shaped budding yeast. *Transmission:* Contact with rose thorns (also called *rose-gardener's disease*). *Clinical picture:* Subcutaneous nodules and ulcers. *Treatment:* Potassium

iodide (KI) or itraconazole for cutaneous forms, and amphotericin B for extracutaneous forms.

- *Aspergillus:* Inhalation causes hypersensitivity reactions *type I and III*, which lead to bronchospasm. May form aspergilloma in lungs. It also releases *aflatoxins*, which have been linked to *liver cancer*. Shows *branching hyphae* under microscope (*Candida* shows *pseudohyphae*). *Note:* *Aspergillus* is the nightmare of any bone marrow transplant unit.
- *Chromoblastomycosis:* Causes cauliflower-like masses with copper-colored sclerotic bodies and broad-based budding (BBB) on microscopy. Treatment: *Itraconazole*
- *Histoplasmosis and blastomycosis:* Transmitted through birds' feces and may cause pneumonia
- *Actinomycosis:* Causes formation of yellow sulfur granules. Treatment: *Penicillin*

Parasites

Entamoeba histolytica

- A parasite that moves by means of *pseudopodia*, and it exists in two forms:
 1. *Mature cyst:* Infective form
 2. *Trophozoite:* Pathogenic form
- *Clinical picture:* Severe watery diarrhea, *with blood and mucus*
- *Complication:* Liver abscesses, mainly involving the *right lobe*
- *Diagnosis:* Stool culture shows *trophozoites with intracytoplasmic RBCs*
- *Treatment:* *Metronidazole*
- *Note:* Homosexual men are frequent carriers

Giardia lamblia

- A parasite that exists in two forms:
 1. *Mature cyst:* Infective form.
 2. *Trophozoite:* Pathogenic form. It is *pear shaped*, with *two nuclei* and *four pairs of flagella*.
- *Clinical picture:* Watery malodorous diarrhea, and abdominal distention and bloating. So when you see a patient on the USMLE who just traveled outside the U.S. recently, and now has abdominal pain, and watery, *nonbloody diarrhea*, you know what to think!
- *Diagnosis:* Stool analysis shows cysts or trophozoites.
- *Treatment:* *Metronidazole*

- *Note: Well water and day care centers* are notorious sources of *Giardia lamblia*.

Trichomonas vaginalis

- A *flagellated protozoon* causing a postmenstrual infection
- *Clinical picture:* Vulvovaginitis and *frothy vaginal discharge*
- *On exam:* Punctate hemorrhages in vagina and on the cervix; also called *strawberry cervix*
- *Diagnosis:* Wet mount prep shows *motile flagellated trichomonads*.
- *Treatment:* Metronidazole

Plasmodium

- A parasite causing *malaria*, transmitted by the *female anopheles*
- *Clinical picture and causative organism:*
 1. *Tertian:* Attacks of fever and sweats every 48 hours: *Plasmodium vivax* and *Plasmodium ovale*
 2. *Quartan:* Attacks of fever and sweats every 72 hours: *Plasmodium malariae*
 3. *Malignant malaria* with variable attack periods: *Plasmodium falciparum*
- *Prophylaxis:* Chloroquine. If patient is chloroquine-resistant, give mefloquine.
- *Treatment*
 1. *P. vivax, P. ovale,* and *P. malariae:* Chloroquine for blood forms, and primaquine for tissue forms
 2. *P. falciparum:* Chloroquine. If chloroquine-resistant, give quinine, mefloquine, or artemether.
- *Notes:*
 1. *P. vivax* and *P. ovale* reproduce in the liver to form *hypnozoites*. These stages can cause multiple relapses (*relapsing malaria*).
 2. African-Americans resist infection by *P. vivax*, because they do not have *Duffy A* and *Duffy B* antigens in their RBCs.
 3. Sickle cell patients are resistant to infection by *P. falciparum*, due to *HbS*.
 4. Antimalarial medications induce hemolysis in patients with *glucose-6-phosphate dehydrogenase (G-6-PD) deficiency*

Leishmania donovani

- *Transmission:* Sandfly
- *Clinical picture:*

1. Visceral form (*kala azar*): Hepatosplenomegaly
2. Cutaneous form: Depends on the cell-mediated immunity (CMI) of the patient:

- If CMI is intact: Ulcer heals with a pale scar, also called an *oriental sore*.
- If CMI is lost: Facial skin nodules, *primarily around the nose*

- *Treatment:* Sodium stibogluconate

Amebas Causing Meningoencephalitis

- *Source:* Swimming in lakes or ponds
- *Types and clinical picture:*
 1. *Naegleria fowleri:* Acute meningoencephalitis
 2. *Acanthamoeba:* Chronic meningoencephalitis, *plus keratitis*
- *Treatment:* Amphotericin B
- *Note:* So when you see a patient on the USMLE who went camping a couple of weeks ago, and swam in a pond, and is now presenting with symptoms of meningitis and encephalopathy, you know what to think!

Trypanosomas

- *Trypanosoma brucei (Gambiense or Rhodesiense):* Transmitted by *tsetse fly*, and causes *African sleeping sickness*, which can be fatal. Treatment: Suramin; however, if there are any signs of CNS involvement, give melarsoprol.
- *Trypanosoma cruzi:* Transmitted by *Reduviid (kissing) bug*, and causes skin chagoma (nodule or papule), also called *Romana sign*. Late stages might develop *Chagas disease* (toxic megacolon, cardiomyopathy, and achalasia). *Treatment:* Nifurtimox

Helminths

- *Ascaris lumbricoides (roundworm):* Life cycle: Ingested in food → intestine → blood → lungs → coughed and swallowed → intestine. This is known as *autoinfection*, which is also done by *strongyloides*. Treatment: Mebendazole or pyrantel pamoate.
- *Ankylostoma duodenale* and *Necator americanus (Hookworm):* Cause *iron-deficiency anemia*. Treatment: Mebendazole or pyrantel pamoate.
- *Trichinella:* From raw pork and causes myositis (diagnosed by high serum creatine phosphokinase [CPK]). First sign of trichinosis: *swollen eyelids*. Treatment: Thiabendazole.

- *Enterobius vermicularis* (pinworm): This worm causes *perianal pruritus*, and is diagnosed by the *scotch tape test*. Treatment: *Mebendazole* or *pyrantel pamoate*.
- *Onchocerca volvulus*: Causes *river blindness* and *intraepithelial granulomas* (lizard skin). Treatment: *Ivermectin*.
- *Wuchereria bancrofti* (filariasis): Causes *elephantiasis*, and is diagnosed by *midnight blood film* (nocturnal periodicity). Treatment: *Diethylcarbamazine* (DEC).
- *Cutaneous larva migrans*: Contracted from *dog's fecal material*, and causes *pruritic red rash with creeping serpentine eruption*. Treatment: *Thiabendazole*.
- *Tinea* (Tapeworm)
 1. *Tinea saginata*: In *beef products*, and it leads to *malabsorption*.
 2. *Tinea solium*: From eating *larvae in pork*, and it leads to *cysticercosis*.
 3. Treatment of tinea: *Niclosamide + laxatives*
 4. Treatment of cysticercosis: *Praziquantel*
- *Diphyllobothrium latum* (tapeworm): Acquired by eating *undercooked fish*, and it causes *vitamin B₁₂ deficiency*. Treatment: *Niclosamide + laxatives*.
- *Echinococcus granulosus* (tapeworm): From contact with dogs leading to fever, hepatomegaly, and *hydatid cyst formation*. Treatment: *Albendazole*.

Chapter 8

Immunology

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Immunity

- *Active*: Generated by the body after exposure to an infection or a vaccine, e.g., antigens
- *Passive*: Donated to the body transplacentally, or through injection of antibodies

Lymphoid Organs

- It is where lymphocytes develop, and they are divided into:
 1. Central: Where cells are formed:
 - T lymphocytes are formed in the Thymus.
 - B lymphocytes are formed in the liver during the fetal period, and in the bone marrow in adults.
 2. Peripheral: Where cells are expressed. This takes place in the spleen, lymph nodes, tonsils, and Peyer’s patches.
- *Cell-mediated immunity (CMI)*: It is the job of T lymphocytes, natural killer (NK) cells, and macrophages, which are destined to kill the organism and its aberrant host cells.

- *Humoral immunity*: It is the job of B lymphocytes, which produce antibodies.

Major Histocompatibility Complex (MHC)

- The MHC is a cluster of genes found in every human and animal cell. It is known as human leukocyte antigen (HLA) in humans, and is located on *chromosome 6*.
- *Function*: The main function of HLA I and HLA II is to label anything they encounter as either *self* or *foreign* material, and then they present that material to T cells as follows (Table 8.1):
 1. HLA I presents to CD8 T cells.
 2. HLA II presents to CD4 T cells.
 3. HLA III genes encode serum proteins and some complement factors.

T Lymphocytes

- They are responsible for cell-mediated immunity.

TABLE 8.1 Human leukocyte antigen (HLA) system.

	HLA I	HLA II
Molecules encoded	A, B, C	DP, DQ, DR
Sites expressed	On membranes of nucleated cells except mature red blood cells (RBCs)	On membranes of dendritic cells, T and B cells and macrophages
CD binding Mechanism of immunity	CD8 on Tc Cell-mediated	CD4 on Th Humoral
Targeted antigens	Endogenous	Exogenous

- **Function:** Attack *intracellular* pathogens, and regulate B-lymphocytes function
- **Formation:**
 1. Totipotent cells from *fetal liver and bone marrow* migrate to the *thymus* to be converted into T cells. In the thymus, they acquire *clusters of differentiation* CD2 and CD3.
 2. T-helper cells also acquire CD4. CD4 T cells differentiate into two types:
 - *Th1*: Release tumor necrosis factor (TNF), alpha and gamma interferon, and interleukin-2
 - *Th2*: Release interleukins 4, 5, 6, and 10
 3. *Cytotoxic T cells (Tc)* acquire CD8: They suppress B-cell function, and *attack virus infected cells*.
- **To sum up:** The CD4 T cells can be divided into:
 1. *Inducer suppressor Th1*: *Induces* CD8 T cells, which in turn *suppress* antibody production of B lymphocytes
 2. *Helper Th2*: *Helps* B lymphocytes to release antibodies
- **T-cell antigen receptor (TCR):**
 1. TCR is epitope specific; it is expressed in association with CD3 on all T cells. Note: CD3 is responsible for signal transduction.
 2. T-cell receptors do not respond to soluble antigens. They only respond to antigen epitopes presented by antigen-presenting cells, e.g., macrophages, B cells, dendritic cells, or by an infected host cell.
 3. Antigen presented in association with HLA I to a CD8-positive cell activates CMI.
 4. Antigen presented in association with HLA II to a CD4 positive cell activates humoral immunity, since Th2 cells produce the cytokines to stimulate B cells.

- **Notes:**

1. T-cell levels can be measured using *anti-CD3 antibodies*.
2. T-cell home: *Periarteriolar* area of spleen, and *paracortical* area of lymph nodes.
3. T cells are immature when they reach the thymus's cortex. They undergo a selection process at the corticomedullary junction to pass to the medulla, where they mature.
4. Only 1% to 2% of T cells leave the thymus, while the rest die via *apoptosis*, which is a programmed cell death, a process of nuclei fragmentation and membrane perforation.
5. Maturation of T cells in the thymus is dependent on their exposure to thymus cells, and *does not require exposure to any antigens*.
6. Natural killer (NK) cells attack pathogens directly without the need for any thymus processing.

B Lymphocytes

- They are responsible for humoral, also called antibody-mediated, immunity.
- **Formation:** They arise from the *fetal liver and bone marrow*, and then they migrate to the peripheral lymphoid tissue for complete maturation.
- **Mechanism:** Stimulation of B lymphocytes gives rise to two subsets of cells:
 1. Plasma cells: Secrete antibodies; the first is always an *immunoglobulin M (IgM)*.
 2. Memory cells: Serve as quiescent cells, which are prepared for a rapid antibody response to the same antigen in the future. Second antigen exposure causes a rapid shift of immunoglobulin released from IgM to IgG.
- **Notes:**
 1. B-cell antigenic receptor is an *IgM* molecule.
 2. B-cell levels can be measured using *fluorescent B cell-specific antibodies*.
 3. B cells live only in the *white pulp of lymphoid organs*, while T cells live in both the *white and red pulps*.
- **Epitope (Ligand)**
 - It is the antigenic determinant of an infectious agent, i.e., the area recognized by lymphocytes. It is formed of repeated amino acids sequences, which is called *valence*.

- **Mechanism:** The epitope binds to the *hypervariable* region of the antibody.
- **Antigens:**
 1. Antigens typically are large proteins or polysaccharides. *Lipids are weak antigens.*
 2. Antigens entering the body through the blood are trapped in *spleen*, while those entering through any other route are trapped in the *lymph nodes*.
 3. Antigens can be detected using antibodies labeled with *fluorescein isothiocyanate* dye, which gives a green color on positive result.
- **Haptens:** Small molecules that are incapable of eliciting an immune response alone, e.g., antibiotics. When combined with a larger molecule, haptens can trigger an immunologic response. *You need a molecular weight of at least 6000 to induce an immunologic response.*
- **Superantigens:** They bind to the MHC of antigen-presenting cells and many T lymphocytes, leading to the release of huge amount of cytokines. A classic example is toxic shock syndrome.
- **Thymus independent antigens:** Antigens that can stimulate B lymphocytes without specificity or the help of T cells. A classic example is *polysaccharide antigens*.
- **Parts:**
 1. Two antigen-binding fragments (Fab), *with an epitope on each fragment*
 2. One complement-binding fragment (Fc) for *tissue fixation and placental transfer*
- **Composition:**
 1. Light and heavy chains are attached by *disulfide bonds*.
 2. Light chain: Contains one variable region (VL), and one constant region (CL), which are connected by a *joining segment*
 3. Heavy chain: Contains one variable region (VH), and three constant regions (CH1), (CH2), (CH3), with a disulfide bond attaching CH1 to CH2.
- **Notes:**
 1. H chain class shifting occurs in the *CH* region, and is mediated by *T cell cytokines*.
 2. Variable regions contain *hypervariable sites*, which bind together to form the *epitope-binding region*, also known as *idiotype*.
 3. *Papain* splits the Ig into two identical Fab fragments and one Fc fragment.
 4. *Pepsin* splits the Ig into one big Fab2 fragment, and it destroys the Fc fragment.
 5. Monoclonal antibodies, which are used as therapy for many diseases, are generated by injecting an animal with a malignant plasma cell. This cell forms a *hybridoma* inside the animal, from which the desired antibody can be isolated.

Antibodies

- An antibody is formed of four chains (Fig. 8.1):
 1. Two light chains: Constant for all Igs, either kappa or lambda, or both
 2. Two heavy chains: Differ for each class of Ig

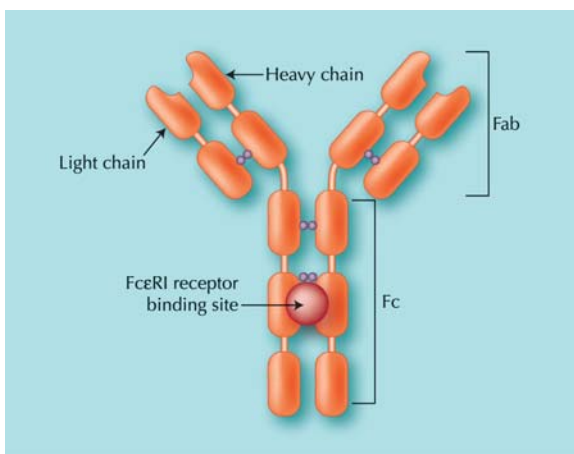


FIG. 8.1 Immunoglobulin structure (IgE)

- **IgG:** It is the most common antibody in the plasma, and is the main antibody in *secondary* immune response. It passes through the placenta, and has four different subtypes, depending on the heavy chain: gamma 1, 2, 3, and 4.
- **IgA:** It is the main Ig in *body secretions*. The heavy chain is the alpha chain. It exists either as a monomer, or a *dimer with a J chain*, along with an optional secretory (S) piece to guide it and protect it from proteolysis. Transforming growth factor beta (TGF- β) stimulates B cells to synthesize IgA.
- **IgM:** It has the biggest molecular weight, and is the main antibody in *primary* immune response. It is the earliest Ig to be detected in the blood after an infection (*IgG in secondary response*). It exists either as a monomer, or a *pentamer with a J chain*.
- **IgE:** Characterized by having *four constant regions on its heavy chain*. It binds to mast cells and basophils, and, upon cross-linking by antigen, degranulation is triggered. It cannot cross the placenta, and it has a role in *type I hypersensitivity* and immunity to *parasites*.

- *IgD*: May serve as a receptor for antigens on the surface of B lymphocytes. Note that IgG can also serve the same function.

Autoimmune Antibodies

- Autoimmune antibodies cause multiple diseases, e.g., autoimmune hemolytic anemia.
- *Types*: Two types of autoantibodies exist: Warm and cold (Table 8.2).
- *Coombs test*: In this test, antibodies on the patient's red blood cells (RBCs) are detected by adding antihuman immunoglobulin, which causes agglutination.
- *ELISA*: Enzyme-linked immunosorbent assay detects antibody or antigen titers by spectrophotometry, i.e., quantification of a color reaction.

Tube Agglutination

- *Definition*: Testing the patient's serum for antibodies against an infectious agent
- *Technique*: Serum is diluted in the presence of a constant amount of antigen, e.g., bacteria. The presence of agglutination at multiple dilutions is needed to diagnose the infection. *Fourfold of a titer* is usually needed to diagnose any pathogen.
- *Notes*:
 1. Titer is the dilution capable of causing agglutination.

TABLE 8.2 Autoimmune antibodies.

	Warm	Cold
Antibodies	IgG	IgM
Coombs' test	Positive	Negative
Associated infections	Chronic lymphocytic Leukemia, Lymphoma, and Lupus (LLL)	Mycoplasma infections

2. A change in the patient's titer could indicate a response to treatment.
3. Myxoviruses, both ortho- and paramyxoviruses, can agglutinate RBCs.

Precipitin Test

- *Definition*: It is a test in which different titers of antigen are allowed to react with an antibody. A classic example is the *Ouchterlony test*.
- *Technique*: The test is done by allowing two different antigens to react with an antibody in a Petri dish. The aim of the test is to estimate the degree of epitope uniformity and cross-reactivity between the two antigens (Fig. 8.2).

Complement Fixation

- It is a process that ends with cell lysis.
- *Classic pathway*:
 1. Initiated by an antigen-antibody complex
 2. *IgM* or *two molecules of IgG* bind to complement factor 1 (*C1*), stimulating it to split *C4*.
 3. *C4* splits and binds with *C2*.
 4. *C4* and *C2* split and bind with *C3*, which forms an enzyme to split *C5*.
 5. Eventually, *C5b* binds to *C6*, *C7*, *C8*, and *C9* to form the *membrane attack complex (MAC)*, which leads to cell lysis through the action of *perforin*.
 6. Remember, it goes like this: 1 → 4 → 2 → 3 → 5 → 6, 7, 8, 9.
- *Alternative pathway*:
 1. Initiated *directly* by *bacteria or aggregates of IgA*
 2. These factors bind with free *C3b* in the serum, which then combines with factors *B* and *D* to

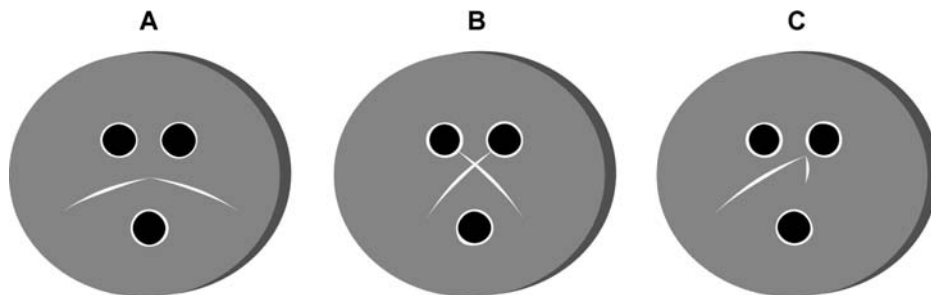


FIG. 8.2 Ouchterlony precipitin test. Note that the upper two circles in each part represent the antigens, while the lower circle represents the antibody. (A) Reaction of identity. (B) Reaction of nonidentity. (C) Reaction of partial identity

form an enzyme. This enzyme remains stable in the serum by means of *properdin*.

- In a process known as *amplification*, the enzyme cleaves C3 into C3a and C3b. C3b continues the cycle of amplification or forms the MAC.
- C1 esterase inhibitor deficiency*: Autosomal dominant disease causing hereditary angioedema. Diagnosis: Low levels of *C4* and *C1 esterase inhibitor*.
 - C5 to C9 deficiency*: Leads to recurrent *meningococcal and gonococcal* infections. So when you see a patient on the USMLE who has been having recurrent gonorrhea and meningitis since childhood, you know what to think!
 - Notes*:
 - Opsonization is performed by *C3b*. Note that antibodies against C3b are present in *type II membranoproliferative glomerulonephritis*.
 - Anaphylaxis is performed by *C3a* and *C5a*.
 - Neutrophil chemotaxis is performed by *C5a*.

Inflammation

- Phases*:
 - Acute: Mediated by *neutrophils*
 - Chronic: Mediated by *lymphocytes and macrophages*
- Mechanism*:
 - Cells produce *interleukin-8 (IL-8)* when stimulated or injured.
 - IL-8 causes *chemotaxis* of neutrophils to the inflammation site, where they bind endothelial adhesion molecules known as *selectins*.
 - This binding step and rolling adhesion initiates movement of inflammation-mediating cells through the capillary wall to the affected tissues, a process known as *diapedesis*.
 - Neutrophils phagocytose foreign bodies and destroy them using oxygen free radicals and hydrogen peroxide (H_2O_2).
 - At the end of the process, IL-8 receptors are downregulated by IL-4 and IL-10.
 - Finally, growth factors are released to heal the site of inflammation.
- Notes*:
 - Thrombin and histamine stimulate *P-selectin* expression on endothelial cells.
 - IL-1 and TNF- α stimulate *E-selectin* expression on endothelial cells.

Cytokines

- Cytokines are signaling proteins, released from cells and act locally.
- Interleukins*: They are cytokines released from one leukocyte to act on another leukocyte.
- Chemokines*: They are chemotactic cytokines, and they exist in two types:
 - Alpha chemokines (cysteine-X-cysteine), e.g., IL-8: They attract *neutrophils* from blood to tissues.
 - Beta chemokines (cysteine-cysteine) e.g., monocyte chemoattractant protein-1 (*MCP-1*): They attract *monocytes* from blood to tissues, where they transform to macrophages.
- Notes*:
 - Gamma-interferon* decreases *IL-4* synthesis (through *Th2 T cells*); however, both gamma-interferon and IL-4 share in the formation of *epithelioid granulomas*.
 - IL-2 and IL-4* initiate the transformation of B lymphocytes into blast cells. This process is maintained by IL-5. *IL-6* performs the final differentiation.
 - IL-1 and IL-8* stimulate chemotaxis.
 - IL-1 and IL-6* are pyrogenes.
 - IL-4 stimulates *IgE*, while IL-5 stimulates *IgA* production.
 - IL-3 stimulates stem cell proliferation in the bone marrow.
 - IL-10 stimulates humoral immunity and inhibits CMI.
 - Tumor necrosis factor (TNF) is released by macrophages, and it causes cachexia and inhibits lipoprotein lipase enzyme. *Tumor necrosis factor- α* combines with *IL-1* to stimulate the acute phase of inflammation.
 - Ig class switching is regulated by *IL-4* and *IL-13*.

Hypersensitivity Reactions

Type I (Atopic) (Anaphylactic) Reaction

- Examples*: Asthma, urticaria, allergic rhinitis, bee stings
- Mechanism*:
 - Antigen binds to Fab portion of IgE on either *mast cells in skin and lungs*, or to *basophils in the blood*
 - Mast cells* are responsible for the initial reaction, and *basophils* for the late phase.

3. Cross-linking causes degranulation, and *histamine* is released, resulting in increased vascular permeability and smooth muscle contraction.

- *Clinical picture*: Angioedema, bronchospasm, and hypotension
- *Treatment*: Epinephrine (1/1000) (*lifesaving*), corticosteroids, and H1 and H2 blockers
- *Testing*: Allergies are best evaluated by *skin testing*, except if the reaction is fatal; then the alternative is radioallergosorbent test (RAST), which measures the allergen-specific IgE levels in serum.
- *Desensitization*: Mechanism involves the stimulation of blocking antibodies (*IgG*) by injection of multiple small doses of the antigen. The blocking antibodies bind to the allergen in the circulation and prevent it from binding to mast cells or basophils.

Type II (Cytotoxic) Reaction

- *Mechanisms*:
 1. Circulating antibodies react with antigens on the *surface* of cells, which leads to cell damage either by phagocytosis or complement activation.
 2. Cells bearing IgG may also be killed by NK cells in a process known as antibody-dependent cell-mediated cytotoxicity (ADCC). Note: NK cells can also kill tumor and virus-infected cells *independent* of the presence of antibody.
- *Hemolytic disease of the newborn*: Rh-negative mothers are given RhoGam at *28 weeks' gestation* and *within 24 hours after delivery* to decrease the risk of Rh sensitization of the mother. By decreasing placental transfer of Rh-positive cells to her circulation, the risk of hemolytic disease of the newborn is decreased for *future* children.
- *Incompatible blood transfusions*: ABO or Rh incompatibility. Patient receiving incompatible blood suffers *fever, chest and back pain, and dyspnea*. First thing to do is to *stop the transfusion* and send the blood product for re-typing and cross-matching.
- *Goodpasture's syndrome*: Glomerulonephritis and pulmonary hemorrhage due to an *IgG* against a glycoprotein on the alveolar and glomerular basement membranes (GBMs). Clinical picture: Hematuria and hemoptysis.
- *Graves' Disease*: Antibodies known as long-acting thyroid stimulators (*LATS*) or thyroid-stimulating immunoglobulin (*TSI*) react with thyroid-stimulating hormone (TSH) receptors, leading to hyperthyroidism. (Discussed in Chapter 10, Pathophysiology.)

Type III (Immune Complex–Mediated) Reaction

- *Mechanism*: Deposition of *antigen-antibody complexes* that cannot be cleared rapidly. Note that immune complexes are normally cleared by phagocytosis. Antigen-antibody complexes are deposited on the wall of blood vessels, injuring its intima and activating the complement pathways. *The main problem here is antigen persistence.*
- *Arthus reaction*: It is a local reaction around blood vessels, most commonly in the skin after injection of an antigen. Immune complexes form, and complement is fixed, leading to edema and chemotaxis of neutrophils. Local tissue damage leads to thrombosis and necrosis. *Note that edema is mediated by C3a and C5a, while chemotaxis is mediated by C5a only.*
- *Serum sickness*: It is due to foreign serum or, more commonly, drugs like penicillin. Clinical picture: Fever, rash, arthralgia, and lymph node enlargement about 5 days after the antigen is introduced.
- *Polyarteritis nodosa* and *rheumatoid arthritis*: Discussed in Chapter 10, Pathophysiology.

Type IV (Cell-Mediated) Reaction

- Also known as *delayed-type hypersensitivity*
- *Mechanism*: Presentation of antigen to CD4⁺ T cells leads to tissue damage, via the release of cytokines and accumulation of neutrophils and macrophages.
- *Note*: Reaction can be transmitted by transfusion of sensitized lymphocytes.
- *Contact dermatitis*: Local eczema 48 hours after contact with irritant, e.g., Poison ivy
- *Tuberculin test*: Induration is formed by antigen presentation in the skin, which is performed by *Langerhans' cells*. Discussed in Chapter 10, Pathophysiology.

Immunologic Tolerance

- *Mechanisms*: Tolerance to self antigens occurs by one of the following mechanisms:
 1. Clonal deletion (negative selection): T cells in thymus and B cells in bone marrow are destroyed if they recognize self antigens.
 2. Clonal anergy (positive selection): Only T and B cells that can recognize MHC, are allowed to proliferate.

- 3. Peripheral suppression: CD8 T cells secrete cytokines to suppress the immune response.
- *Notes:* Tolerance of T cells lasts longer than that of B cells.

Immunologic Diseases

- *Rule:* Know the following as a rule:
 1. Failure of CMI: Infection by *viruses* and *intra-cellular bacteria*
 2. Failure of humoral immunity: Infection by *extracellular bacteria*

Transient Hypogammaglobulinemia

- *Mechanism:* A decrease in serum IgG after maternal immunity wanes. It occurs at around the age of 6 months.
- *Fate:* The defect typically resolves after 1 to 2 months to 1 to 2 years and does not require treatment.

Chronic Mucocutaneous Candidiasis

- *Mechanism:* Disorder of T-cell response to *Candida*
- *Clinical picture:* Recurrent yeast infections of mucous membranes and skin

Bruton's Agammaglobulinemia

- *Mechanism:* An *X-linked recessive* disease, where there are absent or low immunoglobulins. This occurs due to a deficiency of the tyrosine kinase needed for maturation of B lymphocytes.
- *Pathology:* Patient does not have *tonsils* or *germinal centers in the lymph nodes*.
- *Clinical picture:* Patient is usually 6 months of age or older, presenting with recurrent *extracellular bacterial infections*, and *absent tonsils*.
- *Diagnosis:* *Very low IgG level*, and *absence of all other Igs*.

Selective Ig Deficiency

- Deficiency of one or more Ig; the most common is *selective IgA deficiency*.
- *Clinical picture of IgA deficiency:* Recurrent upper and lower respiratory tract infections, allergies, diarrhea, or could even be asymptomatic

Wiskott-Aldrich Syndrome

- *X-linked recessive* disease

- *Mechanism:* Defect in *T cells* and *IgM* only
- *Clinical picture:*
 1. Thrombocytopenia and bleeding
 2. Eczema
 3. Combined T- and B-cell deficiency causing recurrent infections
- *Note:* The gene for the *Wiskott-Aldrich syndrome protein (WASP)* has now been isolated and plays a role in many immune functions.

Severe Combined Immunodeficiency (SCID)

- Absent T cells or B cells due to defective stem cell development
- *Mechanisms:* Multiple inherited causes:
 1. Deficiency in adenosine deaminase (ADA): *Autosomal recessive*
 2. MHC class II deficiency
 3. Defective tyrosine kinase: *Autosomal recessive*
 4. Defective IL-2 receptor: *X-linked*
- *Clinical picture:* Patient is usually *less than 6 months in age* presenting with recurrent bacterial, viral, and fungal infections.
- *Treatment:* Previously fatal, early detection and bone marrow transplantation may be curative.

Chronic Granulomatous Disease (CGD)

- *Mechanism:* *X-linked* deficiency of reduced nicotinamide adenine dinucleotide phosphate (*NADPH oxidase* in *neutrophils*)
- *Clinical picture:* Recurrent fungal and staphylococcal infections. *Suspect it when you see a patient on the USMLE with recurrent oral thrush, diaper rash, abscesses, and granulomas.*
- *Diagnosis:* Inability of cells to reduce *nitroblue tetrazolium dye* to formazan
- *Treatment:* Gamma interferon

Chediak-Higashi Syndrome

- *Mechanism:* *Autosomal recessive* disease, caused by a defect in *microtubule polymerization*. This leads to failure of *chemotaxis and phagocytosis*.
- *Clinical picture:* NAP
 1. Neutropenia with recurrent staphylococcal and streptococcal infections
 2. Albinism
 3. Prolonged bleeding time
- *Associations:* Neurologic defects, e.g., ataxia, neuropathy

TABLE 8.3 Types of rejection.

	Hyperacute	Acute	Chronic
Type	Type II hypersensitivity reaction	Types III and IV hypersensitivity reaction	Fibrosis and necrosis
Timing	Within minutes after graft	Within weeks to months after graft	Within months to years after the transplant
Mechanism	Preformed antibodies attacking the blood vessels of the transplanted organ, causing multiple clots and obstructing its blood supply	Humoral or cell-mediated immunity	Humoral or cell-mediated immunity
Notes	The most relevant test to prevent this rejection is ABO cross-matching	Reversible with immunosuppressants	Not reversible and is the major cause of transplant loss

Ataxia-Telangiectasia Syndrome

- *Mechanism:* Autosomal recessive disorder
- *Clinical picture:*
 1. Combined T- and B-cell deficiency: Recurrent infections
 2. Cerebellar ataxia and oculocutaneous telangiectasia
- *Complications:* Stomach cancer and non-Hodgkin's lymphoma

Leukocyte Adhesion Deficiency

- *Mechanism:* Defect in an adhesion protein *LFA-1* involved in phagocytosis
- *Clinical picture:* Recurrent fungal, staphylococcal, and streptococcal infections at a young age

Transplant Immunology

- *Types of rejection* (Table 8.3).
- *Graft-versus-host disease:* It is triggered when immunocompetent tissues are grafted and donor lymphocytes attack the host cells, leading to organ damage. *Clinical picture:*

1. Hepatitis and jaundice
2. Gastrointestinal upset and diarrhea
3. Morbilliform desquamative maculopapular rash

- *Immunosuppressive medications:* They are used after grafts to prevent rejection.

1. *Cyclosporine and tacrolimus (FK506):* Inhibit activation of T-helper cells and thereby lead to decreased IL-2 secretion. These drugs are known as *calcineurin inhibitors* because they act by binding to *cyclophilins*, which leads to inhibition of calcineurin. *Calcineurin is a transcription activator for IL-2.*
2. *Mycophenolate mofetil or Cellcept:* Inhibits inosine monophosphate (IMP) dehydrogenase, which interferes with the synthesis of purines through a pathway on which T and B cells depend.
3. *Rapamycin (Sirolimus):* Macrolide antibiotic with strong immunosuppressive qualities. It inhibits the *T-cell response to IL-2.*
4. Antilymphocyte globulins, e.g., *OKT3: An antibody against T-cell CD3.* Effective in managing acute rejection.

Chapter 9

Pharmacology

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Pharmacokinetics and Pharmacodynamics

- *Transport:* Water-soluble drugs enter cells through channels, while lipid-soluble ones passively diffuse through any part of the cell membrane.
- *Absorption:*
 1. Most drugs are absorbed in the *small intestine* due to its rich blood supply and extensive villous surface, and it occurs by means of *passive diffusion*.
 2. Stress and food lead to decreased gastric emptying, and hence decreased drug absorption.
- *Total body water (TBW): 42 liters*, divided as follows:
 1. Intracellular: *28 liters*
 2. Extracellular: *14 liters: four liters of plasma and 10 liters of interstitial fluid*
- *Note:* Drugs with a small molecular weight are distributed mainly in the *interstitial fluid*, while those with large molecular weight (e.g., aminoglycosides) are distributed mainly in the *plasma*.

Bioavailability

- *Definition:* It is the portion of the drug reaching the systemic circulation.
- *Bioavailability* = Area under curve (AUC) in the oral form/Area under curve (AUC) in the injected form

- *Area under the curve*: Represents the amount of drug reaching its target tissue
- *Note*: Drugs can be termed *bioequivalent* if their bioavailabilities are similar.

Volume of Distribution (V_d)

- *Definition*: It is the volume of fluid into which a drug is distributed.
- *Serum concentration of a drug* = Total body amount of the drug/ V_d

Classes of Drugs

- *Class I*: All the drug in the system binds to plasma proteins, so the free drug concentration is *low*.
- *Class II*: Partially binds to plasma proteins, so the free drug concentration is *high*
- *Note*: Typically, class II drugs replace class I drugs from their binding sites on plasma proteins; hence, increasing their free plasma concentrations e.g., sulfa drugs (class II) replace tolbutamide (class I)

Drug Metabolism

- Most drugs pass through two phases in order; however, some drugs skip phase I, while others are metabolized in reverse order (e.g., isoniazid [INH]).
- *Phases*:
 1. Phase I: Oxidation, reduction, or hydrolysis; performed by *cytochrome P-450*
 2. Phase II: Conjugation or acetylation
- *Regulators*: If the metabolism of a drug is inhibited, its free concentration will be high, and vice versa. Here are some examples of drug metabolism regulators:
 1. Metabolism inhibiting drugs, e.g., cimetidine, furosemide, chlorpromazine; inhibit cytochrome P-450
 2. Metabolism stimulating drugs, e.g., phenytoin, barbiturates, rifampin; stimulate cytochrome P-450

$t_{1/2}$ and Elimination

- $t_{1/2}$: It is the period of time needed for the drug concentration in the body to be reduced by 50%. $t_{1/2} = 0.7 \times V_d/\text{Drug clearance}$. Note: 90% of the steady state concentration of a drug is achieved in 3.3 $t_{1/2}$.

- *Drug elimination*: 50% of drugs concentration is excreted in 1 $t_{1/2}$. Elimination (excretion) rate = Total drug clearance \times Serum drug concentration. Note: In first-order kinetics, drug elimination is *directly proportional* to its serum concentration. Read more about kinetics in Chapter 11, Biochemistry.

Potency and Efficacy (Fig. 9.1)

- *Potency*: It is the drug dose that achieves 50% of maximum response.
- *Efficacy*: It is the maximum response of a drug.
- *Note*: Competitive inhibition decreases the *potency* of drugs, while noncompetitive inhibition decreases *efficacy* of drugs.

Miscellaneous

- *Therapeutic index* = Toxic dose of a drug/Effective dose. The lower the therapeutic index, the more toxic the drug is, e.g., warfarin. Similarly, safe drugs with low risk of toxic effects have high index, e.g., penicillin.
- *Drug-body relationship*:
 1. *Tolerance*: Loss of the body's response to a certain drug, which could be overcome by increasing the drug's dose
 2. *Tachyphylaxis*: A tolerance reaction that occurs after only one or two doses
 3. *Hyperreactivity*: Response of the body to only very minimal doses of a drug

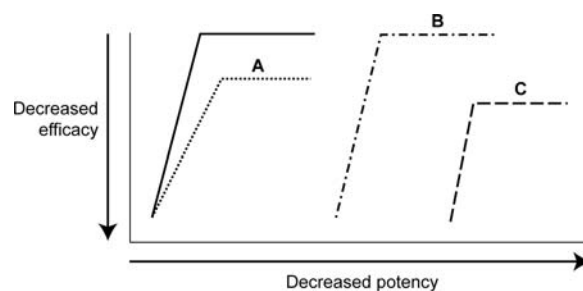


FIG. 9.1 Curve showing maximum potency and efficacy demonstrated by the solid line. Line A is shifted downwards: same potency, lower efficacy. Line B is shifted to the right: same efficacy, lower potency. Line C is shifted downward and to the right: lower potency and lower efficacy

Autonomic Nervous System

- *Parasympathetic nervous system: Essential for life, and functions through muscarinic receptors*
- *Sympathetic nervous system: Functions through norepinephrine on adrenergic receptors*
- *Adrenal medulla: Secretes epinephrine, which acts on adrenergic receptors*
- *Nicotinic receptors: Highest affinity is to nicotine, and lowest is to muscarine. They are blocked by different drugs at different levels, as follows:*
 1. Ganglia level: Blocked by *hexamethonium*
 2. Neuromuscular junctions: Blocked by *tubocurarine*
- *Muscarinic receptors: Highest affinity is to muscarine, and lowest is to nicotine. The most commonly tested receptors are:*
 1. M1: Present in *gastric parietal cells*, and blocked by *pirenzepine*, hence used in treatment of peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD)
 2. M2: Present in cardiac muscle
 3. M3: Present in smooth muscle
- *Note: Skeletal muscles are stimulated though nicotinic receptors.*

Cholinergic Agonists

- *Types:*
 1. Direct activators: acetylcholine, bethanecol, carbachol, and pilocarpine
 2. Cholinesterase inhibitors: block the breakdown of acetylcholine, and are divided into:
 - *Reversible:* Edrophonium, pyridostigmine, neostigmine, physostigmine
 - *Irreversible:* Echothiophate and isoflurophate. Note: *They destroy the cholinesterase by phosphorylating it.*
- *Acetylcholine synthesis:*
 1. Choline is transported inside the neuron along with sodium. This step is inhibited by *hemicholinium*.
 2. Choline-acetyl transferase (CAT) binds choline to acetyl coenzyme A (CoA) to form *acetylcholine*, which is then stored (with adenosine triphosphate [ATP]) in vesicles.

3. When the nerve is stimulated, *calcium influx* occurs and acetylcholine is released from the vesicles. This step is *inhibited by botulinum toxin*, and is *stimulated by black widow spider venom*.

- *Clinical applications:*

1. Pilocarpine: *Used in emergency cases of glaucoma*. It decreases intraocular pressure by opening the trabecular meshwork around canal of Schlemm.
 2. Bethanecol and carbachol: They act mainly on muscarinic receptors, and are used to treat *post-operative atonic bladder and ileus*.
 3. Edrophonium: Used in the *diagnosis of myasthenia gravis (Tensilon test)*
 4. Pyridostigmine: Used in *treatment of myasthenia gravis*, and has a longer half-life than neostigmine, which is also used for the same disease
- *Pralidoxime:* Activates the cholinesterase enzyme. Used to treat *organophosphate poisoning (salivation, sweating, miosis, and diarrhea)*, e.g., *insecticide exposure*

Cholinergic Antagonists

- *Antimuscarinic:*
 1. Atropine: *Mydriatic, cycloplegic, antispasmodic, and antisecretory*. Used clinically to treat *symptomatic bradycardia, organophosphate poisoning, and to dilate the pupil before a retinal exam*. Atropine can induce an attack of narrow angle glaucoma in susceptible patients.
 2. Ipratropium: Used as a bronchodilator inhaler to treat *asthma and chronic obstructive pulmonary disease (COPD)*
 3. Scopolamine: Used as a prophylaxis against *motion sickness*
- *Neuromuscular junction blockers:*
 1. Centrally acting:
 - Diazepam and baclofen: *Increase gamma-aminobutyric acid (GABA) levels*
 - Dantrolene: *Decrease calcium release from the sarcoplasmic reticulum*
 2. Peripherally acting: e.g., succinylcholine and tubocurarine
 3. Competitive (nondepolarizing) and noncompetitive (depolarizing) (Table 9.1)

TABLE 9.1 Neuromuscular blockers.

	Competitive (nondepolarizing)	Noncompetitive (depolarizing)
Example	Curare (competitive)	<i>Succinylcholine</i>
Mechanism of action	<ul style="list-style-type: none"> • Low dose: compete with acetylcholine for the Ach receptors, which could be overcome by administering high doses of acetylcholine • High dose: completely block the ion channels, so administering high doses of acetylcholine would <i>not</i> reverse the action of these blockers 	<ul style="list-style-type: none"> • Phase I: depolarization; cannot be reversed • Phase II: repolarization; can be reversed by cholinesterase inhibitors • Action: muscle <i>fasciculation</i>, followed by paralysis
Elimination	<ul style="list-style-type: none"> • Competitive blockers <i>cannot cross the blood–brain barrier</i> • Elimination takes place mainly by <i>redistribution</i>, plus more pathways for certain drugs as described below • Vecuronium and rocuronium: by <i>hepatic deacetylation</i> • Atracurium: by <i>ester hydrolysis in the plasma</i>; <i>atracurium is the only competitive neuromuscular junction (NMJ) blocker whose dose does not need to be adjusted in patients with renal insufficiency</i> 	<ul style="list-style-type: none"> • This class of NMJ blockers is eliminated by <i>cholinesterase</i> • Deficiency of cholinesterase leads to prolonged action of these medications, which leads to <i>paralysis of respiratory muscles and fatal apnea</i>
Miscellaneous	<ul style="list-style-type: none"> • The effect of these blockers is noted first in <i>small muscles</i>, e.g., facial muscles, and they <i>affect the diaphragm last</i> • Rocuronium: has rapid onset of action, and is used before endotracheal (ET) intubations • Vecuronium and atracurium: used for short minor procedures • Tubocurarine: stimulates <i>histamine</i> release 	<ul style="list-style-type: none"> • Noncompetitive blockers cause an <i>increase in intraocular pressure</i> and in <i>serum potassium levels</i> • Succinylcholine + halothane = <i>malignant hyperthermia</i>; patients suffer from intra- or postoperative <i>muscle rigidity, hyperthermia, and hypercarbia</i>; treatment: 100% O₂ + <i>dantrolene, which inhibits the release of calcium from the sarcoplasmic reticulum</i>

Adrenergic Agonists

- *Norepinephrine synthesis*:
 1. Begins with *tyrosine* uptake into the neuron. Tyrosine is hydroxylated into *DOPA*, which is later processed into *dopamine*.
 2. Dopamine is packed into vesicles and converted into norepinephrine (NE). This packing process is inhibited by *reserpine*.
 3. Nerve stimulation causes calcium influx and release of NE from the vesicles. This step is inhibited by *guanethidine* and *bretylum*.
 4. After release into the synaptic cleft, NE faces one of four destinies:
 - Reuptake into the presynaptic neuron: Inhibited by *cocaine* and *imipramine*
 - Binds to pre- or postsynaptic receptors
 - Metabolized *intranuronally* by monoamine oxidase (*MAO*) into dehydroxymandelic acid (*DHMA*)
 - Metabolized *postsynaptically* by catechol-O-methyl transferase (*COMT*) into vanillyl-mandelic acid (*VMA*)
- *Adrenergic receptors*:
 1. Alpha receptors: Respond best to *epinephrine*, and are divided into:
 - Alpha-1 receptors: Act *postsynaptically* through *stimulation of phospholipase C*; cause vasoconstriction and mydriasis
 - Alpha-2 receptors: Act *presynaptically* through *inhibition of adenylyl cyclase*; inhibit insulin and norepinephrine release
 2. Beta receptors: Respond best to *isoproterenol*, and are divided into:
 - Beta-1 receptors: Abundant in *cardiac muscle*; cause lipolysis, positive inotropy (increased contractility) and positive chronotropy (increased heart rate)
 - Beta-2 receptors: Cause *vasodilatation, bronchodilation, and glycogenolysis*
- *Epinephrine*: Stimulates beta-2 receptors in low doses, and alpha receptors in high doses (Table 9.2). It causes bronchodilation and vasoconstriction. It is a lifesaving medication in the setting of anaphylactic shock, angioedema, asthma, and

TABLE 9.2 Effects of epinephrine, norepinephrine (NE), and isoproterenol.

	Epinephrine	Norepinephrine	Isoproterenol
Systolic blood pressure (SBP)	Increase	Increase	Increase
Diastolic blood pressure (DBP)	Decrease	Increase	Decrease
Heart rate	Increase	Decrease	Increase
Peripheral resistance	Decrease	Increase	Decrease

Note the similarity between epinephrine and isoproterenol. Effect of epinephrine on SBP is inhibited by phenoxybenzamine, while its effect on DBP is inhibited by propranolol.

open-angle glaucoma. Side effects: Tachycardia and hypertension.

- *Norepinephrine*: Used in cases of shock (Table 9.2). Side effects: It may *decrease* renal blood flow.
- *Isoproterenol*: Used in the treatment of acute asthma attacks (Table 9.2)
- *Dopamine*: *Drug of choice in cases of shock* due to its *positive inotropic action*
- *Dobutamine*: Increases cardiac output but can precipitate atrial fibrillation. Used in cases of *congestive heart failure (CHF)* and *inferior wall myocardial infarction*. Note: *Dobutamine does not increase renal blood flow*.
- *Clonidine*: Acts through *agmatine* on *alpha-2 receptors* to decrease blood pressure. Note: Sudden stoppage of clonidine can cause *rebound hypertension*.
- *Indirect adrenergic agonists*:
 1. Mechanism: *Stimulate norepinephrine release*
 2. Amphetamine: Used to treat *narcolepsy* and attention deficit hyperactivity disorder (*ADHD*)
 3. Tyramine: Present in cheese and wine, and is metabolized by *MAO*, so patients must avoid tyramine when taking MAO inhibitors.
- *Direct- and indirect-acting adrenergic agonists*, e.g., ephedrine, used clinically as a *decongestant*

Adrenergic Antagonists

- *Alpha blockers*:
 1. Phenoxybenzamine:
 - *Noncompetitive, irreversible alpha antagonist*. It antagonizes the effect of epinephrine and NE on blood pressure.
 - Indications: *Drug of choice for treatment of hypertension in cases of pheochromocytoma*
 - Side effects: Hypotension and tachycardia
 - Contraindications: Coronary artery disease (CAD)
 - Note: Phentolamine is another *reversible alpha antagonist*.

2. Prazosin, terazosin, and doxazosin:

- Metabolites pass in the urine, except *doxazosin's*, which pass in *stool*.
- Indications: Hypertension and benign prostatic hypertrophy (BPH)
- Side effects: Hypotension, known as *first-dose syncope*; prevented by starting the patient on *one third of the dose and increasing it gradually*. Also make sure that the patient *takes the pill at bedtime*.

3. Yohimbine: An *alpha-2 antagonist* used to treat *impotence*

- *Beta-blockers*: Discussed later in detail

1. Propranolol: Used to relieve thyrotoxicosis-induced tachycardia
2. Timolol: Used to treat *open-angle glaucoma*
3. Nadolol: A *long-acting beta-blocker*, used to treat *social phobias*
4. Cardioselective beta-blockers, e.g., atenolol, esmolol, pindolol
5. Labetalol: *Combined alpha- and beta- blocker*

Parkinson's Disease

Pathophysiology

- *Mechanism*: Depletion of *dopamine* in the *substantia nigra*
- *Causes*: Multiple; always consider exposure to 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (*MPTP*) or *metoclopramide*.
- *Clinical picture*: *Rigidity, resting tremor, and bradykinesia*.

L-Dopa

- It is the *mainstay of treatment*.
- *Mechanism*: It *crosses the blood-brain barrier* and is then converted in the *substantia nigra* to dopamine.

It is not converted to dopamine in the peripheral circulation; hence there are no systemic dopaminergic effects.

- *Wearing-off effect*: Due to degeneration of the substantia nigra
- *On-off phenomenon*: Fluctuation of L-dopa levels, due to its *short half-life*
- *Sinemet*: L-dopa is combined with carbidopa in one pill. Carbidopa inhibits *dopamine decarboxylase*, hence maintains higher L-dopa concentrations.
- *Side effects*: 4 C's:
 1. Emetic Center: Vomiting
 2. Central nervous system (CNS): Dyskinesia, which entails involuntary, purposeless movements
 3. Cardiovascular system (CVS): Tachycardia and arrhythmias
 4. Catecholamine oxidation: Brownish discoloration of the saliva and urine
- *Contraindications*:
 1. Vitamin B₆: It increases the peripheral metabolism of L-dopa.
 2. Do not give with MAO inhibitors: Hypertensive crisis, due to high levels of catecholamines
- *Note*: L-dopa should always be taken on an empty stomach, as the presence of *leucine* or *isoleucine* in the stomach can prevent L-dopa absorption.

Other Drugs

- *Bromocriptine*: A dopamine agonist
- *Antimuscarinic agents*, e.g., benztropine, which treats all symptoms of parkinsonism *except bradykinesia*
- *Amantadine*: An antiviral that *increases synthesis and uptake of dopamine*
- *Selegiline*: *MAO-B* inhibitor that increases dopamine levels. Note: MAO-A metabolizes NE and serotonin only, not dopamine.

Sedatives and Hypnotics

Benzodiazepines (BDZs)

- *Mechanism*: Stimulate *GABA-A*, which increases neuronal *chloride influx*
- *Action*: Sedative in low doses, and hypnotic in high doses by acting on *stage 4* of the sleep cycle
- *Metabolism*: *In the liver*, and excreted in the urine
- *Indications*:

1. BDZ of choice in alcohol withdrawal and delirium tremens: *Chlordiazepoxide*
 2. BDZ of choice in grand-mal seizures: *Diazepam*
 3. BDZ of choice in absence seizures: *Clonazepam*
 4. BDZ of choice in panic attacks: *Alprazolam*
 5. BDZ of choice to *initiate* sleep: *Triazolam*, which is short-acting
 6. BDZ of choice to *maintain* sleep: *Temazepam*, which is intermediate-acting
- *Notes*:
 1. *GABA-B* works on *K* channels, not *chloride* channels.
 2. BDZ rebound causes an increase in sleep latency.
 3. BDZ withdrawal causes *anxiety, palpitations, and withdrawal seizures*. Withdrawal is treated by giving *BDZ*.

Barbiturates

- *Mechanism*: Same as BDZ, *plus inhibition of the Na-K pump*
- *Examples*:
 1. Thiopental: A barbiturate used for *induction of anesthesia*
 2. Phenobarbitone: The drug of choice to treat *pediatric febrile convulsions*
- *Note*: Barbiturates are *not* used for analgesia.

Other Drugs

- *Zolpidem (Ambien)*: Short-acting hypnotic
- *Buspirone (BuSpar)*: A sedative; acts as a *serotonin 1A agonist*
- *Flumazenil*: A *GABA antagonist*; used to reverse *BDZ action in overdose*

Opioids

Pain and Sensation Receptors

- *Periaqueductal gray matter*: In dorsal column of spinal cord
- *Medial thalamus*: Deep pain center
- *Amygdala of limbic system*: Emotions

Morphine

- *Mechanism*: Inhibits the release of pain stimuli and substance P

- **Actions:**
 1. Analgesia: Due to *increase in the pain threshold*
 2. *Euphoria*: Due to stimulation of the *ventral tegmentum*
 3. *Pin-point pupils*: Due to stimulation of *Edinger-Westphal oculomotor nucleus*
 4. Emesis: Due to stimulation of *chemoreceptor trigger zone*
 5. Fluid retention: Due to *stimulation of antidiuretic hormone (ADH) secretion*
 6. Others: Antitussive, increases intracranial pressure and histamine release, and also causes constipation
- **Indications:** *Pain, diarrhea, and cough*
- **Elimination:** In urine and bile in the form of *morphine-6-glucuronide*
- **Tolerance:** Common to all effects except *constipation* and *pupillary constriction*

Other Opioids

- **Meperidine:** Used for analgesia. Side effects: Increase in peripheral blood flow and dilated pupils
- **Methadone:** Used to treat patients suffering *morphine and heroin withdrawal*
- **Propoxyphene:** A derivative of *methadone*, which works best when combined with acetaminophen. Toxicity: Cardiotoxicity and pulmonary edema.
- **Codeine:** Best when combined with acetaminophen, mainly as an antitussive.

Naloxone

- An opioid antagonist that works by *competitive inhibition*; works in *30 seconds* and maintains its action for approximately *2 hours*
- **Indications:** To reverse opioid-induced respiratory depression or coma
- **Note:**
 1. Naltrexone is another antagonist with a half-life of *2 days*
 2. Pentazocine and buprenorphine: Opioid *agonist/antagonist*. They cause analgesia by acting on the *spinal centers*.

Opiates Withdrawal

- **Stages of withdrawal (“cold turkey”):**
 1. First stage: *Lacrimation, rhinorrhea, and muscle aches*

2. Second stage: *Excessive sweating*
3. Third stage: *Excessive micturition and defecation, vomiting, and diarrhea*

- **Treatment of withdrawal:** *Methadone and clonidine*

Antidepressants

- **Facts:** Know these two facts well: A patient’s mood is regulated by *norepinephrine* and *serotonin*, and mania is the mirror image of depression.
- **Medications:** TCA, SSRI, MAOI, and mood stabilizers

Tricyclic Antidepressants (TCAs)

- TCAs take *3–4 weeks* to achieve a therapeutic effect.
- **Mechanism:** They *block the reuptake of norepinephrine*.
- **Indications:**
 1. Major depressive disorder
 2. Imipramine: TCA of choice to treat *enuresis*
 3. Clomipramine: TCA of choice to treat *obsessive-compulsive disorder (OCD)*. *Note that the drug of choice in general to treat OCD is SSRI.*
- **Side effects:**
 1. *Anticholinergic effects:* Urinary retention, constipation, xerostomia
 2. Toxicity (low therapeutic index): Hypotension, *prolonged Q-T interval*
- **Note:** Amoxapine and maprotiline are second-generation TCAs.

Selective Serotonin Reuptake Inhibitors (SSRIs)

- **Mechanism:**
 1. Inhibit *presynaptic* serotonin reuptake
 2. *Inhibit cytochrome P-450* system, hence increasing free levels of other drugs
- **Indications:** Major depressive disorder, OCD, anorexia and bulimia nervosa, *premature ejaculation*, and panic attacks
- **Side effects:** *Delayed ejaculation*, hence used to treat *premature ejaculation*. It also causes insomnia, tremors, and weight loss.
- **Examples:** Fluoxetine, paroxetine, sertraline

Monoamine Oxidase Inhibitors (MAOIs)

- *Indications: Atypical and resistant depression*
- *Complications:*
 1. Tyramine hypertensive crisis: If given with a tyramine-containing substance (red wine or cheese). Treatment: *Phentolamine plus nifedipine.*
 2. Serotonin syndrome: If given with SSRI. Clinical picture: *Muscle rigidity, hyperreflexia, and clonus.* Treatment: Serotonin antagonist, e.g., *Cyproheptadine.*
- *Examples:* Phenelzine, tranylcypromine

Mood Stabilizers

- *Mechanism:* Lithium acts via the *phosphatidylinositol system.*
- *Indication: Bipolar disorder*
- *Lithium side effects:*
 1. *Teratogenicity: Ebstein anomaly.*
 2. *Hypothyroidism*
 3. *Nephrogenic diabetes insipidus*
 4. *Toxicity: Vomiting, diarrhea, tremors, and nystagmus.* Note: Therapeutic level of lithium: 0.6–1.2 mEq/L
- *Examples:* Lithium, carbamazepine

Antipsychotics (Neuroleptics)

Mechanism

- *General mechanism: Block dopamine (D2) receptors in the mesolimbic system.* Note: There are five dopamine receptors; only the *first and fifth activate adenylyl cyclase enzyme (via Gs)*, while the rest inhibit it (via Gi).
- *Clozapine and risperidone: Block 5-hydroxytryptamine-2 (5-HT-2) receptors*
- *Chlorpromazine: Blocks adrenergic and muscarinic receptors*

Indications

- *Psychosis*
- *Vomiting:* All antipsychotics *except thioridazine* are strong antiemetics, as they also block *D2 receptors* present in the chemoreceptor trigger zone. However, we do not use these drugs in practice for that purpose.

Side Effects

- *Akathisia:* Subjective feeling of restlessness. *Treatment:* Propranolol.
- *Tardive dyskinesia:* Abnormal movements and posturing. *Prevention:* Benztropine. *Treatment:* Discontinue the drug and switch to another neuroleptic.
- *Neuroleptic malignant syndrome:* Rigidity and hyperthermia, due to severe actin-myosin coupling resulting in excessive ATP production. Treatment: *Dantrolene.*
- *Anticholinergic effects,* e.g., urinary retention, constipation, xerostomia.
- *Drug-specific side effects:*
 1. Clozapine: *Agranulocytosis*
 2. Chlorpromazine: *Bluish-gray skin discoloration*
 3. Thioridazine: *Orthostatic hypotension and retinal pigmentation*

Anticonvulsants

- *General mechanism: Inhibit initiation and transmission of signals*
- *General side effect:* Most of the drugs listed below cause *osteomalacia*

Phenytoin

- *Mechanism: Blocks sodium channels*
- *Elimination:* Metabolized by *hepatic hydroxylation*
- *Side effects:*
 1. Gingival hyperplasia
 2. Megaloblastic anemia: Due to *vitamin B₁₂ deficiency*
 3. Hyperglycemia: Due to *inhibition of insulin secretion*
 4. Polyuria: Due to *inhibition of ADH secretion,* causing central diabetes insipidus
 5. Fetal hydantoin syndrome: Newborn suffers *cleft lip or cleft palate, nail hypoplasia, and cupid bow of upper lip (double curved upper lip resembling cupid bow)*

Carbamazepine

- *Mechanism: Blocks sodium channels*
- *Indications:* Grand-mal seizures, trigeminal *neuralgia,* glossopharyngeal *neuralgia,* and bipolar disorder
- *Side effects:* Bone marrow depression and hepatotoxicity

Other Anticonvulsants

- *Phenobarbitone*: Mechanism: Increases levels of *GABA*. Side effects: *Rash*. It is the drug of choice to treat *pediatric febrile convulsions*. Note: *Primidone* is the precursor of phenobarbitone.
- *Valproic acid*: Acts by increasing *GABA* levels. It is hepatotoxic.
- *Lamotrigine*: Acts by inhibiting the release of glutamate and aspartate
- *Ethosuximide*: Causes *Stevens-Johnson syndrome* (rash and renal failure)

Drugs of Choice

- *Grand-mal seizures*: *Phenytoin* or *carbamazepine*
- *Absence (petit-mal) seizures*: *Ethosuximide* or *valproic acid*
- *Myoclonic seizures*: *Clonazepam*
- *Febrile seizures*: *Phenobarbitone*
- *Status epilepticus*: *Diazepam* first, followed by fosphenytoin

Glaucoma

- *Decrease aqueous humor synthesis*:
 1. Diuretics: Mainly carbonic anhydrase inhibitors, e.g., acetazolamide
 2. Beta-blockers, e.g., timolol
- *Increase aqueous humor excretion*:
 1. Cholinergic agonists, e.g., pilocarpine: Stimulate contraction of the ciliary muscles and increase the outflow of aqueous humor through the trabecular meshwork
 2. Alpha-agonists, e.g., epinephrine
 3. Prostaglandins, e.g., latanoprost

Anesthesia

- *Steps*: Starts with *induction*, followed by *maintenance* and finally *recovery*
- *Stages*: There are four stages of anesthesia:
 1. Stage I: *Analgesia*
 2. Stage II: *Excitement*. Easily bypassed by giving *thiopental*
 3. Stage III: *Surgical anesthesia*
 4. Stage IV: *Fatal*, due to inhibition of respiratory and vasomotor centers

Inhaled Anesthetics

- *Minimum alveolar Concentration (MAC)*: It is the amount of anesthetic needed to anesthetize 50% of patients. *The lower the MAC, the stronger the drug*; e.g., halothane is a strong anesthetic (low MAC), while nitric oxide is a weak anesthetic (high MAC).
- *Blood/gas partition coefficient*: Solubility of the drug in the blood is determined by this coefficient. The higher the coefficient, the more time the drug needs to achieve induction or recovery. Note: *Nitric oxide has a very low coefficient; hence, it is the fastest anesthetic to achieve steady state, and is the first to be cleared from the body.*
- *Clinical applications*:
 1. Halothane: A bromide-containing drug. It is the *anesthetic of choice for children*. It is hepatotoxic in adults if used more than once in a *3-week period*.
 2. Methoxyflurane: *Most potent inhalant anesthetic*. It does not lead to uterine atony; therefore, it is the *preferred anesthetic during obstetric procedures*.
 3. The fluranes, e.g., enflurane, isoflurane. They are contraindicated in patients with renal failure.
- *Notes*:
 1. Diffusion of the drug into the lungs is directly proportional to the *functional residual capacity (FRC)*.
 2. All inhaled anesthetics increase cerebral perfusion and cause bronchodilation.

Intravenous Anesthetics

- *Thiopental*: A potent anesthetic that bypasses the excitation stage of anesthesia. It has a short half-life and carries the risk of laryngospasm.
- *Propofol*: Lowers intracranial pressure. Ketamine and propofol may cause *dissociative anesthesia*.
- *BDZ*, e.g., midazolam; reversed with *flumazenil*
- *Opioids*, e.g., fentanyl; reversed by *naloxone*

Local Anesthetics

- Given with epinephrine *to prolong their absorption*; however, should not be combined with epinephrine in end organs (ears, nose, fingers, penis, and toes)
- *Note*: Tetracaine and bupivacaine have a rapid onset and long duration of action.

Diuretics

Thiazides

- *Hydrochlorothiazide (HCTZ) is recommended as the first line of therapy for hypertension (HTN) patients.*
- *Mechanism:*
 1. Decreases NaCl absorption at the level of the distal convoluted tubule (DCT)
 2. Vasodilatation through release of *prostaglandins*. This leads to a decrease in peripheral resistance (PR) and cardiac output (CO): ($BP = CO \times PR$).
- *Indications:*
 1. CVS: Hypertension, CHF
 2. Renal: Nephrogenic diabetes insipidus
 3. Nephrotic syndrome: Metolazone is used for treatment for some cases.
- *Side effects:*
 1. *Two hypo's:* Hypotension and hypokalemia
 2. *Three hyper's:* Hypercalcemia, hyperuricemia, and hyperglycemia
- *Contraindications:* Severe, recurrent gout attacks and hypercalcemia
- *Examples:* Beside HCTZ, other thiazides include chlorthalidone and indapamide.

Loop Diuretics

- *Mechanism:* Inhibit $Na/K/2Cl$ co-transport at the level of *thick ascending limb of loop of Henle*
- *Indications:*
 1. HTN and fluid overload, e.g., CHF exacerbation
 2. Hypercalcemia
- *Side effects:* *Ototoxicity, nephrotoxicity, hypocalcemia, and hypokalemia*
- *Examples:* *Furosemide. Bumetanide and torsemide* are stronger loop diuretics.

K-Sparing Diuretics

- *Spironolactone:*
 1. Mechanism: K-sparing, *antialdosterone* diuretic that acts via *canrenone*
 2. Indication: *HTN secondary to hyperaldosteronism*

3. Side effects: *Gynecomastia* and hyperkalemia

- *Amiloride and triamterene:*
 1. Mechanism: Block *Na channels in collecting ducts*
 2. Side effects: Leg cramps and hyperkalemia

Carbonic Anhydrase Inhibitors

- *Mechanism:* Inhibit reabsorption of HCO_3 in the *proximal convoluted tubules*. This result in *hyperchloremic metabolic acidosis with alkaline urine*.
- *Indications:*
 1. Open-angle glaucoma
 2. Prevention of *mountain sickness syndrome* (cerebral and pulmonary edema and nausea)
 3. Elevated intracranial pressure
- *Example:* Acetazolamide (*Diamox*)

Congestive Heart Failure (CHF)

- *Definition:* It is failure of the pumping function of the heart; could be systolic or diastolic, left- or right-sided, or even low or high output failure. Most coronary ischemia leads to *left-sided systolic dysfunction*. Discussed in Chapter 10, Pathophysiology.
- *Drugs:*
 1. Diuretics: Discussed earlier in detail
 2. Vasodilators: Angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blockers (ARBs). *Hydralazine combined with nitrates* have been proven to be beneficial in *African-American* patients with CHF.
 3. Inotropic agents: Digoxin and phosphodiesterase inhibitors
 4. Beta-blockers: Every patient with CHF *must be* on beta-blockers.

Diuretics

- Low cardiac output causes decreased renal blood flow, which leads to stimulation of the renin-angiotensin-aldosterone system and ultimately salt and water retention.
- *Examples:* *Furosemide, hydrochlorothiazide*
- *Note:* Spironolactone is beneficial in *severe* CHF, and has been proven to *reduce morbidity and mortality*.

Angiotensin-Converting Enzyme Inhibitors (ACEIs)

- *Mechanism:*
 1. Inhibit conversion of angiotensin I to angiotensin II, which leads to inhibition of aldosterone formation. This then leads to decreased preload and afterload.
 2. *Decrease remodeling of the myocardium* (remodeling worsens CHF), and *delay progression of diabetic nephropathy*.
- *Side effects:*
 1. Hypotension
 2. Hyperkalemia and elevated creatinine
 3. Dry cough: Due to accumulation of *bradykinins* in the lungs. If this occurs, you can switch the patient from ACEI to ARB.
 4. Angioedema: *More common in African Americans*
- *Contraindications:* *Bilateral renal artery stenosis. Note that ACEIs are the drugs of choice for treatment of HTN in cases of unilateral renal artery stenosis.*
- *Examples of ACEI:* Enalapril, lisinopril, captopril
- *Examples of ARBs:* Losartan, irbesartan

Digoxin

- *Mechanism:* *Inhibits Na-K adenosine triphosphatase (ATPase)*, which leads to increased intracellular Na and Ca, and in turn leads to increased myocardial contractility.
- *Indications:*
 1. *Left-sided systolic dysfunction (not right or diastolic)*
 2. Arrhythmia: Decreases conduction velocity in atrioventricular (AV) node
- *Elimination:* Excreted in the *urine*
- *Toxicity:* Hypokalemia, nausea and vomiting, *yellow vision*, and haloes. Toxicity risk is increased in the presence of *hypokalemia, hypomagnesemia, hypercalcemia, diuretics, or quinidine*.
- *Treatment of toxicity:* *Potassium and digoxin binding fragments (Digibind)*
- *Notes:*
 1. Digitoxin has *longer half-life and more affinity* than digoxin, and is excreted in *bile*.
 2. Digoxin and digitoxin have been proven to decrease the frequency and duration of hospitalization secondary to CHF; however, *they do not decrease mortality*.

Phosphodiesterase Inhibitors

- *Mechanism:*
 1. Inhibit phosphodiesterase enzyme, which leads to increased cAMP. cAMP activates Ca channels by phosphorylation, leading to *Ca influx*.
 2. *Inodilators:* These drugs act as *inotropics and vasodilators*.
- *Examples:* Amrinone, milrinone

Beta-Blockers

- *Mechanism:*
 1. Negative inotropic and negative chronotropic action, leading to *decreased myocardial oxygen consumption*
 2. Block the renin-angiotensin-aldosterone system
- *Indications:* Hypertension, chronic glaucoma, chronic migraine, and *thyrotoxicosis*. Any patient with CHF or CAD *must be placed on beta-blockers*, as they *decrease myocardial oxygen consumption*.
- *Side effects:* Bradycardia and AV block, hypotension, sexual dysfunction, fatigue
- *Contraindications:*
 1. Vasospastic (Prinzmetal) angina: It allows free vasoconstrictor alpha action.
 2. Diabetes mellitus (relative contraindication): It masks signs of hypoglycemia. Also cause *fasting hypoglycemia* due to inhibition of *glycogenolysis*.
 3. Severe asthma and chronic obstructive pulmonary disease (COPD): It might worsen breathing.
- *Complication:* Sudden stoppage leads to *rebound tachycardia and arrhythmia*.
- *Examples:* Carvedilol, metoprolol, propranolol
- *Note:* They have been proven to significantly *decrease morbidity and mortality secondary to CHF*.

Antiangina

Nitrates

- *Mechanism:* Metabolized to *nitric oxide*, which inhibits the myosin light chain kinase of vascular smooth muscles via phosphorylation. This leads to elevated cGMP and vasodilatation of blood vessels, including coronary arteries.
- *Indications:* *Angina, pulmonary edema, and esophageal spasm*
- *Side effects:* *Throbbing headache*

- *Disadvantages: Tolerance*, so a nitrate-free interval of at least 6 hours daily is necessary.
- *Examples:* Nitroglycerin, isosorbide dinitrate, Iso-sorbide mononitrate

Calcium Channel Blockers

- *Nifedipine:*
 1. Mechanism: Coronary and peripheral vasodilator. *It does not have any inotropic or chronotropic actions.*
 2. Side effects: Hypotension, flushing, and headache
- *Verapamil:*
 1. Mechanism: Negative inotropy and chronotropy. *Its effects on the coronaries are very mild.*
 2. Side effects: *Constipation* and increased risk of digoxin toxicity
- *Diltiazem:*
 1. Mechanism: Vasodilator, and negative inotropy and chronotropy
 2. Indications: Angina, and rate control in arrhythmias, e.g., atrial fibrillation

Antiarrhythmics

- Most common cause of arrhythmia is *reentry due to unidirectional block*.
- *Classes and drugs:* See Table 9.3.

Clinical Applications

- *Atrial fibrillation:* Current treatment focuses on *anticoagulation* with warfarin (target international normalized ratio [INR]: 2–3), and *controlling the heart rate* with digoxin, beta-blockers, or calcium channel blockers.
- *Ventricular tachycardia/fibrillation:* Treated by electrical cardioversion, epinephrine, lidocaine, and amiodarone
- *Torsades de pointes:* Polymorphic ventricular tachycardia; treated in the same way as ventricular tachycardia *plus magnesium and overdrive pacing*

Antihypertensives

- Blood pressure is controlled by baroreceptors in the *aortic arch* and *carotid sinus*, signaling the CNS via *vagus* and *glossopharyngeal* nerves, respectively.
- *Definition:* Hypertension is persistently elevated blood pressure beyond 140/90.
- *Types:* Hypertension could be only *systolic* (e.g., thyrotoxicosis), *diastolic*, or *both*. HTN could also be idiopathic or secondary to a cause, e.g., pheochromocytoma, hyperaldosteronism, renal artery stenosis.
- *Drugs:*
 1. Diuretics: *HCTZ is the initial drug of choice in any patient with HTN.*

TABLE 9.3 Antiarrhythmics.

Class	Mechanism	Phase of action potential affected	Medications
I	Block Na channels	IA: Phase 0 IB: Phase 3 IC: Phase 0	IA <ul style="list-style-type: none"> • Quinidine: Causes <i>Q-T prolongation</i>, digoxin toxicity, and <i>cinchonism</i> manifested by <i>tinnitus, blurry vision, and headache</i> • Procainamide: metabolized in the liver and excreted in the urine; it can cause <i>lupus-like syndrome</i>, which is diagnosed by positive <i>antihistone antibodies</i> • Disopyramide: a peripheral vasoconstrictor with anticholinergic effects IB <ul style="list-style-type: none"> • E.g., lidocaine, mexiletine IC <ul style="list-style-type: none"> • E.g., propafenone, flecainide
II	Beta-blockers	Phase 4	Beta-blockers
III	Block K channels	Phase 3	<ul style="list-style-type: none"> • Sotalol: it is also a beta-blocker • Bretylium: inhibits NE release • Amiodarone: combined class I, II, III, and IV actions; side effects: <i>corneal opacity, hypo-, or hyperthyroidism and interstitial pulmonary fibrosis</i>
IV	Calcium channel blockers	All phases; it shortens the whole action potential	Calcium channel blockers

2. ACEI and ARBs: Discussed earlier
3. Beta-blockers and calcium channel blockers: Discussed earlier
4. Centrally acting medications: Alpha methyl dopa and clonidine
5. Vasodilators: Hydralazine, minoxidil, and sodium nitroprusside

Centrally Acting Medications

- *Alpha methyl dopa:*
 1. Mechanism: Decreases sympathetic outflow from the CNS
 2. Indication: *Drug of choice for hypertension during pregnancy*
- *Clonidine:* Acts through *agmatine* on *alpha-2 receptors* to decrease sympathetic outflow from the CNS. Side effects: Fluid retention. Precautions: Sudden stoppage leads to *rebound hypertension*.

Vasodilators

- *Hydralazine:* Also used in CHF. Side effects: Reflex tachycardia and lupus-like syndrome (diagnosed by positive *antihistone antibodies*).
- *Minoxidil:* Important side effect is *hypertrichosis*
- *Sodium nitroprusside:* Used as a drip in hypertensive emergencies. Side effect: *Cyanide poisoning*; treated with *nitrates and thiosulfate*.

Drugs of Choice

- *Rule:* Remember that HCTZ is the initial drug of choice in any patient with HTN, plus the following scenarios.
- *HTN plus diabetes mellitus (DM):* ACEI or ARB. They delay progression of diabetic nephropathy
- *HTN plus severe COPD or asthma:* Calcium channel blockers
- *HTN in African-Americans:* Diuretics or calcium channel blockers
- *HTN in elderly:* Diuretics or calcium channel blockers
- *HTN in pregnancy:* Alpha methyl dopa or hydralazine
- *HTN secondary to hyperaldosteronism:* Spironolactone

Antiplatelets

Salicylates (Aspirin)

- *Mechanism:* Irreversible inhibition of *cyclooxygenase 2*, which normally converts arachidonic acid to prostaglandin H_2 (*first step in thromboxane A_2 [TXA_2] synthesis*)
- *Duration of action:* Having irreversible action makes the platelets incapable of resynthesizing TXA_2 during their 7-day life cycle
- *Elimination:* Aspirin is deacetylated by means of *esterase* into salicylic acid, which has analgesic and antipyretic effects, and only in *high doses an antiinflammatory effect*.
- *Other effects:*
 1. Increase fluid and salt retention
 2. Renal failure: Large doses for long duration cause *analgesic nephropathy*
 3. Hasten the closure of ductus arteriosus
 4. Decrease the incidence of colorectal cancer
- *Complications:*
 1. *Reye's syndrome:* Occurs due to treating a viral infection in children with salicylates. Clinical picture: *Suggestive history* along with *hepatomegaly, jaundice, hypoglycemia, and hyperammonemia*. Rule: You can never go wrong with ibuprofen or acetaminophen for fever in children, *but never aspirin*.
 2. *Salicylism:* Mild toxicity manifested by *tinnitus and headache*
 3. *Salicylate toxicity:* Salicylism, *respiratory alkalosis* followed by *metabolic acidosis* and renal failure. *Treatment:* *Alkalinization of urine, and hemodialysis*. *Mechanism:* Salicylates *uncouple oxidative phosphorylation* and *stimulate the respiratory center*.
- *Note:* Alkaline urine causes increased excretion of *salicylates* and *uric acid*.

Other Antiplatelets

- *Dipyridamole:* Inhibits *phosphodiesterase* enzyme. Used in combination with aspirin to treat patients with *ischemic stroke*.
- *Clopidogrel:* Mechanism: Inhibits *binding of adenosine diphosphate (ADP)* to platelets. Indications: Recent coronary artery disease (CAD), ischemic cerebrovascular accident (CVA), and peripheral vascular disease (PVD).

- *Ticlopidine*: Mechanism: Inhibits *ADP* production. Side effect: *Neutropenia*.

Cholesterol-Lowering Agents

- See Table 9.5.

Anticoagulants

Thrombolytics

- *Mechanism*: Convert *plasminogen* to *plasmin*, which in turn breaks down fibrin.
- *Indications*:
 1. Ischemic CVA: Beneficial only in the *first 3 hours after onset of symptoms*
 2. *ST-elevation myocardial infarction*: Beneficial only in the *first 12 hours*
 3. *Pulmonary embolism with hemodynamic instability*
 4. Local anticoagulation, e.g., clotted hemodialysis catheter
- *Side effects*: Bleeding, e.g., intracranial
- *Examples*: Alteplase (TPA), urokinase, streptokinase,
- heparin, and warfarin (Table 9.4).

Asthma and Chronic Obstructive Pulmonary Disease (COPD)

Asthma

- *Inhaled steroids*, e.g., beclomethasone, fluticasone. It is the mainstay of therapy. Steroids *suppress the hyperreactivity of airways* to various stimuli. Side effect: *Oral thrush*, prevented by *washing the mouth after inhalation*.
- *Beta-2 agonist inhalers*: Act as bronchodilators. They could be short acting, e.g., albuterol, or long acting, e.g., salmeterol.
- *Anticholinergic inhalers*, e.g., ipratropium. They cause bronchodilation and suppress the airways' secretions.
- *Mast cell stabilizers*, e.g., cromolyn, nedocromil. *Best for allergic asthma*. They stabilize mast cells and decrease histamine release.

TABLE 9.4 Heparin and Warfarin.

	Heparin	Warfarin
Mechanism	<ul style="list-style-type: none"> • Stimulates <i>antithrombin III</i>, which inactivates clotting factors • Enoxaparin: a low molecular weight SQ heparin as potent and efficient as unfractionated heparin, <i>but it does not prolong the activated partial thromboplastin time (aPTT)</i> 	Inhibits <i>vitamin K epoxide reductase</i> , which leads to inactivation of vitamin K–dependent clotting factors, namely <i>factors II, VII, IX, X, protein C, and protein S</i> ; this enzyme is essential for <i>carboxylation</i> of these clotting factors
Coagulation pathway	Intrinsic	Extrinsic
Route	IV or SQ, never intramuscular, as it could cause hematomas	Only oral
Coagulation profile and therapeutic goal	<ul style="list-style-type: none"> • Prolongs <i>aPTT</i> • Therapeutic goal is <i>1.5–2 times the control</i> 	<ul style="list-style-type: none"> • Prolongs prothrombin time (<i>PT</i>) and <i>international normalized ratio (INR)</i> • Therapeutic goal in most conditions is an INR of <i>2–3 (2.5–3.5 for patients with mechanical heart valves)</i>
Indications	Clotting e.g., deep venous thrombosis (DVT), pulmonary embolism	Clotting, e.g., DVT, pulmonary embolism
Use in pregnancy	Safe	Teratogenic
Side effects	<ul style="list-style-type: none"> • Bleeding tendency in susceptible patients • Heparin-induced thrombocytopenia; manifests as thrombosis or bleeding • Alopecia and osteoporosis 	Bleeding tendency in susceptible patients
Reversal	<i>Protamine sulfate</i>	<ul style="list-style-type: none"> • <i>Fresh frozen plasma</i> in emergencies or if the patient is bleeding • <i>Vitamin K</i> in nonemergency situations

TABLE 9.5 Cholesterol lowering medications.

Class	Examples	Mechanism	Indications	Side effects
Statins	Atorvastatin Simvastatin	Inhibit hepatic hydroxymethylglutaryl coenzyme A (HMG CoA) reductase enzyme, which normally converts HMG-CoA to mevalonic acid	<ul style="list-style-type: none"> • High total cholesterol • High LDL 	<ul style="list-style-type: none"> • Elevated liver enzymes • Myositis: patient presents with muscle aches and elevated creatine phosphokinase (CPK)
Fibrates	Clofibrate Gemfibrozil	<ul style="list-style-type: none"> • Stimulate lipoprotein lipase enzyme • Stimulate cholesterol excretion in bile and stools 	<ul style="list-style-type: none"> • Hypertriglyceridemia • Type III dyslipidemia 	<ul style="list-style-type: none"> • Cholesterol and gallstones • Malignancy, especially due to clofibrate
Bile acid sequestrants	Cholestyramine Colestipol	Inhibit enterohepatic circulation, so the liver uptakes LDL cholesterol from circulation to synthesize bile	<ul style="list-style-type: none"> • Type II dyslipidemia • Itching in obstructive jaundice 	<ul style="list-style-type: none"> • Deficiency of fat-soluble vitamins: A, D, E, and K • Folic acid deficiency
Niacin	Niacin	Inhibits triglyceride lipolysis in adipose tissue	<ul style="list-style-type: none"> • Low HDL • Type IIb dyslipidemia 	<ul style="list-style-type: none"> • Flushing and pruritus: prevented by taking an aspirin a half-hour before each dose • Hyperuricemia • Hyperglycemia
Probucol	Probucol	Inhibits oxidation of LDL cholesterol, thus prevents foam cell formation	<ul style="list-style-type: none"> • Atherosclerosis • Type II dyslipidemia 	Probucol prolongs Q-T interval

- *Theophylline*: Bronchodilator. Side effects: *Arrhythmia and seizures*
- *Leukotriene inhibitors*, e.g., montelukast. *Last resort in severe asthma.*

Chronic Obstructive Pulmonary Disease

- *Oxygen*: It is the mainstay of therapy, and is the only treatment that decreases morbidity and mortality of COPD patients.
- *Others*: As in asthma (see above)
- *Note*: Exacerbations of asthma and COPD are treated with breathing treatments, *short courses of systemic steroids, and antibiotics if needed.*

Gastroesophageal Reflux Disease (GERD)

H2 Blockers

- *Mechanism*: Block histamine-2 receptors
- *Indications*: GERD, peptic ulcer disease

- *Side effects*: Gynecomastia, galactorrhea, and infertility. *These effects are seen mainly with cimetidine.*
- *Notes*:

1. *H1 receptors are present in smooth muscles. H1 blockers, e.g., diphenhydramine, are used to treat allergic conditions, but might cause sedation.*
2. *H2 receptors are linked to adenylate cyclase system, while H1 receptors are linked to the phosphatidylinositol system.*

- *Examples*: Cimetidine, famotidine, ranitidine

Proton Pump Inhibitors (PPIs)

- *Mechanism*: Block *H/K-ATPase* pump in gastric parietal cells
- *Side effects*: *Achlorhydria*
- *Note*: *They are the first line of treatment for GERD and peptic ulcer*
- *Examples*: Omeprazole, lansoprazole

Antacids

- *Aluminum hydroxide*: Causes *constipation*
- *Magnesium hydroxide*: Causes *diarrhea*

- *Sodium bicarbonate*: Causes alkalosis, flatulence, and rebound hyperacidity
- *Note*: Antacids can bind drugs in the stomach, preventing their absorption, e.g., digoxin.

Helicobacter pylori

- The *most common infection worldwide*. It resides in the *gastric antrum* and causes ulcers in the *duodenal bulb*, but can also cause *gastric ulcers*.
- *Diagnosis*: *Test of choice is Clo test after antral biopsy*. Other ways include serum anti-*H. pylori* antibodies, stool *H. pylori* antigens or breath urease test.
- *Treatment*:
 1. *Amoxicillin + clarithromycin + PPI for 2 weeks*
 2. If penicillin allergy: *Metronidazole + tetracycline + bismuth for 2 weeks*

Others

- *Misoprostol*: Stimulates *prostaglandin I₂ and E₂*, which inhibits protein kinase of H/K pump. This leads to increased gastric *mucus* and *bicarbonate* secretion.
- *Mucosal protectors*, e.g., *sucralfate* and *bismuth*. *Note*: They need an *acidic medium* to react with mucus and form a protective gel layer.

Gastrointestinal (GI) Motility

Antiemetics

- Recall the two centers controlling the process of vomiting:
 1. Chemoreceptor trigger zone: In the *4th ventricle*, *outside* blood–brain barrier
 2. Vomiting center: In the *medulla oblongata*, *inside* the blood–brain barrier
- *Ondansetron*: A serotonin (5-HT-3) receptor antagonist
- *Drugs of choice*:
 1. Vertigo-induced emesis: *Meclizine*
 2. Motion sickness-induced emesis: *Scopolamine*
 3. Chemotherapy-induced emesis: *Tetrahydrocannabinol*
 4. Cisplatin-induced emesis: *Granisetron*

Constipation and Diarrhea

- *Constipation*: Treated with any of the following:
 1. Stool softeners, e.g., sodium docusate, milk of magnesia
 2. Colon irritants, e.g., castor oil, which acts via *emodin*
 3. Bulking agents, e.g., bran, which acts by *water retention in the colon*
- *Diarrhea*: Treated with any of the following:
 1. Antimotility medications, e.g., diphenoxylate, loperamide. These medications can precipitate *toxic megacolon*.
 2. Adsorbents, e.g., pectin, kaolin. *Note*: They *cannot adsorb digoxin*.
 3. Salicylates and bismuth: Act by decreasing intestinal secretions

Antibacterial

- *Folate antagonists*: Sulfonamides, trimethoprim
- *Cell wall synthesis inhibitors*: Penicillin (PCN), cephalosporins, vancomycin, imipenem
- *Protein synthesis inhibitors*: Tetracycline, aminoglycosides, macrolides, chloramphenicol, clindamycin. *Note*: Only two protein synthesis inhibitors work AT 30S of ribosome: *Aminoglycosides* and *Tetracycline*. *All others work on 50S*.
- *Others*: Quinolones, metronidazole, anti-TB drugs.

Sulfonamides

- *Mechanism*: *Para-aminobenzoic acid (PABA) analogue* that inhibits *dihydropteroate synthase*
- *Indications*:
 1. *Pneumocystis jiroveci* (formerly *Pneumocystis carinii* pneumonia [PCP]): Used in the form of *SMX/TMP*
 2. Toxoplasmosis: Used as *sulfadiazine combined with trimethoprim*
 3. Ulcerative colitis: Used in the form of *sulfasalazine*
 4. Burns: Used topically in the form of *sulfacetamide*
- *Side effects*: *Hemolysis in glucose-6-phosphate dehydrogenase (G-6-PD) deficiency* and nephrotoxicity

Trimethoprim

- *Mechanism*: Inhibits *dihydrofolate reductase* enzyme, which normally converts folate to tetrahydrofolate
- *Side effect*: *Megaloblastic anemia*

- *Notes:*

1. Trimethoprim molecules are *not charged*, so, unlike penicillin, they *can* cross the prostatic membrane and can be used to treat *prostatitis*.
2. SMX/TMP: Sulfamethoxazole/trimethoprim (SMX/TMP) combined in the ratio of 5:1. Indications: *urinary tract infection (UTI)* and *PCP*

Penicillin (PCN)

- *Mechanism:* It targets the *cross-linking* process by inhibiting *transpeptidase* and *penicillin binding proteins*. This leads to accumulation of *Penicillin* and increased activity of *Autolysins*, ending in failure of the bacteria to form cell wall.
- *Resistance:* Two main mechanisms:
 1. Release of penicillinase: It breaks the *C-N bond* of penicillin.
 2. Closure of *Porin* channels through which PCN enters the cells
- *Indications:* Staphylococci, streptococci, *Listeria monocytogenes*
- *Types of PCN:*
 1. Penicillin V (oral): Used for anaerobic oral infections, e.g., dental caries
 2. Penicillin G (intravenous): *Cannot be given orally*, as it is destroyed by HCL
 3. Penicillinase-resistant PCN, e.g., cloxacillin, dicloxacillin, nafcillin
 4. Antipseudomonas PCN, e.g., piperacillin, which is usually combined with tazobactam. Also ticarcillin and carbenicillin
 5. Broad-spectrum PCNs:
 - *Amoxicillin* + clavulanic acid: Used for subacute bacterial endocarditis
 - *Ampicillin* + sulbactam: Used for listeriosis
 - *Note:* *Clavulanic acid* and *sulbactam* are *penicillinase inhibitors*.
- *Side effects:*
 1. Anaphylaxis and allergy
 2. Ampicillin: *Maculopapular rash* and *diarrhea*
 3. *Methicillin:* *Interstitial nephritis*
 4. Antipseudomonas PCN: *Platelet dysfunction* and *bleeding*
 5. Carbenicillin: *Hypernatremia* and *hypokalemia*
- *Notes:*
 1. Nafcillin is excreted in the *bile*
 2. Probenecid inhibits renal excretion of PCN, but increases renal excretion of uric acid

Cephalosporins

- *First generation*, e.g., cephalexin, cefazolin. Covers *Escherichia coli* and *Klebsiella*
- *Second generation:*
 1. Coverage: Same as first generation, as well as *Haemophilus*, *Enterobacter*, and *Neisseria*
 2. Cefaclor: Causes *serum sickness*
 3. Cefuroxime: Crosses *blood-brain barrier*
- *Third generation*, e.g., cefotaxime, ceftriaxone
 1. Coverage: Same as second generation, as well as *Serratia* and *Pseudomonas aeruginosa*
 2. Ceftazidime: Cephalosporin of choice for *Pseudomonas* infections
- *Fourth generation:* Cefepime. Covers *Pseudomonas aeruginosa*
- *Side effects:*
 1. Cefamandole and cefoperazone can cause *bleeding* by *antagonizing vitamin K*. They also have *Antabuse (disulfiram)-like action*.
 2. Allergy: Cross-sensitivity with PCN occurs in *10% of patients*.
- *Elimination:* Urine, except for *ceftriaxone* and *cefoperazone*, which are *eliminated in stool*

Vancomycin

- *Mechanism:* *Bactericidal*. It inhibits *peptidoglycan synthesis*.
- *Indications:*
 1. Methicillin-resistant *Staphylococcus aureus* (MRSA) infections
 2. *Clostridium difficile* colitis: Must be given *orally; only orally*
- *Resistance:* Switch of *D-ala* into *D-lac* in the bacterial cell wall
- *Side effects:*
 1. *Red-man syndrome:* Flushing and shock that occurs after rapid infusion causes increased histamine release. *Treatment:* *Slow the infusion rate*.
 2. Hearing loss: Occurs in patients with renal failure, due to impaired excretion
- A penicillinase-resistant beta-lactam that has broad coverage. It is usually administered with *cilastatin*, which inhibits *dihydropeptidase* enzyme.

- *Indications:* Drug of choice to treat *Enterobacter*
- *Side effects:* Neutropenia and eosinophilia

Tetracycline

- *Mechanism:* Inhibits addition of aminoacyl-A to the elongating protein chain
- *Indications:*
 1. Tetracycline: *Acne vulgaris*
 2. Doxycycline: *Lyme disease* and cholera
- *Resistance:* Efflux of drug from bacterial cell via *tet-A* magnesium-operated gate
- *Absorption:* Inhibited by milk and antacids
- *Elimination:* Urine, except for doxycycline, which is excreted in stool
- *Side effects:* Photosensitivity, teeth discoloration, and GI upset, so it should not be taken on an empty stomach
- *Note:* Minocycline can cross the blood–brain barrier

Aminoglycosides

- *Examples:* Streptomycin, neomycin, gentamicin, tobramycin
- *Mechanism:* Inhibit assembly of proteins and formation of polysomes
- *Indications:* Endocarditis, tularemia, TB, pyelonephritis
- *Resistance:* Modification and decreased cellular uptake
- *Side effects:* Ototoxicity, nephrotoxicity, and worsening of myasthenia gravis due to inhibition of presynaptic release and postsynaptic sensitivity of acetylcholine
- *Note:* Neomycin is the only aminoglycoside that cannot be given intrathecally.

Macrolides

- *Examples:* Erythromycin, clarithromycin, azithromycin
- *Mechanism:* Inhibit translocation
- *Indication:* Best alternative for PCN-allergic patients. It is the drug of choice for atypical pneumonia, e.g., *Mycoplasma*, *Legionella*
- *Resistance:* Decreased uptake, and release of erythromycin esterase
- *Elimination:* Bile, except that clarithromycin is eliminated in the urine
- *Side effects:* Ototoxic, cholestatic jaundice

Chloramphenicol

- *Mechanism:* Inhibits peptidyl transferase
- *Indication:* Drug of choice for *Salmonella* infections. Not done in practice

- *Resistance:* Acetylation
- *Side effects:*

1. Anemia: Hemolytic and aplastic
2. *Gray-baby syndrome:* Teratogenic effects manifested by hypotension and diffuse cyanosis, due to deficient uridine diphosphate (UDP)-glucuronyl transferase

Clindamycin

- *Indications:* Anaerobic infections
- *Side effect:* Pseudomembranous colitis. A common case on the USMLE: A patient who was recently on antibiotics presents with watery, malodorous diarrhea. Cause: *Clostridium difficile*. Diagnosis: Examining the stools for toxins. Treatment: Oral metronidazole or oral vancomycin (oral as it acts locally). Note: *C. difficile* toxins are directed against the glucosyltransferase portion of Rho proteins.

Quinolones

- *Mechanism:* Enter cells through porin channels to inhibit DNA gyrase (topoisomerase II), and hence inhibit the replication process
- *Examples and indications:*
 1. Ciprofloxacin: Drug of choice to treat UTI and cystic fibrosis infections
 2. Norfloxacin: Used to treat UTI and prostatitis, also used as a prophylaxis against spontaneous bacterial peritonitis (SBP) in patients with upper GI bleeding
 3. Nalidixic acid: A nonfluorinated quinolone
- *Resistance:* Mutation of the A subunit of DNA gyrase, or blocking of Porin channels
- *Absorption:* Just like tetracycline, is inhibited by antacids
- *Side effects:* Nephrotoxicity, GI upset, and teratogenicity manifested by delayed formation of cartilage.

Metronidazole

- *Mechanism:* Accumulates toxins inside the pathogen cells
- *Indications:* Giardiasis, anaerobes, and most abdominal infections
- *Side effects:*
 1. Antabuse (disulfiram)-like action, so advise the patient to avoid alcohol
 2. Metallic taste and GI upset

Antituberculosis

- *Isoniazid (INH): Mechanism:* Prevents synthesis of mycolic acid in bacterial cell wall. *Side effects:* Peripheral neuritis due to vitamin B_6 deficiency and hepatotoxicity. *So, when asked on the USMLE about another pill that needs to be given for a patient on INH, it is vitamin B_6 .*
- *Rifampicin: Mechanism:* Inhibits transcription by binding to DNA-dependent RNA polymerase. *Indications:* Close contacts to cases with meningitis. *Side effects:* Orange discoloration of body fluids
- *Pyrazinamide:* Causes hyperuricemia and gout
- *Ethambutol:* Causes optic neuritis
- *Ethionamide:* Causes hepatitis and GI upset

Antiviral

Amantadine

- *Mechanism:* Inhibits uncoating of virus and release of new virions; also inhibits M2 membrane protein
- *Indications:* Influenza A virus infections
- *Side effects:* Teratogenicity, and toxicity causes cerebellar damage, e.g., ataxia
- *Notes:*
 1. Amantadine penetrates blood–brain barrier and is excreted unchanged in the urine.
 2. Rimantadine is similar to amantadine, except that it does *not* cross the blood-brain barrier and is excreted in the urine in the form of metabolites.
 3. Zanamivir is an antiinfluenza A and B drug that acts by inhibiting neuraminidase.

Acyclovir

- *Mechanism:* Guanosine analogue that inhibits both DNA polymerase and thymidine kinase
- *Indications:* Herpes simplex viruses 1 and 2 (*HSV1* and *HSV2*), Epstein-Barr virus (*EBV*)
- *Side effects:* Nephrotoxicity due to crystalluria; prevented by increasing fluid intake during therapy
- *Resistance:* Absence of thymidine kinase, e.g., cytomegalovirus (CMV)
- *Notes:*
 1. Acyclovir does not cure the disease. It only shortens the duration of the rash, and decreases the risk of postherpetic complications.
 2. Vidarabine works the same as acyclovir, and is the drug of choice for herpes encephalitis.

3. Idoxuridine works the same as acyclovir, and is the drug of choice for herpes keratitis.

Ganciclovir

- *Mechanism:* A guanosine analogue that inhibits DNA polymerase
- *Indications:* CMV infections
- *Side effects:* Teratogenicity and neutropenia
- *Notes:* Famciclovir works the same as ganciclovir. *Indications:* herpes zoster (shingles)

Foscarnet

- *Mechanism:* Inhibits DNA and RNA polymerases
- *Indications:* CMV infections resistant to ganciclovir
- *Side effects:* Hypokalemia, hypocalcemia, hypomagnesemia, and nephrotoxicity

Ribavirin

- *Mechanism:* Inhibits viral messenger RNA (mRNA) synthesis by inhibiting inosine -5'-monophosphate (IMP) dehydrogenase
- *Indications:* Respiratory syncytial virus (*RSV*) infections
- *Side effects:* Teratogenicity and hemolytic anemia

Interferon

- *Mechanism:* Inhibits viral RNA translation
- *Indications:* Hepatitis B and C, Kaposi sarcoma
- *Side effects:* Elevated transaminases and creatinine, and neutropenia

Anti-HIV

- *Reverse transcriptase inhibitors:*
 1. Zidovudine (AZT): Inhibits HIV replication. Side effects: Severe headache. *Note:* It is given to pregnant HIV patients to decrease risk of fetal transmission.
 2. Didanosine (ddi), zalcitabine, and lamivudine: All cause pancreatitis and peripheral neuropathy.
- *HIV protease inhibitors*, e.g., indinavir and ritonavir. Side effects: elevated liver transaminases and indinavir causes nephrolithiasis.

Antifungal

Griseofulvin

- *Mechanism: Disrupts fungal mitotic spindle*
- *Indications: Microsporium, Epidermophyton, and trichophyton*
- *Side effects: Hepatotoxicity*
- *Contraindications: Acute intermittent porphyria*

Amphotericin B

- *Mechanism: Disrupts cell wall after binding to ergosterol, which leads to K depletion and cell demise*
- *Side effects: Thrombophlebitis, fever, and nephrotoxicity*
- *Note: Nystatins used topically for candidiasis work just like Amphotericin.*

Flucytosine

- *Mechanism: Enters cell via permease and converts to 5-fluorodeoxyuridine monophosphate (5F-dUMP), which inhibits formation of deoxythymidine monophosphate (dTMP) and DNA*
- *Indications: Used in combination with amphotericin B to treat cryptococcal meningitis*
- *Resistance: Increasing cellular cytosine concentration*
- *Side effects: Bone marrow depression*

Ketoconazole

- *Mechanism: Prevents synthesis of ergosterol of the fungal cell wall*
- *Side effects: Gynecomastia, and inhibition of cytochrome P-450*
- *Note: Fluconazole is a drug that functions similarly, with the exception that it can cross the blood–brain barrier and that it does not inhibit cytochrome P-450*

Antiprotozoal and Antiparasitic

Antiprotozoal

- *Amebiasis: Infective form is cysts, which transform inside the body into trophozoites. Amebicides are classified into:*
 1. Luminal: *Diloxanide furoate*
 2. Systemic: *Chloroquine, emetine, dehydroemetine*
 3. Combined: *Metronidazole*

- *Malaria: Antimalarial could act either in:*
 1. Tissues: *Primaquine*
 2. Blood: *Chloroquine*
- *Chagas disease (Trypanosoma cruzi): Nifurtimox*
- *Sleeping sickness (Trypanosoma brucei gambiense): Suramin*
- *Trypanosoma brucei rhodesiense: Melarsoprol*
- *Leishmania: Sodium stibogluconate*
- *Toxoplasma gondii: Sulfadiazine + pyrimethamine*
- *Giardia lamblia: Metronidazole*
- *Fasciola hepatica: Bithionol*
- *Note: G-6-PD–deficient patients suffer hemolysis upon receiving antimalarial drugs, as they oxidize reduced glutathione, which leads to accumulation of toxic substances inside the red blood cells (RBCs) and hemolysis ensues.*

Antiparasitic

- *Mebendazole: Destroys parasitic microtubules and decreases their glucose uptake*
- *Pyrantel pamoate: A neuromuscular blocker*
- *Note: Mebendazole and Ivermectin are contraindicated during pregnancy.*
- *River blindness (onchocerciasis): Ivermectin*
- *Pinworm (enterobiasis): Mebendazole or pyrantel pamoate*
- *Roundworm (ascariasis): Same as pinworm*
- *Hookworm (ankylostoma): Same as pinworm*
- *Filariasis (Wuchereria bancrofti): Diethylcarbamazine (DEC)*
- *Whipworm (trichuriasis): Mebendazole*
- *Threadworm (Strongyloides): Thiabendazole*
- *Trichinosis: Thiabendazole*
- *Tapeworm (Cestodes): Niclosamides + laxatives*
- *Schistosoma and cysticercosis: Praziquantel*

Chemotherapeutics

- *Cancer: Gene 53 on chromosome 17 was found to be mutated in most patients with cancer. Studies are in progress to use this knowledge to prevent or treat cancer.*
- *Cell cycle: Figure 9.2 shows the four phases of the cell cycle:*
 1. M phase: *Mitosis*. Some cells go to G0 phase as a transit between M and G1.
 2. G1 phase
 3. S phase: *Replication*
 4. G2 phase: *DNA polymerase action*

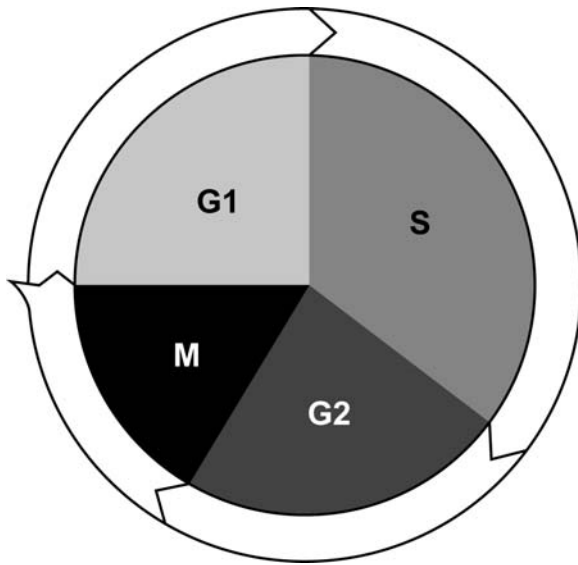


FIG. 9.2 Cell cycle

- **Resistance:** Achieved through extrusion of the drug outside of the cancer cell through an *ATP-dependent 6-transmembrane spanning pump*

Alkylating Agents

- **Mechanism:** Intercalate DNA and arrest cell cycle at any phase
- **Cyclophosphamide:** Causes hemorrhagic cystitis, due to excretion of *acrolein* in the urine. This side effect is prevented by giving *MESNA*.
- **Busulfan:** Causes pulmonary fibrosis and increased skin pigmentation
- **Nitrosoureas**, e.g., carmustine: Used in the treatment of brain cancer

Antimetabolites

- **Mechanism:** Arrest S phase
- **Side effects:** Bone marrow depression and stomatitis
- **Methotrexate:** Inhibits *dihydrofolate reductase* enzyme, which leads to drop in the levels of *purines*, *serine*, and *methionine* in the body. It should always be used in conjunction with *folinic acid (citrovorum factor)*.
- **5-Fluorouracil:** It inhibits *thymidylate synthase* via 5F-dUMP. Could cause *hand-foot syndrome*. Do not forget to give *folic acid supplementation* during treatment.
- **6-Mercaptopurine:** It is the form by which *azathioprine* acts inside the body. It needs two enzymes to

work appropriately: *hypoxanthine-guanine phosphoribosyltransferase (HGPRT)* and *xanthine oxidase*. So, HGPRT deficiency (*Lesch-Nyhan syndrome*) and *allopurinol (xanthine oxidase inhibitor)* interfere with action of *azathioprine* and *6-mercaptopurine*.

Antitumor Antibiotics

- **Mechanism:** Arrest G2 phase by destroying DNA polymerase
- **Doxorubicin:** Cause cardiotoxicity via oxygen radicals. This side effect is prevented by giving *Dexasone*.
- **Bleomycin:** Causes pulmonary fibrosis
- **Actinomycin D**

Plant Alkaloids (Spindle Poisons)

- **Mechanism:** Arrest M phase by destroying microtubules
- **Side effects:** Peripheral neuritis
- **Examples:** Vincristine, vinblastine, etoposide, Taxol
- **Note:** Etoposide also blocks G2 phase by inhibiting *topoisomerase II*.

Platinum

- **Mechanism:** Acts on all phases, mainly G1 and S phases.
- **Cisplatin:** Causes ototoxicity, nephrotoxicity, and neurotoxicity
- **Carboplatin:** Causes bone marrow depression (*myelotoxicity*)

General Side Effects

- **GI upset:** Nausea and vomiting
- **Alopecia and skin rash**
- **Bone marrow depression:** Most dangerous is *neutropenia* (absolute neutrophil count <500), which puts the patient at risk of fulminant infections. Neutropenia is treated with *granulocyte colony-stimulating factor (G-CSF)*, e.g., *filgrastim*, plus prophylactic broad-spectrum antibiotics.

Endocrine System

Antithyroid

- **Propylthiouracil (PTU) and methimazole:** Inhibit oxidation and coupling processes. PTU also inhibits peripheral conversion of T_4 to T_3 .

- *Na thiocyanate*: Inhibits accumulation of iodine in the thyroid gland
- *Iodide*: Inhibits release of thyroid hormones

Insulin

- Insulin is secreted from beta cells of the pancreas.
- Upon eating, glucose blocks K channels and opens Ca channels in the beta cells, which leads to insulin secretion in a pulsatile fashion: an early large phase followed by a smaller one.
- Diabetic pancreas either *does not release any insulin (DM type I)*, or it releases it in *one small phase only (DM type II)*.
- Insulin secreted in response to oral glucose is more than that secreted in response to injected glucose; *the secret lies in the stimulation of GI enzymes by oral glucose*.
- *Actions of insulin*:
 1. Increase cellular uptake of glucose everywhere *except brain, kidney tubules, and RBCs*
 2. Increase cellular uptake of amino acids and K, and stimulate lipogenesis
- *Types of insulin*: Onset of action doubles from 1–2 to 4 hours in the different types and the duration doubles from 6–12 to 24 hours, as follows:
 1. Rapid and short-acting: Crystalline insulin. *Used in emergencies*. Onset of action = 1 hour. Duration of action = 6 hours.
 2. Intermediate: Lente, semilente, neutral protamine Hagedorn (NPH). Onset of action = 2 hours (= 1 × 2). Duration of action = 12 hours (= 6 × 2)
 3. Long acting: Ultralente, protamine zinc insulin (PZI). Onset of action = 4 hours (= 2 × 2). Duration of action = 24 hours (= 12 × 2).
- *Troubleshooting*:
 1. Skin allergy and *lipodystrophy* (atrophy of subcutaneous tissues): Common at site of injection
 2. *Somogyi phenomenon*: High early morning blood sugar in response to a preceding nocturnal drop of blood sugar. Treated by *decreasing* the evening insulin dose.
 3. *Dawn phenomenon*: High early morning blood sugar that is *not* preceded by any drop. Occurs due to early morning catecholamine surge. Treated by *increasing* the evening insulin dose.

Oral Hypoglycemics

- *Sulfonylureas*: Mechanism: Increase insulin release and tissue sensitivity, which is achieved by *blocking*

K channels and opening Ca channels in the beta cells of pancreas. Metabolism: *Liver*. Elimination: *Urine*. Examples and side effects:

1. Glyburide: High risk of *hypoglycemia*
2. Chlorpropamide: *Disulfiram-like action*, and can cause syndrome of inappropriate ADH (*SIADH*)
3. Others: Glipizide, tolbutamide

- *Biguanides, e.g., metformin*. Mechanism: *Inhibit hepatic gluconeogenesis*. Side effects and contraindications:

1. Alcoholism or IV dye + metformin: High risk of *lactic acidosis*
2. Renal failure: Absolute contraindication for using metformin

- *Thiazolidinediones (TZD)*, e.g., rosiglitazone, pioglitazone. Mechanism: *Decrease insulin resistance*
- *Alpha-glucosidase inhibitors*, e.g., acarbose. Mechanism: Inhibit carbohydrate absorption. Side effects: GI upset and flatulence

Miscellaneous Endocrine Notes

- *Osteoporosis*: Treated by bisphosphonates, e.g., alendronate. They act by *inhibiting osteoclastic activity*. Side effects: *Esophagitis*.
- *Finasteride*: Inhibits *5-alpha-reductase enzyme*, which normally converts testosterone into dihydrotestosterone. Indication: *Benign prostatic hypertrophy*.
- *Flutamide*: *Testosterone receptor antagonist* used in treatment of *prostate cancer*
- *Leuprolide*: Luteinizing hormone–releasing hormone (*LHRH*) *agonist* used in the treatment of *prostate cancer*. The idea here is that it causes *persistent* rather than *pulsatile* gonadotrophins secretion.
- *Clomiphene*: *Anti-estrogen* used to treat anovulation
- *Cyproterone acetate*: *Antiandrogen* used to treat hirsutism in patients with polycystic ovaries syndrome (PCOS)
- *Tamoxifen*: *Anti-estrogen* used in the treatment of breast cancer. Side effects: *Endometrial cancer, hot flashes, thromboembolism, hypercalcemia, and low low-density lipoprotein (LDL)*.
- *Mifepristone (RU-486)*: *Antiprogesterone* used as an abortifacient
- *Metyrapone*: *Antiadrenal* used in the treatment of Cushing's syndrome. It acts by inhibiting *11-hydroxylase enzyme*.
- *Aminoglutethimide*: *Antiadrenal* used in the treatment of Cushing's syndrome. It acts by inhibiting the *Desmolase enzyme*. Normally, desmolase is stimulated by adrenocorticotrophic hormone (ACTH)

to convert cholesterol into *pregnenolone* (first step in steroid synthesis).

- *Sildenafil*: Inhibits *cGMP* phosphodiesterase enzyme and is used in the treatment of erectile dysfunction. Side effects: Headache, flushing, and priapism. Contraindicated in any patient using nitrates.
- *Alprostadil*: Local prostaglandin used as an injection into the corpora cavernosa to treat some cases of erectile dysfunction, though it is inconvenient
- *Anabolic steroids*: Cause small testicular size, low sperm count, low high-density lipoprotein (HDL) and high blood pressure
- *Glucocorticoids*: Increase only neutrophil count and decrease all other cell counts
- *Hypercalcemia*: Treat with fluids first, followed by aggressive diuresis using furosemide (*Lasix*)
- *Hypercalcemia of malignancy*, e.g., squamous cell cancer of the lung; treat with mithramycin (*plicamycin*) or bisphosphonates, e.g.: pamidronate

Rheumatoid Arthritis

Nonsteroidal Antiinflammatory Drugs (NSAIDs)

- *Examples*: Acetaminophen, phenacetin, salicylates, and indomethacin
- *Acetaminophen toxicity*: Liver damage. Antidote: *N-acetylcysteine*.
- *Phenacetin*: Nephrotoxic, and can cause papillary carcinoma of the kidneys
- *Sulindac* and *etodolac*: Potent NSAIDs, but commonly cause GI upset
- *Phenylbutazone*: Causes aplastic anemia and rash
- *Piroxicam*: Decreases excretion of lithium; hence increases risk of toxicity
- *Celecoxib*: Cyclooxygenase-2 (COX-2) inhibitor
- *General side effects*:
 1. GI upset and peptic ulcer disease (PUD)
 2. Analgesic nephropathy

Disease Modifying Antirheumatic Drugs (DMARDs)

- *Methotrexate*:
 1. Mechanism: Immunosuppression and folic acid antagonism
 2. Side effects: Bone marrow depression, elevated liver enzymes, mucositis, and megaloblastic anemia

Hydroxychloroquine:

1. Mechanism: Antimalarial drug that acts by stabilizing the lysosomes
2. Side effects: Retinopathy, renal failure, and hemolysis in G-6-PD deficiency. So, patients on this medication need annual fundoscopic exam.
3. Note: Primaquine is another antimalarial used to radically cure *plasmodium vivax*.

Sulfasalazine:

1. Composition: 5-aminosalicylic acid + sulfapyridine
2. Mechanism: Works through the *sulfapyridine* portion, where in inflammatory bowel disease it works through the 5-aminosalicylic portion
3. Side effects: Reversible infertility in males

Gold salts: Taken up by macrophages and lysosomes and stop bone destruction. Side effects: Rash and stomatitis. Antidote: *Dimercaprol*.

Penicillamine: Analogue of cysteine. Indications: Rheumatoid arthritis and *Wilson's disease* (copper chelator).

Others

- *Anti-tumor necrosis factor*: e.g., infliximab, adalimumab, and etanercept. Side effects: Overwhelming infections, so annual purified protein derivative (PPD) is necessary.
- *Steroids*: Systemic and local steroids provide symptomatic relief and may slow the progression of the disease.

Gout

Acute gout

- *Treatment of choice*: Oral indomethacin
- *Colchicine*: Depolymerizes tubulin and decreases leukocyte entry into the cells. Side effects: Diarrhea and GI upset. Long-term use may cause aplastic anemia.

Chronic Gout

- *Allopurinol*:
 1. Mechanism: Converts inside the body to *alloxanthine*, which inhibits *xanthine oxidase*. Xanthine oxidase normally regulates the conversion of hypoxanthine to xanthine and xanthine to uric acid.
 2. Indications: High serum plus high urinary uric acid levels

- *Probenecid*:
 1. Mechanism: *Blocks uric acid reabsorption* in proximal convoluted tubule
 2. Indications: *High serum plus low urinary uric acid level*
 3. Note: Sulfapyridine is another drug that acts exactly like probenecid. Remember: Probenecid inhibits renal excretion of PCN.

Toxicology

- *First aid*: First measure in any patient with any toxicity is securing an *Airway*, maintaining *Breathing*, and establishing *Circulation* (ABC)
- *Activated charcoal*: Helps decrease or even block absorption of toxins in the stomach, and it works for everything except *Lithium*, *Iron*, and *Cyanide* (LIC)

Lead

- *Clinical picture*: Patient who just moved to a house with classic old *paint* and an old *pipe system*, now presenting with *abdominal pain* and *anemia*
- *Diagnosis*: High blood lead ($>20 \mu\text{g/dL}$), RBC protoporphyrin, and zinc protoporphyrin levels. Also a pathognomonic finding is *basophilic stippling of the RBCs*, which can be detected by the *Wright-Giemsa* stain.
- *Antidote*: *Ethylenediaminetetraacetic acid (EDTA)* or *dimercaprol (succimer)*
- *Note*: EDTA can cause fatal *hypocalcemia* on rapid IV infusion.

Ethylene Glycol (Antifreeze)

- *Clinical picture*: *High anion gap metabolic acidosis*, and *oxalate crystals* in urine
- *Treatment*: *Ethanol and hemodialysis*

- *Note*: Methanol (bootleg; moonshine) is converted inside the body into formic acid and formaldehyde, which cause *high anion gap metabolic acidosis* and *blindness*, respectively. Treatment: *Ethanol*.

Cyanide

- It has a *bitter almond* odor, and makes the blood *cherry red* in color.
- *Mechanism*: Inhibits cytochrome oxidase and cellular oxygen uptake.
- *Cause*: Cyanide toxicity is common to happen due to *Na nitroprusside*
- *Treatment*: *Nitrites* and *sodium thiosulfate*

Arsenic

- Heavy metal with *garlic* odor that interferes with *oxidative phosphorylation*
- *Clinical picture*: *Polyneuritis*, *skin hyperpigmentation*, liver and kidney failure
- *Treatment*: Gastric lavage, *dimercaprol*, and hemodialysis

Others

- *Opioids*: *Pinpoint pupils*, respiratory depression and hypothermia. Antidote: *Naloxone*. Remember: *Benzodiazepine (BDZ)* is reversed by *flumazenil*, not *naloxone*.
- *Carbon monoxide*: It is wintertime and a family has been spending the entire weekend at home *in front of the fireplace or inside a closed garage*. Now they all presented to the emergency room with *confusion*, *headache*, and *dizziness*. Treatment: *Hyperbaric or 100% oxygen*, and treat the cause.
- *Mercury*: *Ataxia*, vomiting, diarrhea, and renal failure. Treatment: *Dimercaprol or penicillamine*.
- *Iron*: *Hemorrhagic gastroenteritis*. Treatment: Iron chelators, e.g., *desferrioxamine*.

Chapter 10

Pathophysiology

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Cell Physiology

Cell Membrane

- *Lipid bilayer*: It allows the direct passage of fat-soluble molecules; water soluble-ones, on the other hand, only cross the membrane through *channels*.
- *Proteins*:
 1. Transmembranous proteins: Serve as channels to transport *ions*
 2. Peripheral proteins: Serve as *hormone receptors*

Cell Transport

- *Simple diffusion*: Does *not* require energy or carrier proteins, e.g., O₂, CO₂
- *Facilitated diffusion*: Requires a carrier protein but is energy *independent*, e.g., Glucose
- *Active transport*: Requires *both* a protein carrier and energy, e.g., Na/K and H/K pumps
- *Secondary active transport*: The simple diffusion of one substance produces energy that is consumed in the active transport of another substance. These two substances may be moving in the same direction (i.e., cotransport or symport, e.g., Na/K/2Cl), or in opposite directions (i.e., countertransport, e.g., Na/Ca or Na/H pumps)
- *Reflection coefficient*: Used to determine permeability of substances in water:
 1. Coefficient of *one*: Solute is impermeable, so H₂O permeability is *maximal*.
 2. Coefficient of *zero*: Solute is permeable, so H₂O permeability is *minimal*.
- *Note*: Some substances have an inhibitory effect on the transport of others. Example: Galactose inhibits the facilitated diffusion of glucose into intestinal cells

Intercellular Connections

- *Tight junctions*: Could be tight, not allowing passage of molecules, e.g., renal distal convoluted tubule, or permeable, e.g., proximal convoluted tubule
- *Gap junctions*: as in myocardium

Action Potential

- The resting membrane potential (RMP) of a nerve is -70 mV ; therefore, *the nerve cell is more permeable to K than Na*.
- *Action potentials (APs)*: They are all *stereotypical in size and shape, propagating*, and follow the *all-or-none* rule.
- *Rate*: Action potentials travel faster if the fiber is *thicker* and if it is coated with *myelin*, as that allows the signals to jump from one Ranvier node to the next (*saltatory conduction*).
- *Miniature end-plate potentials*: Occur due to *the opening of multiple ion channels* and the release of a small amount of neurotransmitters
- *Depolarization of AP*: Occurs due to *Na influx*. Na channels and thus depolarization can be inhibited by *tetradotoxin*.
- *Repolarization of AP*: Occurs due to *K efflux*
- *Absolute refractory period (ARP)*: During this period, no other stimulus can trigger another action potential *no matter how strong it is*.
- *Relative refractory period (RRP)*: During this period, another action potential *can be triggered only if the stimulus is strong*.
- *Summation*:
 1. *Spatial summation*: Occurs if two stimulatory impulses hit their target at the same time
 2. *Temporal summation*: Occurs if two stimulatory impulses hit their target right after each other
 3. *Facilitation* (augmentation or posttetanic potentiation): Occurs when an extra amount of transmitter hits the target causing strong stimulation

Skeletal Muscle

- *A band*: Thick band formed of *myosin*
- *I band*: Thin band formed of *actin* and *troponin*: troponin C for calcium, troponin T for tropomyosin, and troponin I, which inhibits the actin-myosin binding
- *Z line*: Runs in the middle of every *I* band
- *M line*: Runs in the middle of every *A* band. See Fig. 10.1 for lines and bands of skeletal muscle.

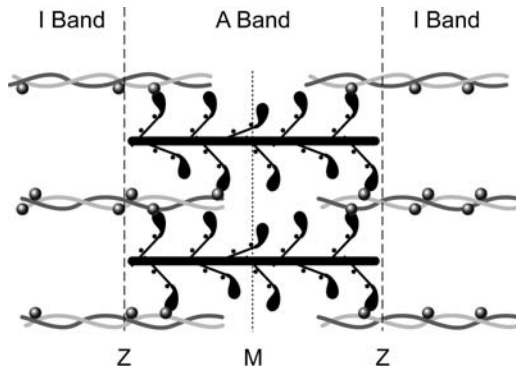


FIG. 10.1 Muscle fibers. Thin transverse lines represent actin, while thick ones represent myosin

- **Transverse tubules:** Located at the *junction of the A and I bands*, and have a *dihydropyridine regulatory receptor*
- **Sarcoplasmic reticulum:** Forms *cisterns* in the *transverse tubules*. The cisterns store calcium bound to *calcisequestrin*, which is attached to Ca release channels. Calcium release is regulated by *ryanodine receptors*.
- **Muscle contraction:**
 1. **Isometric:** Contraction occurs *without* muscle shortening
 2. **Isotonic:** Contraction occurs *with* shortening
 3. **Iso-inertial:** If contraction is against a constant load or torque
- **Muscle tension** (Fig. 10.2):
 1. **Passive tension:** No muscle contraction
 2. **Total tension:** Full muscle contraction
 3. **Active tension:** The difference between passive and total tension
- **Cardiac muscle:** *Just like skeletal muscle, the cardiac muscle is a striated muscle* and it contracts in the same mechanism, except that the calcium is released from both the sarcoplasmic reticulum *and the extra-cellular matrix*.

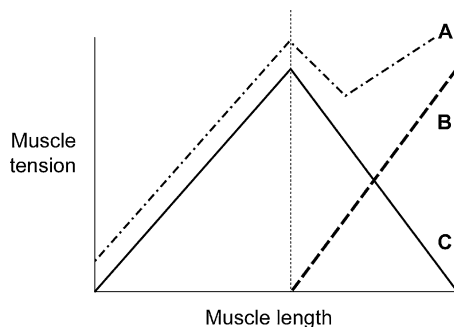


FIG. 10.2 Curve A: Total tension. Curve B: Passive tension. Curve C: Active tension

Smooth Muscle

- **Contraction:** Depends on *Ca-calmodulin* interaction, which stimulates *myosin light chain kinase*. The kinase phosphorylates myosin, which in turn stimulates muscle contraction.
- **Forms:**
 1. Single unit, e.g., gastrointestinal (GI) tract and urogenital system. They contract in response to *hormones and transmitters* and exhibit *pacemaker activity*, i.e., the stomach performs *three* slow waves/min and the duodenum about *12* waves/min.
 2. Multiunit, e.g., iris and ciliary muscles. They contract in response to *nerve stimulation* and do *not* exhibit slow waves or pacemaker activity.

Endocrinology

Pituitary Gland

Parts and Actions

- **Anterior pituitary:** Releases follicle-stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), and prolactin. Growth hormone and prolactin are released from acidophil cells, while all others are released from basophil cells.
- **Posterior pituitary:**
 1. Supraoptic nucleus: Releases antidiuretic hormone (ADH), which acts on intercalated cells of the kidneys via *V2*, and on blood vessels via *V1* receptors
 2. Paraventricular nucleus: Releases *oxytocin*, which stimulates the contraction of the *uterus*, and *muscles surrounding the mammary glands' acini* during breast-feeding

Hyperprolactinemia

- Prolactin release is inhibited by dopamine and dopamine agonists.
- Normal serum prolactin level is *less than 20 ng/mL*. *During pregnancy, a level up to 200 ng/mL is still considered normal*.
- **Causes:**
 1. Physiologic: *Pregnancy and lactation*
 2. Pituitary: *Chromophobe adenoma* (prolactinoma) and empty sella syndrome
 3. Endocrinal: *Hypothyroidism* and chronic renal failure
 4. Drugs: Antipsychotics, *via inhibition of dopamine*

- **Clinical picture:**
 1. Amenorrhea, infertility, and milky nipple discharge (galactorrhea)
 2. Headache, vomiting, and bitemporal hemianopia: Due to high intracranial pressure
- **Diagnosis:** Serum prolactin level greater than 200 ng/mL, and computed tomography (CT) or magnetic resonance imaging (MRI) of the brain to rule out a pituitary adenoma
- **Treatment:**
 1. Dopamine agonists (e.g., bromocriptine): Treatment of choice
 2. Hypophysectomy: Done only in severe complicated cases

Acromegaly

- Caused by excess GH after closure of the epiphysis. If it occurs before epiphysial closure, it causes gigantism (Andre the giant).
- **Cause:** Acidophil adenoma. In gigantism, it is mainly acidophil hyperplasia.
- **Clinical picture:**
 1. Large head with widely spaced teeth, large hands, and feet (Fig. 10.3)
 2. Impaired glucose tolerance
- **Diagnosis:**
 1. High serum insulin-like growth factor (IGF) level: It is the best next step.
 2. Glucose suppression test: Used to confirm diagnosis if IGF is high
- **Treatment:**
 1. Growth hormone antagonist, e.g., somatostatin, bromocriptine
 2. Surgery, i.e., hypophysectomy: If failed medical treatment



FIG. 10.3 Acromegaly

Hypopituitarism

- **Causes:** Tumor or injury; however, a very important cause is infarction of the anterior pituitary in the postpartum period (Sheehan's syndrome).
- **Clinical picture (in order of occurrence):** Hypogonadism, hypothyroidism, and finally hypoadrenalism
- **Diagnosis:** Low sex hormones, thyroid and cortisol levels, along with low FSH, LH, TSH, and ACTH. If the latter stimulatory hormones are elevated, this suggests polyglandular deficiency syndrome (Schmidt's syndrome).
- **Treatment:** Hormone replacement. Start with steroid replacement first.
- **Note:** Kallmann syndrome: Low gonadotropin-releasing hormone (GnRH), FSH, and LH, leading to anosmia and amenorrhea, and is associated with cleft lip/palate

Antidiuretic Hormone Disorders

- **Syndrome of inappropriate ADH secretion (SIADH):** Excessive ADH secretion leading to oliguria with a high urinary Na content and osmolality. Treatment: Fluid restriction and treating the underlying cause is the best next step. Hypertonic saline, lithium, and demeclocycline are used for severe cases.
- **Diabetes insipidus (DI):** Either due to decreased ADH secretion (central diabetes insipidus) or decreased sensitivity (nephrogenic diabetes insipidus). This leads to polyuria with low urine osmolality. Treatment: Central DI: desmopressin (deamino-8-D-arginine vasopressin [DDAVP]); nephrogenic DI: thiazide diuretics.
- **Note:** Normal serum osmolality = 280 mOsm/L

Thyroid Gland

Thyroxine Synthesis

- **Transport:** Iodide is transported into the thyroid cells. This process is inhibited by thiocyanate, perchlorate, and high iodine levels (Wolff-Chaikoff effect).
- **Oxidation:** By peroxidase enzyme, and is inhibited by propylthiouracil (PTU) and methimazole
- **Organification and coupling:** Inhibited by PTU and methimazole
- **Deiodination:** Performed by the deiodinase enzyme
- **Conversion:** Thyroxine (T_4) is converted to triiodothyronine (T_3) peripherally (T_3 is three times more potent than T_4); conversion is inhibited by PTU and beta-blockers.
- **Binding to globulin:** Only the free (unbound) thyroid hormone is active.

Regulation

- Thyrotropin-releasing hormone (TRH) from the hypothalamus stimulates TSH release from the pituitary.
- T_3 exhibits feedback inhibition of TSH.

Actions of Thyroid Hormones

- *Mechanism:* Stimulate Na/K adenosine triphosphatase (ATPase), which leads to increased oxygen consumption in all cells except the *brain, gonads, and the spleen*
- *Cardiovascular system (CVS):* Increase stroke volume, heart rate, and cardiac output
- *Central nervous system (CNS):* Maturation of the nervous system
- *Metabolic:* Stimulate glycogenolysis, gluconeogenesis, and lipolysis. So high thyroxine leads to low cholesterol levels and vice versa.
- *Blood:* Increase 2,3-diphosphoglycerate (DPG), which promotes O_2 dissociation from hemoglobin
- *Notes:*
 1. Calcitonin is released from parafollicular (C) cells of thyroid gland and functions to decrease bone resorption. *Medullary carcinoma of the thyroid originates from C cells, which are derived from the fourth pharyngeal pouch.*
 2. Thyroid and steroid hormones act on nuclear receptors.

Thyrotoxicosis

- Graves' disease is linked to human leukocyte antigen (*HLA*)-*DR3* and *HLA-B8*.
- *Mechanism:* Thyroid-stimulating immunoglobulins (TSIs), also known as long-acting thyroid stimulators (LATS)
- *Clinical picture:* Heat intolerance, exophthalmia, sweating, tremors, increased appetite, weight loss, and diarrhea
- *On exam:*
 1. Exophthalmia, lid retraction, and lid lag (Fig. 10.4)
 2. Thyromegaly (goiter): *Moves up and down with deglutition*
 3. Tremors of extremities, and excessive sweating
- *Complication:* Tachycardia and arrhythmia, e.g., atrial fibrillation
- *Diagnosis:*
 1. Low TSH, and high T_3 or T_4 .
 2. *Thyroid ultrasound and thyroid iodine uptake scan revealing a hot spot (Diffuse increased uptake is diagnostic of Graves' disease)*



FIG. 10.4 Exophthalmia

- *Treatment:*
 1. Best is radioactive iodine: *Hypothyroidism* is a common complication.
 2. Medical: Methimazole or propylthiouracil. Beta-blockers help alleviate the adrenergic symptoms, e.g., tachycardia, anxiety. *Note that methimazole is contraindicated during pregnancy as it can cause aplasia cutis (congenital absence of skin).*
 3. Surgery: Reserved for large compressive goiters
- *Note:* Exophthalmia occurs due to edema, fat and round cell infiltration behind the eye, along with weakness of extraocular muscles.
- *Thyrotoxic crisis (thyroid storm):* A fatal extreme hyperthyroidism characterized by *altered mental status, fever, tremors, and tachycardia*. Treatment is urgent and includes all of the following:
 1. Cooling: Using ice. Salicylates are contraindicated as they unbind thyroxine in the serum
 2. PTU: Inhibits synthesis and peripheral conversion
 3. Beta-blockers, e.g., propranolol, and steroids: They both inhibit thyroxine release.

Hypothyroidism

- *Clinical picture:* Cold intolerance, constipation, fatigue, weight gain, and dry skin.
- *On exam:* Delayed relaxation phase of deep tendon reflexes, and nonpitting edema on shin of tibia (*myxedema*). Note that myxedema can also happen in hyperthyroidism.

- **Diagnosis:**

1. High TSH, and low T₃ or T₄
2. Check for *antithyroglobulin*, *antimicrosomal*, and *antithyroperoxidase antibodies* to rule out *Hashimoto thyroiditis*.

- **Treatment:** Thyroxine replacement therapy

- **Notes:**

1. Cretinism is a neonatal form of hypothyroidism due to iodine deficiency during pregnancy. Newborn is *pale*, has a *puffy face*, *pot belly*, and *mental retardation*.
2. Myxedema coma: A fatal extreme hypothyroidism characterized by coma, hypothermia, and muscle rigidity. Treatment: IV thyroxine.
3. Hypothyroid female patients tend to have iron-deficiency anemia due to high susceptibility for menorrhagia.

Thyroiditis

- **De Quervain thyroiditis:** Due to *giant cell infiltration* triggered by a *viral* infection. This leads to painful enlargement of the thyroid. Patient presents with *sore throat radiating to the ears*.
- **Hashimoto's thyroiditis:** Common in females and progresses to *hypothyroidism*. Commonly associated with autoimmune disorders, e.g., diabetes mellitus (DM)
- **Diagnosis of thyroiditis:**
 1. *Diffuse low iodine uptake* on thyroid scan
 2. Hashimoto's: Elevated *antithyroglobulin* and *antimicrosomal* antibodies.
- **Treatment:** Nonsteroidal antiinflammatory drugs (NSAIDs). Thyroxine therapy for Hashimoto's patients is needed.

Thyroid Cancer

- **Papillary:** *Most common*. Metastasize through lymphatics. Treatment: Surgery.
- **Follicular:** Metastasize through blood (*skull* is the most common site). So when you see a patient on the USMLE with thyroid cancer and a hot tender mass on his skull, it is most likely follicular cancer. Treatment: Surgery and radioactive iodine. Note: Hürthle cell carcinoma is a subtype of follicular carcinoma.
- **Anaplastic:** Large firm tumor, common in the elderly, with poor prognosis. Treatment: Surgery and radiation therapy.
- **Medullary:** Arises from C cells and secretes calcitonin. Microscopy shows *amyloid stroma*. Treatment: Surgery. Note: This tumor is radioresistant.

Solitary Thyroid Nodule

- **If palpable:** Fine-needle aspiration (FNA) and biopsy are always needed.
- **If not palpable:** FNA should be done only if nodule is bigger than *1.5 cm*.
- **Note:** *Hot nodules* are mostly toxic, and *cold nodules* are mostly malignant.

Thyroglossal Cyst

- **Mechanism:** Nonobliteration of a part of the *thyroglossal track*
- **Clinical picture:** Midline neck cystic swelling that *moves up with tongue protrusion*
- **Complication:** Rupture leaving a *thyroglossal fistula*
- **Treatment:** Excision via *Sistrunk operation*

Parathyroid Gland

Parathyroid Hormone (PTH) (Released from Chief Cells)

- **Bone:** Increase *both osteoblasts and osteoclasts* activity with an end result of bone resorption to increase serum Ca
- **Kidney:**
 1. Increase *reabsorption of Ca* and *excretion of P*.
 2. Stimulate hydroxylation of vitamin D.
- **Intestine:** Increases calcium absorption, and decreases P absorption
- **Note:** Vitamin D is hydroxylated twice, once in the liver (25-OH) and then in the kidneys (1-OH). Vitamin D increases *both* serum Ca and P by stimulating intestinal absorption and bone resorption. These actions are regulated by *calbindin D-28*.

Regulation

- Serum calcium regulates the release or inhibition of PTH.
- 1,25-OH vitamin D causes feedback inhibition on its own formation.
- **Ultraviolet B** light is essential for regulating the release and action of vitamin D. So, suspect vitamin D deficiency in patients living in areas with no sun exposure, e.g.: prisons, nursing homes.

Hyperparathyroidism

- **Cause:** Adenoma (*most common cause*), hyperplasia, or secondary to another cause, e.g., renal failure.
- **Clinical picture:**
 1. Hypercalcemia: Causes constipation, polyuria, kidney stones, and fatigue

2. Osteitis fibrosa cystica: Causes bone pains and fractures
 3. CNS: Altered mental status and *corneal band keratopathy*
- *Treatment: Calcium chelators, and surgery in severe cases*
 - *Treatment of symptomatic hypercalcemia: Infusion of 3 to 4 L of normal saline followed by furosemide. Note that you have to fill the tank first.*
 - *Notes:*
 1. Multiple endocrine neoplasia (MEN) I and II must be ruled out in any case of hyperparathyroidism.
 2. Pseudohypoparathyroidism (Albright hereditary osteodystrophy): *X-linked dominant syndrome where PTH is abundant but organs are resistant to it due to a defective Gs.*

Multiple Endocrine Neoplasia (MEN)

- *Type I (Wermer syndrome):* Helpful to remember “PPP”: Involves Pituitary gland, Pancreas and Parathyroid glands.
- *Type IIa (Sipple syndrome):* helpful to remember the glands as “TAP”:
 1. Thyroid glands: Medullary carcinoma
 2. Adrenal glands: Pheochromocytoma
 3. Parathyroid glands: Hyperparathyroidism
- *Type IIb:* Just like IIa except for parathyroid being replaced by *neuromas* “TAN”

Adrenal Gland

Parts and Actions

- *Zona glomerulosa:* Aldosterone; increases *Na* absorption and *K* excretion
- *Zona fasciculata:* Cortisol; acts like aldosterone, plus antiinflammatory action by stimulating lipocortin and *decreasing interleukin-2, eosinophils, and lymphocytes*
- *Zona reticularis:* Dehydroepiandrosterone (DHEAS) and androstenedione
- *Note: Cortisol stimulates gluconeogenesis and inhibits glycogenolysis, while glucagon stimulates both processes.*

Regulation

- CRH from the hypothalamus stimulates ACTH release from the pituitary.
- ACTH stimulates cholesterol desmolase in the adrenal glands.
- Renin converts angiotensinogen to angiotensin I, which later converts to angiotensin II via angiotensin-

converting enzyme (ACE). Angiotensin II is then converted to aldosterone, which performs a negative feedback inhibition on renin.

Cushing Syndrome

- *Causes:*
 1. Cushing disease: Excessive secretion of ACTH
 2. Adrenal adenoma or hyperplasia: Excessive secretion of cortisol (low ACTH)
 3. Ectopic ACTH secretion, e.g., small cell cancer of the lung
- *Clinical picture (Fig. 10.5)*
 1. *Moon face, buffalo hump, trunk obesity*
 2. *Striae rubrae and thin limbs*
 3. *Polycythemia and hirsutism*
- *Diagnosis: Dexamethasone suppression test*
- *Treatment: Ketoconazole*

Conn's Syndrome (Primary Hyperaldosteronism)

- *Clinical picture: Hypokalemic hypertension and metabolic alkalosis. Suspect in any patient with resistant hypertension (HTN) and unexplained hypokalemia.*
- *Diagnosis: High serum aldosterone/renin activity ratio. Salt loading test is used for confirmation.*
- *Treatment: Antialdosterone agent, e.g., spironolactone*
- *Note: These patients normally have polyuria, but at a certain aldosterone level the kidneys do not respond to aldosterone (aldosterone escape phenomenon).*



FIG. 10.5 Cushing syndrome

Pheochromocytoma

- A rare, *neural crest remnant* tumor arising from *chromaffin tissue*
- *Rule of tens*: 10% are extraadrenal, 10% bilateral, and 10% malignant
- *Clinical picture*: *Panic attack–like picture* and *labile hypertension*. Patient present with *episodes* of sweating, anxiety, tremors, palpitations, and resistant HTN.
- *Diagnosis*:
 1. Elevated 24-hour urine concentration of vanillylmandelic acid (VMA), metanephrines, and free catecholamines
 2. Once diagnosis is confirmed, the tumor must be located by performing a *CT of the abdomen*. If tumor is not found, *metaiodobenzylguanidine (MIBG) scan* is done.
- *Treatment*: Drug of choice is alpha-blockers, e.g., *phenoxybenzamine*, followed by surgical resection of the tumor.

Adrenal Insufficiency

- *Cause*:
 1. Primary (Addison's disease): Due to adrenal cortex dysfunction
 2. Secondary: Due to pituitary dysfunction
- *Clinical picture*:
 1. *Resistant hypotension* and *hypoglycemia*
 2. Primary cases may also have *hyperpigmentation of mucous membranes* due to *high melanocyte-stimulating hormone (MSH) levels*. Secondary causes do not have this feature.
- *Diagnosis*: *Cosyntropin stimulation test*
- *Treatment*: Systemic steroids, e.g.: Hydrocortisone
- *Notes*:
 1. Addisonian crisis: A fatal extreme hypoadrenalism that occurs due to severe stress or sudden stoppage of long-term steroid therapy without tapering
 2. Waterhouse-Friderichsen syndrome: It is an adrenal insufficiency that occurs due to adrenal hemorrhage. It is caused by *Neisseria meningitidis*. So when you see a patient on the USMLE with meningitis who suffers sudden severe hypotension, you know what to think!

Gonads

- *Males*:
 1. LH stimulates Leydig cells to form testosterone.
 2. FSH stimulates Sertoli cells to form sperms and release *inhibin*.

- *Females*:

1. LH stimulates *theca cells* to form *androgens*.
2. FSH stimulates *granulosa cells* to convert androgens to estrogen via *aromatase enzyme*.

Estrogen

- *Types*:

1. Estrone (E1): Estrogen of menopause
2. Estradiol (E2): Estrogen of *reproductive age*, and is the most potent form
3. Estriol (E3): Estrogen of *pregnancy*, secreted by the *placenta*
4. Diethylstilbestrol (*DES*): A drug no longer given due to the risk of vaginal adenosis, *clear cell adenocarcinoma*, incompetent cervix, and *abortion*

- *Sources*:

1. Graafian follicle: The source of E2 during the first half of the menstrual cycle
2. Corpus luteum: The source of E2 during the second half of the menstrual cycle
3. Placenta: The source of E3 during pregnancy
4. Adipose tissue: Peripheral conversion of androgens to estrogen by *aromatase*

Progesterone

- *Source*: Secreted by the corpus luteum and the placenta
- *Actions*: Table 10.1 lists the actions of estrogen and progesterone

Androgen

- *Source*:

1. Testes and ovaries: Testosterone
2. Adrenal glands: Dihydrotestosterone (DHT). *This is the most potent androgen.*

- *Actions*:

1. Secondary male sexual characters: Hair distribution, tone of voice, and muscle size
2. Spermatogenesis and libido stimulation

Pancreas

- It has both exocrine and endocrine functions, the latter being regulated with:
 1. Alpha cells: Release *glucagon*
 2. Beta cells: Release *insulin*
 3. Delta cells: Release *somatostatin*

TABLE 10.1 Actions of estrogen and progesterone.

	Estrogen	Progesterone
Breasts	<ul style="list-style-type: none"> • Develops <i>duct system</i> • Increases fat deposition 	<ul style="list-style-type: none"> • Develops <i>acinar system</i> • Blocks prolactin action on the breast
Kidneys	<ul style="list-style-type: none"> • Increases salt and water retention 	<ul style="list-style-type: none"> • Induces diuresis
Pituitary	<ul style="list-style-type: none"> • Feedback inhibition of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) • When estrogen level exceeds 200 pg/mL, it promotes ovulation by inducing an <i>LH surge</i> 	<ul style="list-style-type: none"> • Feedback inhibition of FSH and LH
Genitalia	<ul style="list-style-type: none"> • Increases epithelial thickness and vascularity • Induces <i>copious and alkaline</i> cervical mucus production • Inhibits ovulation 	<ul style="list-style-type: none"> • Decreases epithelial thickness and vascularity • Induces <i>scanty and viscid</i> cervical mucus production • Regulates formation of mucus plug during pregnancy • Inhibits ovulation • Inhibits uterine contractions • Increases body basal temperature
Miscellaneous	<ul style="list-style-type: none"> • Bone: stimulates osteoblasts, closes epiphysis, and protects against osteoporosis • Vascular: <i>increases risk of thromboembolism</i> and serum high-density lipoprotein (HDL) 	

Diabetes Mellitus (DM)

- **Definition:** It is impaired glucose tolerance, which has two types (Table 10.2)
- **Clinical picture:** Polyuria, polydipsia, polyphagia, and weight loss
- **Complications:**
 1. Neuropathy, nephropathy, and *lastly retinopathy*. The mechanism here is *small vessel atherosclerosis* due to *nonenzymatic glycosylation*.
 2. DM can also cause large vessel atherosclerosis, leading to strokes and coronary artery disease (CAD).
 3. Oculomotor nerve (III) palsy affecting the extraocular muscle action.
- **Diagnosis:** High *fasting* glucose above 126 mg is the screening test of choice.
- **Follow-up:** Hemoglobin A_{1c} (HbA_{1c}) gives an idea about control of blood sugar over the last 3 months. Target is below 6.5%. Fructosamine gives an idea about control of blood sugar over the last 3 weeks.

- **Treatment:** See Chapter 9, Pharmacology.

- **Notes:**

1. Major risk factor for complications in DM is *duration of the disease*.
2. Neuropathic leg ulcers occur mainly in the sole and are caused by different organisms, but never by *Clostridium*. Treatment: Debridement.
3. Most common cause of death in patients with DM type 1 is:
 - First decade of life: Diabetic ketoacidosis (DKA)
 - Second decade: Renal failure
4. Hypoglycemia is a common complication in patients with DM, especially:
 - On *sulfonylureas*, e.g., *glyburide*
 - *Excessive exogenous insulin injection* (high insulin and low C peptide)
 - **Alcoholism:** Due to *impaired gluconeogenesis*. Mechanism: *High reduced nicotinamide*

TABLE 10.2 Types of diabetes mellitus (DM).

	DM-1	DM-2
Mechanism	Viral destruction of beta cells, leading to absence of insulin secretion Underlying mechanism is antiinsulin and antiislet cell antibodies	Insulin resistance
Genetics	Weak, but linked to human leukocyte antigens (HLAs) DR3 and DR4	Strong genetic predisposition but it is not HLA linked
Insulin level	Very low or absent	Normal
Obesity	Not common	Very common
Complications	Very common	Not common
Treatment	Insulin	Oral hypoglycemics or insulin

adenine dinucleotide (NADH), converting pyruvate to lactate, and oxaloacetate to malate

5. Glucagonoma: A malignant tumor, presents with hyperglycemia and migrating erythematous skin lesions. So when you see a patient on the USMLE with high blood sugars and unexplained fleeting rash, you know what to think!

Diabetic Ketoacidosis (DKA)

- *Clinical picture:*
 1. Severe diffuse *abdominal pain and vomiting* with no obvious explanation or gross abnormality on exam
 2. *Fruity breath* and hyperventilation (*Kussmaul breathing*)
- *Diagnosis:*
 1. High blood glucose and *high anion gap metabolic acidosis*
 2. *Ketones* in urine and serum
- *Treatment:* Aggressive *hydration, insulin, and potassium* replacement
- *Complications during treatment:*
 1. Rapid drop of blood glucose: Causes cerebral edema
 2. Insulin therapy leads to hypophosphatemia, which causes *muscles paralysis*.
- *Hyperosmolar coma:* Presents and looks just like DKA, without the high anion gap, metabolic acidosis, or ketones. Treated similarly.

Others

- *Thymoma:* Diseases associated with this benign tumor are myasthenia gravis, pure red cell aplasia, systemic lupus erythematosus (SLE), mediastinal syndrome, polymyositis, and neutrophilic agranulocytosis.
- *Pinealoma:* A *germ cell tumor* that presents with high intracranial pressure (headache, nausea, vomiting, blurry vision) and is treated by surgical resection followed by radiation therapy. Clinical picture: 3 *P's:* Precocious puberty, *Papilledema*, and *Parinaud* syndrome (paralysis of upward gaze of the eyes).

Drug-Induced Endocrinal Disorders

- *Iodine and thyroxine:* Hyperthyroidism
- *Lithium:* Hypothyroidism and diabetes insipidus

- *Amiodarone:* Hypothyroidism or hyperthyroidism.
- *Carbamazepine and chlorpropamide:* SIADH
- *Ketoconazole:* Adrenal insufficiency
- *Metoclopramide:* Hyperprolactinemia
- *Steroids:* Hyperglycemia and cushingoid features

Gastrointestinal System

- *Musculature:* The entire GI system is made of smooth muscles except the *upper third of esophagus, the pharynx, and the external anal sphincter* (helpful to remember “UPS”), which are made of skeletal muscles.
- *Nerve supply:* Local GI nerve plexuses are:
 1. *Submucous* Meissner plexus: Regulates *Secretions*
 2. *Myenteric* Auerbach plexus: Regulates *Motility*

Digestion

- The swallowing center is located in the *medulla oblongata* and it initiates peristalsis in the pharynx, which goes through two phases:
 1. Primary peristalsis: Mediated by gravity pushing food down the esophagus
 2. Secondary peristalsis: Active peristalsis that follows to clear the remains left behind in the esophagus
- Lower esophageal sphincter relaxation is mediated by *contact with the food bolus*, and this process is regulated by vasoactive intestinal peptide (*VIP*).
- Once food reaches the stomach, receptive relaxation takes place, which is mediated by *cholecystikinin (CCK)*.
- The stomach performs *three slow waves per minute*; also, *motilin* initiates *migratory myoelectric complex* every *60 to 90 minutes* to clear the gastric remains left behind.
- Gastric emptying process is hastened by *isotonic food in duodenum*, and is slowed down by *CCK* or the presence of *fat* or *excess hydrogen ions in the duodenum*.
- Once food reaches the stomach, the ileum starts performing peristalsis and the ileocecal valve relaxes. This is known as the *gastroileal reflex*.
- *Sodium and glucose* pass from the intestinal lumen into the cells by a *cotransport* mechanism, then they pass into the circulation by *facilitated diffusion*.
- Amino acids and peptides are also absorbed by *Na cotransport*. *Fructose is the only monosaccharide absorbed in the intestine by facilitated diffusion without cotransport*.

Hormones and Mediators

- **Gastrin:** Secretion is stimulated by *phenylalanine* and *tryptophan*. Actions of gastrin:
 1. Stimulates HCL secretion
 2. Hypertrophy of gastric and intestinal mucosa
- **Cholecystokinin (CCK):** Secreted by *I cells* of duodenum and jejunum, which are stimulated by *free fatty acids* and *monoglycerols*. Actions of CCK:
 1. Contraction of gallbladder's wall and relaxation of sphincter of Oddi
 2. Stimulates pancreatic *enzyme* secretion
 3. Delays gastric emptying and stimulates growth of the exocrine pancreas
- **Secretin:** Secreted by S cells of duodenum, and it stimulates *pancreatic bicarbonate* secretion
- **Somatostatin:** Secreted by D cells of pancreas, and it inhibits *all GI hormones*
- **Histamine:** Stimulates *HCL secretion* (remember H2 blockers?)
- **Gastrointestinal peptide (GIP):** Stimulates pancreatic *insulin* secretion. *That is the reason oral glucose stimulates insulin secretion in large amounts compared to IV glucose.*
- **Vasoactive intestinal peptide (VIP):** It is the mediator of *pancreatic cholera*, stimulates gastric HCL and pancreatic bicarbonate secretion, and also regulates relaxation of lower esophageal sphincter.

Secretions

Saliva

- A *hypotonic* solution, rich in *K* and *HCO₃*, and deficient in *Na* and *Cl*
- **Aldosterone** regulates the Na/K transfer in and out of salivary ducts.
- Parasympathetic system (cranial nerves *VII* and *IX*): *Abundant and watery* saliva
- Sympathetic system via the *cyclic adenosine monophosphate (cAMP)* system causes saliva to be *scanty and viscid*
- Lingual lipase cleaves triglycerides into *monoglycerols and free fatty acids*
- Lingual amylase (*ptyalin*) is responsible for *starch* digestion. It works on *alpha 1-4* bonds.

Gastric Secretions

- Parietal cells of the stomach secrete *HCL* and *intrinsic factor*. Intrinsic factor binds to vitamin

B₁₂ all the way to the ileum where *only B₁₂* gets absorbed (without intrinsic factor). Ileal resection leads to *vitamin B₁₂ deficiency*, *steatorrhea*, and *recurrent oxalate stones*.

- In pernicious anemia, there is autoimmune destruction of parietal cells and intrinsic factor, and this carries an increased risk of developing *gastric adenocarcinoma*.
- Low HCl content of the stomach puts it at risk of infection with *Salmonella*.
- Chief cells secrete *pepsinogen*, which further breaks down to *pepsin*.
- G cells secrete gastrin, which stimulates HCl secretion by parietal cells.

Pancreatic Secretions

- The pancreas secretes an *isotonic* fluid with *high HCO₃* and a *low Cl* content.
- Pancreatic amylase: Breaks down *starch* into *oligosaccharides and maltose*
- Pancreatic lipase: Digests *fat*. *Elevated in pancreatitis (best marker)*.
- Pancreatic proteases, e.g., Elastase, trypsin, and chemotrypsin: Break down *protein* into shorter amino acid chains
- Trypsinogen is cleaved to form trypsin by duodenal enterokinase. Trypsin (as well as thrombin) digests proteins at the *arginine-glycine* bond.
- Bentiromide is used to assess the pancreatic function by measuring the duodenal chemotrypsin and its ability to cleave para-aminobenzoic acid (PABA).
- Note: All pancreatic enzymes are released in an inactive form to protect pancreas from digesting itself.

Bile

- *Secreted by the liver* and *stored in the gallbladder*.
- Composition: Mainly *water*, plus bile salts, cholesterol, and bilirubin
- Bilirubin may cause jaundice. There are two types of bilirubin:
 1. Direct (conjugated): Passes in the urine and stools
 2. Indirect (unconjugated): Incapable of passing into urine or stools, but it can cross blood-brain barrier. *This is the form that causes kernicterus in neonatal jaundice.*
- Note: Amount of secretions:
 1. Salivary: *1.5 liters/day*
 2. Gastric: *2.5 liters/day*
 3. Pancreatico-biliary: *1 liter/day*
 4. Succus entericus: *3 liters/day*

Physiology of the Liver

- Liver is the body's heaviest visceral organ.
- *Blood supply*: Mainly through the *portal vein*, and to a lesser extent hepatic artery
- *Space of Disse*: Glancing at the hepatic lobule, the space of Disse is located between the blood sinusoids and hepatocytes. It contains *Ito (stellate) cells*, which serve for *synthesizing collagen* and *storing vitamin A*. Also in the walls of sinusoids lie the *Kupffer cells*, which serve as *liver macrophages*.
- *Functions of liver*: Storage of energy in the form of glycogen, and synthesizing plasma proteins, fat, and finally bile salts for absorption of fat.
- *Liver function tests*:
 1. Aspartate aminotransferase (AST) (serum glutamic-oxaloacetic transaminase [SGOT]): Present in hepatocytes' *mitochondria*. It has a *short half-life* and is a *nonspecific* test for liver function.
 2. Alanine aminotransferase (ALT) (serum glutamic-pyruvic transaminase [SGPT]): Present in the *cytoplasm*, has a *long half-life* and is *specific* to the liver. In *alcoholism*, $AST:ALT > 2$.
 3. Alkaline phosphatase: Present in hepatocyte membranes and bones. Elevation is suggestive of biliary obstruction or bone destruction.
 4. Gamma-glutamyl transferase (GGT): Specific to the liver, especially alcoholic liver disease
 5. Bilirubin: The majority circulating is indirect (0.8 mg), and it cannot pass in the urine or stools, but it can cross the blood–brain barrier. Direct (0.2 mg) may pass into urine and stools but cannot cross the BBB, and is more suggestive of biliary obstruction.
 6. Albumin (4 to 5 g): It is the best indicator of the *chronicity* of liver disease.
 7. Prothrombin time (PT): It is the best indicator of the *severity and prognosis* of liver disease.
 8. Globulins (2 to 3 g): *Immunoglobulin G (IgG)* is elevated in *chronic hepatitis*, *IgA* in *alcoholic liver disease*, and *IgM* in *biliary cirrhosis*.
 9. Alpha-fetoprotein (Normal < 25 ng/mL): Hepatoma marker, but can also rise in pregnancy.

Dysphagia

- *Mechanism*: It can occur due to an internal obstruction, e.g., tumor, or external compression, e.g., tumor, *enlarged left atrium*, or lymph nodes.
- *Clinical picture keywords*:
 1. Dysphagia mainly to liquids: *Achalasia*
 2. Dysphagia mainly to solids: *Tumor*, e.g., malignancy
 3. Dysphagia and regurgitation of undigested food: *Zenker's diverticulum*

4. Dysphagia and long-standing gastroesophageal reflux disease (GERD): *Esophageal strictures*
5. Dysphagia and tight shiny skin: *Scleroderma*

- *Diagnosis*: Best next step is *barium swallow*, then an esophagogastroduodenoscopy (EGD) if barium swallow is inconclusive.
- *Note*: Oropharyngeal dysphagia usually occurs after major cerebrovascular accidents (CVAs), and is evaluated using videoesophagography.

Esophageal Varices

- *Mechanism*: Dilated portosystemic shunts between the *left gastric* and *azygos veins*, most commonly due to *portal hypertension*
- *Clinical picture*: Patient with *liver cirrhosis* vomiting *bright red blood*
- *Treatment*: *Sandostatin* (octreotide) and EGD to perform *banding* or *sclerotherapy*
- *Note*: Balloon tamponade is used only if the above measures failed.

Achalasia

- *Mechanism*: It is *abnormal peristalsis of esophagus* and *incomplete relaxation of lower sphincter*, due to *loss of Auerbach plexus*.
- *Clinical picture*: *Dysphagia*; *more to liquids*, and *regurgitation of meals*
- *Diagnosis*:



FIG. 10.6 Bird's-beak sign of achalasia

1. Barium swallow shows *bird's-beak sign* (Fig. 10.6).
 2. Esophageal manometry shows high intraesophageal pressure (>25 mm Hg).
- **Treatment:** Myotomy (*best*), dilatation, or botulinum toxin injection
 - **Note:** Postmortem, brown spots of digested hemoglobin can be seen in the esophageal wall ("*leopard spots*").

Diffuse Esophageal Spasm

- **Clinical picture:** Chest pain related to meals; often confused with angina
- **Diagnosis:** Barium swallow shows *corkscrew esophagus*.
- **Treatment:** Calcium channel blockers to relax the smooth muscle

Plummer-Vinson Syndrome

- **Clinical picture:** Esophageal webs, atrophic glossitis, and iron-deficiency anemia
- **Complication:** High risk of developing esophageal squamous cell cancer
- **Treatment:** Dilatation and iron-replacement therapy

Peptic Ulcer Disease (PUD)

- **Location and cause:**
 1. Gastric: Common on the *lesser curvature*, due to damaged protective layer
 2. Duodenum: Duodenal bulb, due to hyperacidity or *Helicobacter pylori* infection, which is a gram-negative rod normally residing in the antrum
- **Clinical picture:**
 1. Gastric: Epigastric pain that worsens immediately after eating
 2. Duodenal: Epigastric pain relieved with eating, but resumes an hour later
- **Complications:**
 1. Perforation of an ulcer in the posterior duodenal wall leads to injury of the *gastroduodenal artery*, so suspect it any patient with duodenal ulcer who develops severe abdominal pain and becomes hemodynamically unstable
 2. Perforation: Presents with abdominal pain. Patient has *tympanic abdomen* on percussion and upright abdominal x-ray shows *air under diaphragm*.
- **Treatment:** Proton pump inhibitor (PPI) for 6 weeks; if no improvement, perform EGD and test for *H. pylori* by biopsy (*Clo test*), stool antigens, or urease breath test. Surgery is reserved for severe cases.

- **Treatment of *H. pylori*:** Triple therapy: amoxicillin, clarithromycin, and PPI for 2 weeks. *If the patient has a penicillin allergy, the second preferred combination is tetracycline, metronidazole, and bismuth for 2 weeks.*

- **GERD:** Long-standing gastroesophageal reflux disease (GERD) may result in replacement of the distal esophageal *stratified squamous epithelium* with gastric *columnar epithelium*. This is known as *Barrett's esophagus* and is associated with a high risk of *adenocarcinoma*. Any other carcinoma in the esophagus is a *squamous cell carcinoma*, for which *smoking* and *alcohol* are two major risk factors. Patients with esophageal cancer have dysphagia, more to *solids* (unlike achalasia).

- **Zollinger-Ellison syndrome:**

1. It is hypergastrinemia due to either *antral G cell hyperplasia* or a *gastrinoma in the pancreas*.
2. Clinical picture: Multiple recurrent peptic ulcers and chronic diarrhea
3. Diagnosis: *High fasting serum gastrin and positive secretin stimulation test*
4. Treatment: PPI, and surgical resection of the gastrinoma

- **Notes:**

1. Barrett's esophagus treatment: Cisapride and PPI
2. Barrett's esophagus with no dysplasia: Annual EGD. Low-grade dysplasia: EGD every 6 months. High-grade dysplasia: Esophagectomy.
3. *Vitamin C inhibits reduction of nitrite to nitrosamine, which decreases the risk of atrophic gastritis and stomach cancer.*
4. *In duodenal ulcers, there is hypertrophy of Brunner glands.*
5. Acute gastritis shows *erosions*, while chronic gastritis shows *atrophy and infiltration with mononuclear cells*.
6. *Patients with long-standing GERD may develop esophageal strictures and webs causing dysphagia. They are known as Schatzki rings.*
7. Severe repeated vomiting and retching can lead to a tear in the gastric mucosa near the gastroesophageal junction. This tear is known as a *Mallory-Weiss tear*. Clinical picture: *Severe repeated nonbloody vomiting, which ends up with episodes of coffee-ground emesis. If esophageal perforation happens in this setting, it is known as Boerhaave's esophagus.*

Celiac Sprue

- **Mechanism:** A *gluten-associated* disease that causes atrophy of the small intestinal villi and malabsorption. It is associated with *HLA-DQ2*.
- **Clinical picture:**

1. *Chronic osmotic diarrhea, i.e., related to meals, and improves by fasting*
 2. Vesiculopapular skin lesions known as *dermatitis herpetiformis*.
- **Diagnosis:**
 1. *Small intestine biopsy* is the gold standard.
 2. High serum level of *IgA antiendomysial, antigliadin, and tissue transglutaminase antibodies*
 3. Abnormal *D-xylose* test
 4. Low *albumin, iron, and calcium* levels in the blood
 - **Complication:** If an elderly patient with celiac sprue deteriorates suddenly, suspect *T-cell lymphoma of small intestine*.
 - **Treatment:** *Gluten-free diet*

Intestinal Obstruction

- Most common cause is *adhesions*, e.g., secondary to surgery
- **Clinical picture:** *Abdominal pain, constipation, and vomiting*
- **Diagnosis:** Upright abdominal x-ray shows *air fluid levels* (Fig. 10.7)
- **Treatment:** Supportive; surgery for complicated nonresolving cases



FIG. 10.7 Air-fluid levels of intestinal obstruction

Appendicitis

- **Anatomic hint:** The appendix is found intraoperatively *by following the taeniae coli to their confluence*.
- **Clinical picture:** Periumbilical abdominal pain that later migrates toward the right lower quadrant, plus constipation, nausea, and vomiting
- **On exam:** Tenderness on deep palpation at *McBurney's point* is pathognomonic, *i.e., tenderness at the junction of the medial two thirds and lateral one third of a line between the umbilicus and right anterior superior iliac spine*
- **Diagnosis:** CT of abdomen and pelvis
- **Treatment:** Surgical, *i.e., appendectomy*
- **Note:** If a patient with appendicitis develops fever and jaundice, think of *portal vein septic clot (pyelophlebitis)*.
Diagnosis: CT scan to look for gas in the portal vein.

Inflammatory Bowel Disease (IBD)

(Table 10.3)

Mesenteric Ischemia

- Suspect in any patient with arrhythmia, e.g., atrial fibrillation or heart disease
- **Clinical picture:** Vague diffuse abdominal pain induced only by eating, *also called intestinal angina*
- **Complication:** Ischemic colitis: severe abdominal pain and bleeding per rectum
- **On exam:** *Normal*. The hallmark is abdominal pain *out of proportion* to exam.
- **Diagnosis:**
 1. Gold standard for diagnosis is *mesenteric angiography*.
 2. CT scan of abdomen: Pathognomonic *thumb-printing sign*
 3. Elevated venous *lactic acid*
- **Treatment:** Surgery

Irritable Bowel Syndrome (IBS)

- Common in middle-aged patients with stressed-out personalities.
- **Clinical picture:** *At least 3 months* of unexplained abdominal pain with diarrhea or constipation or both, *mainly associated with eating, and relieved by bowel movements*
- **Diagnosis:** Diagnosis of exclusion. The key here will be the *stressed-out personality* and *the normal workup*.
- **Treatment:**
 1. Constipation predominant form: *Tegaserod*
 2. Diarrhea predominant form: *Alosteron*

TABLE 10.3 Inflammatory bowel diseases (IBDs).

	Crohn's disease	Ulcerative colitis
Location	Anywhere except the rectum; most common in ileocecal segment	Anywhere in the colon; most common in the rectum
Extent of lesions	Skip lesions and cobblestoning	Diffuse
Depth of lesions	Deep, causing fistulas and abscesses	Superficial
Effect of smoking	Worsens symptoms	Improves symptoms
Symptoms	Abdominal pain, diarrhea and mass in the right lower quadrant (RLQ) of abdomen	Abdominal pain and bloody diarrhea
Barium enema	String sign	Loss of colonic haustrations
Treatment	Sulfasalazine, mesalamine, or steroids Fistula: treated by metronidazole or infliximab; if failed, perform fistulotomy	Sulfasalazine, mesalamine, or steroids
Malignant transformation	High, need annual colonoscopy	High, need annual colonoscopy
Extraintestinal manifestations	Possible, but not as common as in ulcerative colitis	Arthritis, scleritis, uveitis, pyoderma gangrenosum, and sclerosing cholangitis If any patient with IBD develops jaundice, do endoscopic retrograde cholangiopancreatography (ERCP) to rule out sclerosing cholangitis
Microscopy	Noncaseating granuloma	Crypt abscesses and ulcers

- *Note:* Currently, we prefer to avoid Tegaserod and Alosteron due to black box warning and some reported fatal adverse effects.

Diarrhea

- *Definition:* It is an increase in the amount or frequency of bowel movements of a person compared to his usual habit.
- *Types:*
 1. Osmotic: *Related to meals*, and improves with fasting; suggests a malabsorption or motility disorder
 2. Secretory: Mediated by toxins, thus not related to meals and *does not improve with fasting*
- *Giardiasis:* Targets the duodenum and upper jejunum. Causes *watery diarrhea with excessive mucus*. Diagnosis: Stool analysis. Treatment: Metronidazole.
- *Rotavirus:* It is the most common cause of diarrhea in children. It is most common during the winter months and causes *watery diarrhea*.
- *Campylobacter jejuni:* Causes *bloody diarrhea*. Treatment: *Erythromycin*.
- *Cryptosporidium parvum:* Causes watery diarrhea in patients with HIV.

Colon Cancer

- *Risk factors:*
 1. Old age, and low-fiber and high-fat diet
 2. Inflammatory bowel disease (IBD)
 3. Familial adenomatous polyposis (FAP) and hereditary non-polyposis colon cancer (HNPCC)
 4. Adenomatous polyps with *villous* component. Signs suggestive of malignancy in polyps include:

bigger than *1 cm in diameter*, more than three in number, and having a *villous component*, e.g., villous, tubulovillous. A benign polyp can turn malignant due to mutation of *DDC* and *p53* genes.

- *Screening:*
 1. Starting at age 40: Performing annual digital rectal exam (DRE)
 2. Starting at age 50: Checking for *occult blood in stools through DRE annually*, plus *colonoscopy every 10 years or sigmoidoscopy every 5 years. Start earlier in high-risk groups.*
- *Location:* Most common site is the *rectosigmoid area*
- *Metastases:* Most common site of metastasis is the *liver*
- *Clinical picture:*
 1. Asymptomatic or altered bowel habits, e.g., constipation, bleeding per rectum
 2. Anemia and weight loss. *Any elderly person with unexplained iron-deficiency anemia must have a colonoscopy to rule out colon cancer.*
- *Diagnosis:*
 1. Colonoscopy and biopsy are diagnostic.
 2. Barium enema shows *apple-core sign* (Fig. 10.8)
 3. Elevated serum *carcinoembryonic antigen (CEA)*
- *Treatment:* Surgery, radiation, and chemotherapy

Familial Adenomatous Polyposis (FAP)

- *Mechanism:* FAP is an autosomal dominant disease that occurs due to a mutation of the *APC* gene on

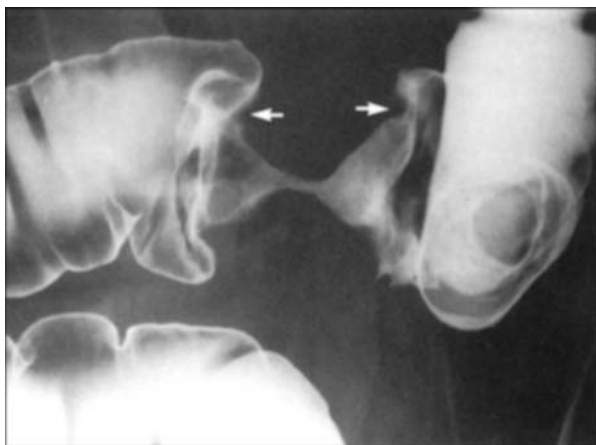


FIG. 10.8 Apple-core sign of colon cancer (arrows)

chromosome 5. Polyps in this disease get larger in size due to a mutation of the *ras* gene.

- **Clinical picture:** Lower abdominal pain and bleeding per rectum
- **Diagnosis:** Colonoscopy
- **Treatment:** Once discovered, patients must undergo proctocolectomy by age 20, as it has a 100% potential of transformation into colon cancer.
- **Notes:**
 1. *Peutz-Jeghers syndrome:* Colonic polyps and oral and anal hyperpigmented lesions
 2. *Gardner's syndrome:* FAP, sebaceous cysts, osteomas, and desmoid tumor
 3. *Turcot's syndrome:* Same as Gardner's, plus neurovascular tumors

Diverticular Disease

- **Mechanism:** It is an outpouching of *mucosa* and *submucosa* in the colon, mostly in the *sigmoid* portion; never in the *rectum*.
- **Clinical picture:** Lower left quadrant (LLQ) abdominal pain and bleeding per rectum
- **Diagnosis:** Barium enema, CT abdomen, or colonoscopy shows the *sawtooth* appearance.
- **Complications**
 1. Painless bright red bleeding per rectum: Diverticular disease is the most common cause of lower GI bleeding in the elderly. *Bleeding stops spontaneously.*
 2. Diverticulae can become infected, leading to *diverticulitis*. Clinical picture: LLQ abdominal pain, fever, leukocytosis. Treatment: Ciprofloxacin and metronidazole.

- **Notes:**

1. Bleeding in diverticular disease occurs due to rupture of a blood vessel around the neck of a diverticulum. *Again, this bleeding stops spontaneously.*
2. Surgery, e.g., *sigmoidectomy* is indicated only in severe complicated cases of diverticular disease, such as recurrent attacks, perforation, abscess formation.
3. Atrioventricular (AV) malformations are another common cause of painless, bright-red bleeding per rectum. They are most common in the *cecum* and *ascending colon*. Diagnosis: Angiography or colonoscopy. Treatment: Electrocoagulation, local vasopressin, or segmental colectomy in severe resistant cases.

Hepatitis

- It is an inflammation of the hepatic tissue.
- **Causes:** Could be viral, e.g. hepatitis A, B, or C, cytomegalovirus (CMV), Epstein-Barr virus (EBV), or autoimmune (which is diagnosed by positive *anti-smooth muscle antibody* and *antinuclear antibody [ANA]*).
- **Pathology:** *Lymphocytic infiltration of the liver*. Discussed in Chapter 7, Microbiology.

Liver Cirrhosis

- **Mechanism:** It is *fibrosis and nodule formation in the liver* as a sequel of a primary disease, mainly hepatitis.
- **Pathologically:** Divided into two types:
 1. Micronodular (<3 mm): As in alcoholism (*AST:ALT >2*)
 2. Macronodular (≥ 3 mm): As in hepatocellular carcinoma
- **Other causes:**
 1. Hemochromatosis:
 - It is either congenital (*HFE gene AR mutation*) or acquired iron overload.
 - Clinical picture: Liver cirrhosis, bronze-colored skin in exposed areas, congestive heart failure (CHF), and hyperglycemia, hence the term *bronze diabetes*
 - Diagnosis: High iron, ferritin, and transferrin. Biopsy of the liver stains well with Prussian blue due to high iron content.
 - Treatment: Phlebotomy and iron chelation therapy

2. Wilson's disease

- Mechanism: Genetic *ceruloplasmin* deficiency
 - Clinical picture: Liver cirrhosis, renal tubular damage, Kayser-Fleischer rings in corneas (Fig. 10.9), and basal ganglia injury causing *wing beating tremors* and extrapyramidal symptoms
 - Diagnosis: Low serum ceruloplasmin, and high copper levels in liver and urine. These patients also have glucosuria and amino aciduria.
 - Treatment: Copper chelating agents, e.g., penicillamine
 - Think of Wilson's in a patient with *recurrent hepatitis*.
- *Clinical picture of cirrhosis: Hepatosplenomegaly* and:
 1. Wasting of the temporalis muscles
 2. Parotid enlargement
 3. Jaundice and fetor hepaticus; smelly breath due to *mercaptans*
 4. Gynecomastia: Usually unilateral and tender enlargement of breast glands
 5. Palmar erythema and flapping tremors (*asterixis*)
 6. Spider angiomata
 7. Female hair distribution: Due to *testosterone deficiency*
 8. Hyperdynamic circulation: Due to *vasodilator effect of toxins*
 9. Pancytopenia: Due to *hypersplenism*
 - *Portal hypertension*: Patients with cirrhosis are at risk of portal hypertension (>12 mm Hg), which leads to *hepatosplenomegaly, gastropathy, ascites*, and opening of portosystemic shunts:
 1. Esophageal varices: Due to shunting of *left gastric* with *azygos* veins
 2. Hemorrhoids: Shunting of *superior and middle rectal* with *inferior rectal* veins

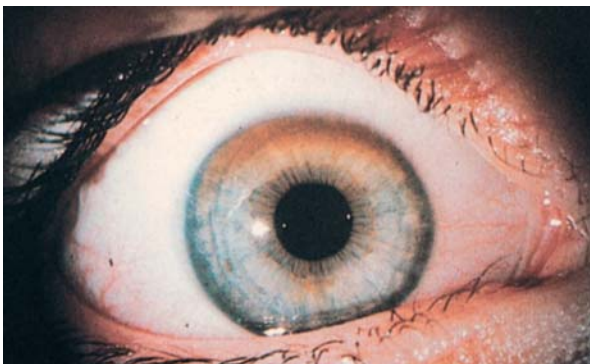


FIG. 10.9 Kayser-Fleischer ring

3. Caput medusa: Shunting of *paraumbilical* with *inferior epigastric* veins

- *Pathology*: Liver shows *Mallory bodies*, fatty change, intrahepatic cholestasis, and fibrosis around the central vein.
- *Treatment*: Correct cause of cirrhosis, plus *beta-blockers for portal hypertension*, e.g.: Propranolol.
- *Note*: Cirrhotic patients have *low serum albumin* and *high beta and gamma globulin*.

Hepatic Encephalopathy

- It is a neuropsychiatric complication of liver cell failure.
- *Clinical picture*: A cirrhotic patient with *reversed sleep rhythm* and confusion, progressing to lethargy and stupor, and maybe coma and death.
- *Diagnosis*: Elevated serum *ammonia* level
- *Treatment*:
 1. Lactulose and enemas: To wash out intestinal contents. *Lactulose is preferred as it is a nonabsorbable disaccharide.*
 2. *Neomycin* or metronidazole: To kill intestinal flora metabolizing proteins

Ascites

- *Definition*: It is accumulation of fluid in the peritoneum.
- Serum/ascitic albumin gradient (SAAG): ≥ 1.1 is suggestive of cirrhosis, while <1.1 is suggestive of TB, malignancy, or pancreatitis.
- *Nature*: How to know if the fluid is exudate or transudate? See Table 10.4.
- *Treatment*:
 1. Salt and fluid restriction, spironolactone, and furosemide. In large symptomatic ascites, paracentesis should be performed.
 2. In case of recurrent ascites refractory to medical treatment, transjugular intrahepatic portosystemic shunt (*TIPSS*) should be performed. It is also indicated for recurrent bleeding esophageal varices.

TABLE 10.4 Exudate and transudate diagnostic criteria.

Criteria	Exudate	Transudate
Ascitic protein:serum protein	>0.5	<0.5
Ascitic lactate dehydrogenase (LDH):serum LDH	>0.6	<0.6
Specific gravity	>1018	<1018

Spontaneous Bacterial Peritonitis (SBP)

- A complication of ascites due to *Escherichia coli* or less likely *Klebsiella*
- *Clinical picture*: Ascites, plus diffusely red warm and tender abdomen
- *Diagnosis*: Paracentesis, showing neutrophil count of $>250/\text{mm}^3$, is diagnostic.
- *Treatment*: Drug of choice is third-generation cephalosporin, e.g., cefotaxime.

Biliary Cirrhosis

- *Mechanism*: Common in middle-aged women. It may be either primary or secondary to biliary obstruction.
- *Clinical picture*: Middle-aged woman with:
 1. Liver cirrhosis, itching, dark urine, and clay-colored stools
 2. Vitamin K and Vitamin D deficiency
- *Diagnosis*:
 1. Primary: High levels of *antimitochondrial antibodies*
 2. Secondary: Ultrasound of liver; if that shows dilatation of intrahepatic ducts, endoscopic retrograde cholangiopancreatography (ERCP) should be done next to manage the extrahepatic obstruction.
- *Treatment*: Ursodiol, and relieving the obstruction

Gallstones

- *Types*: Mostly cholesterol stones, but could also be pigment or mixed stones
- *Risk factors (4 F's)*: Female, fat, fertile, and in her forties
- *Clinical picture*: Epigastric and right upper quadrant abdominal pain with eating, especially after ingestion of *fatty meals*
- *On exam*: Right upper quadrant tenderness at the tip of the right ninth costal cartilage (*Murphy's sign*).
- *Complications*:
 1. Cholecystitis: Appears on ultrasound as thickening of the gallbladder wall with surrounding inflammatory fluid
 2. Cholangitis: Inflammation of the common bile duct (CBD), due an obstruction downstream. It presents with *Charcot's triad* of fever, pain, and jaundice.
- *Diagnosis*:
 1. Ultrasound of gallbladder: If that shows dilatation of intrahepatic ducts, the next best step is

ERCP. Most gallstones, unlike kidney stones, are radiolucent, so x-ray is not helpful

2. Stones in the CBD can cause significant elevation of *alkaline phosphatase* and *direct bilirubin*; the rest of liver function tests may also be slightly elevated.
- *Treatment*:
 1. *Cholecystectomy*: Gallstones are not treated unless they are symptomatic.
 2. Treatment of cholangitis: Antibiotics, followed by surgery if needed

Jaundice

- It is yellowish discoloration of the skin and mucous membranes due to hyperbilirubinemia.
- *Causes of indirect hyperbilirubinemia*: Hemolysis, and congenital, as discussed below. Indirect bilirubin is elevated, so urine and stool color is normal.
- *Causes of direct hyperbilirubinemia*: Biliary obstruction, and congenital as below. Direct bilirubin is elevated, so urine is tea colored and stools are clay colored. First thing to do in obstructive jaundice is *hepatobiliary ultrasound*; if there is dilatation of the intrahepatic or extrahepatic biliary tree, that means there is extrahepatic biliary obstruction, and ERCP should be the next step. Palpable gallbladder in obstructive jaundice is suggestive of malignancy (*Courvoisier sign*).
- *Hepatocellular jaundice*: Occurs due to two defects: defective uptake and conjugation resulting in high indirect bilirubin, and defective excretion resulting in high direct bilirubin. This leads to dark urine and dark stools.

Congenital Hyperbilirubinemia

- *Crigler-Najjar syndrome*: Occurs due to deficiency of uridine diphosphate (UDP) glucuronyl transferase. The bilirubin elevated is mainly indirect, so kernicterus is a risk.
- *Gilbert syndrome (autosomal dominant [AD])*: Occurs due to presence of only small amount of UDP glucuronyl transferase plus defective uptake, so indirect bilirubin rises only if the patient fasts or experiences severe stress or exercise.
- *Dubin-Johnson syndrome (autosomal recessive [AR])*: Occurs to defective hepatic excretion. The bilirubin elevated here is direct bilirubin, and the liver macroscopically is brown or black. There is a high coproporphyrin I/coproporphyrin III ratio.

- *Note:* The last place for jaundice to disappear is the sclera, the reason being its high *elastin* content, which has high affinity to bilirubin

Acute Pancreatitis

- *Causes* in descending order: *Alcohol*, *gallstones*, and *hypertriglyceridemia*. Other less common causes are mumps and pancreas divisum. In pancreas divisum, the *accessory duct* becomes the main duct of the pancreas.
- *Clinical picture:* Epigastric abdominal pain radiating to the back, and is decreased by leaning forward
- *Physical exam:* Not conclusive except for hemorrhagic types, which may show bruising around the umbilicus (*Cullen's sign*) or in the left flank (*Grey Turner sign*). Remember *Cullen's* by imagining a bruise curving around the belly button.
- *Diagnosis:*
 1. High serum lipase (specific) and amylase (nonspecific)
 2. CT of the abdomen: Shows edema of the pancreas with stranding of its fat
 3. Abdominal X-ray shows *sentinel loop* or *colon cut-off* signs.
 4. Ultrasound of the gallbladder if gallstones are the suspected cause
- *Complications:* Hypocalcemia, disseminated intravascular coagulopathy (DIC), and pseudocyst formation
- *Treatment:* Bowel rest, aggressive hydration, and pain control
- *Note:* Persistent fever and toxemia after treatment is suggestive of pancreatic abscess, and repeat CT of the abdomen should be the next step.

Chronic Pancreatitis

- *Mechanism:* Occurs due to repeated attacks of pancreatitis
- *Diagnosis:*
 1. X-ray of the abdomen: *Calcifications*
 2. ERCP pancreatogram: *Chain of lakes* appearance of pancreatic duct
- *Clinical picture:*
 1. Recurrent attacks of abdominal pain and acute pancreatitis
 2. *Malabsorption:* Steatorrhea and vitamin A, D, E, and K deficiency
 3. *Hyperglycemia*

4. Vitamin B₁₂ deficiency

- *Treatment:* Pancreatic enzymes replacement
- *Note:* In both acute and chronic pancreatitis, D-xylose test is normal.

Pancreatic Cancer

- A very aggressive malignancy, not curable even with chemotherapy. Lifetime expectancy is *less than 6 months* in most cases.
- *Clinical picture:*
 1. Epigastric pain radiating to the back, decreased by leaning forward
 2. *Painless obstructive jaundice* and *weight loss*
 3. Palpable gallbladder, also called *Courvoisier sign*
- *Diagnosis:* CT of abdomen and high serum levels of CA 19-9; confirmed with *biopsy*
- *Complications:* Migratory thrombophlebitis (*Trousseau syndrome*)
- *Treatment:* Palliative surgery; best is pancreaticoduodenectomy (*Whipple's*)

Splenic Rupture

- *Causes:* Common in severe abdominal trauma, especially with fractured left ribs
- *Clinical picture:* Severe abdominal pain, hemodynamic instability, and left shoulder pain due to diaphragm irritation (*referred pain*)
- *Diagnosis:* CT or ultrasound of the abdomen
- *Treatment:* Resuscitation first, then emergent splenectomy
- *Remember:* Vaccinate the patient before splenectomy against *Haemophilus influenzae B*, streptococcus pneumoniae, and meningococci to avoid a fulminant infection postoperatively; the worst is usually the *pneumococcal infection*.

Respiratory System

Important Definitions (Fig. 10.10)

- *Tidal volume (TV):* It is the amount of air that enters the lung on a normal inspiration; it is equal to 500 cc.
- *Inspiratory reserve volume (IRV):* It is the amount of air that enters the lung on forced inspiration.
- *Expiratory reserve volume (ERV):* It is the amount of air left in the lung after a normal expiration.
- *Residual volume (RV):* It is the amount of air left in the lung after a forced expiration.

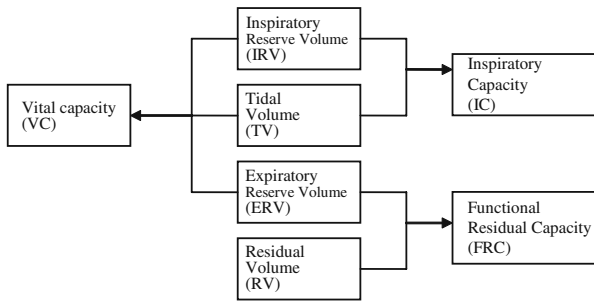


FIG. 10.10 Lung volumes and capacities. Total lung capacity (TLC) = IRV + TV + ERV + RV

- *Notes:*
 1. *Residual volume cannot be measured by spirometry, and the only way to measure it is complete pulmonary function tests (PFTs).*
 2. *Functional residual capacity (FRC) is reduced in any disease with low lung volume, e.g., lung collapse or fibrosis. FRC is increased in any disease with large lung volume, e.g., emphysema.*

Pulmonary Function Tests

- The number to remember here is *80%*, below which the PFT is abnormal.
- *Obstructive lung diseases, e.g., chronic obstructive pulmonary disease (COPD):* Low forced vital capacity (FVC) and *very low* forced expiratory volume in 1 second (FEV_1) resulting in a FEV_1/FVC ratio of *less than 80%*; however, total lung capacity (TLC) is *above 80%*.
- *Restrictive lung diseases, e.g., interstitial lung disease:* Low FVC and *equally low* FEV_1 , so the *ratio is more than 80%*; however *TLC is below 80%*.
- *Mixed (obstructive and restrictive):* $FEV_1/FVC < 80%$ and $TLC < 80%$

Dead Space

- *Anatomic dead space:* About *150 mL* and is measured by the *Fowler method*.
- *Physiologic dead space:* Measured by the *Bohr method*

Respiratory Muscles

- *Passive inspiration:* *Diaphragm*
- *Forced inspiration:* *External intercostals and accessory muscles*

- *Passive expiration:* *Passive*
- *Forced expiration:* *Internal intercostals and abdominal muscles*

Compliance

- *Definition:* It is the *lung's distensibility, which is inversely proportionate to the lung elasticity.*
- *Note:* At FRC level, the forces of lung collapse and chest wall expansion are equal in power and opposite in direction.

Bronchioalveolar Pulmonary System

- Maximum resistance to airflow occurs at the level of the *medium-sized bronchi*.
- There is a *fourth power inverse proportion* between the radius of the airway and airflow resistance.
- Surfactant (*dipalmitoyl-phosphatidylcholine*) is formed by *type II pneumocytes* and is completely formed by the *35th week of gestation*. It lines the alveoli to keep them open by *decreasing their surface tension and increasing their compliance*.
- Large alveoli are stable; it is the small ones that easily collapse in the absence of surfactant.
- During the respiratory cycle, alveolar pressure and intrapleural pressure (*measured by a balloon catheter in esophagus*) change as shown in Fig. 10.11.
- Ventilation and perfusion are highest in the lung bases and least in the apices.
- Ventilation/perfusion ratio (V/Q): *At the apex = 1–3, at base = 0.6–0.8.*
- If V/Q ratio is equal to zero, that suggests complete airway obstruction, while extremely elevated V/Q ratio suggests circulation pathology, resulting in perfusion defect, e.g., pulmonary embolism.

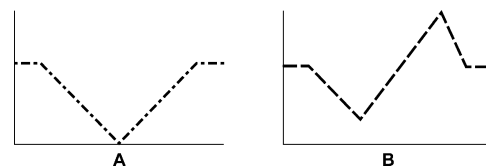


FIG. 10.11 (A) Intrapleural pressure changes during respiratory cycle. (B) Alveolar pressure changes during respiratory cycle

Breathing and Gases

- *Respiratory centers:*
 1. Medullary reticular formation contains the major respiratory centers:
 - Dorsal group: Controls *inspiration*
 - Ventral group: Controls *expiration*
 2. Apneustic and pneumotaxic centers in the *pons* inhibit inspiration
- Gases:
 1. Diffusion limited: *Oxygen* and carbon monoxide (CO)
 2. Perfusion limited: *Carbon dioxide (CO₂)*, NO₂, and oxygen
- *Chemoreceptors:*
 1. Central: In the medulla; stimulated by *high CO₂* and *H*
 2. Peripheral: In the carotid and aortic bodies; stimulated by *low oxygen* and *high CO₂* and *H*. So when the USMLE asks about how breathing is stimulated in a patient with low oxygen but normal CO₂, the answer is obviously *peripheral receptors*.
- *Hering-Breuer reflex:* It is inhibition of inspiration due to stretch of lung tissue.
- Notes:
 1. Hypoxia causes vasodilatation everywhere in the body *except the lungs, where it causes vasoconstriction*.
 2. CO₂ is transported in the blood mainly in the form of *bicarbonate* and to a lesser extent bound to hemoglobin.
 3. Pulmonary venous congestion leads to rapid shallow breathing due to stimulation of *J receptors*.

Asthma

- *Mechanism:* It is an inflammatory process of the airways characterized by *reversible bronchospasm* and increased airway secretions.
- *Clinical picture:* *Shortness of breath, wheezing, and chronic cough*
- *Diagnosis:* PFTs and *methacholine challenge test*
- *Treatment:*
 1. *Inhaled steroids:* It is the mainstay of treatment. Steroids *suppress the hyperreactivity of airways* to various stimuli. Side effects: *Oral thrush*, which is prevented by *washing the mouth after inhalation*.

2. Exercise-induced asthma: *Albuterol* before exercise
3. Allergy-induced asthma: *Mast cell stabilizer* inhaler, e.g., nedocromil
4. Others: See Chapter 9, Pharmacology

- Notes:
 1. Atopic (extrinsic allergic) asthma is mediated by antigen antibody complexes on mast cells and release of interleukins and O₂ radicals by eosinophils and T lymphocytes.
 2. Sputum from asthmatic patients shows *Charcot-Leyden crystals*, a breakdown product of *eosinophils*.

Chronic Obstructive Pulmonary Disease (COPD)

- *Mechanism:* It is a mixture of *chronic bronchitis* and *emphysema*, leading to *expiratory* airway obstruction.
- *Chronic bronchitis:* Expectant cough for at least 3 *successive months* that last for at least 2 *successive years*.
- *Emphysema:* Dilatation of the air spaces *distal to terminal bronchioles*, mainly *centroacinar (panacinar only in α_1 -antitrypsin deficiency)*
- *Clinical picture:*
 1. Blue bloaters: Patients with predominant *bronchitis* have *cough* accompanied by cyanosis and edema.
 2. Pink puffer: Patients with predominant *emphysema* have *dyspnea*, which causes them to *huff and puff* on expiration.
- *On exam:* Increased *anteroposterior* dimension of the chest
- *Diagnosis:*
 1. PFTs: Show obstructive picture (*FEV₁/FVC < 80*)
 2. Chest x-ray: Hyperinflated lungs and flattened diaphragm (Fig. 10.12)
- *Complications:* Multiple, the most significant is *cor pulmonale*, which is right ventricular failure. Refer to discussion of CHF, below, for more details.
- *Treatment:* *Oxygen* is the mainstay of treatment of COPD, and is the only factor that reduces morbidity and mortality. See Chapter 9, Pharmacology.
- Notes:
 1. In emphysema, there is a *low α_1 -globulin level*.
 2. Patients with α_1 -antitrypsin deficiency also have recurrent hepatitis. So on the USMLE look for a patient who was born with emphysema and is presenting with unexplained elevated transaminases.



FIG. 10.12 Emphysema

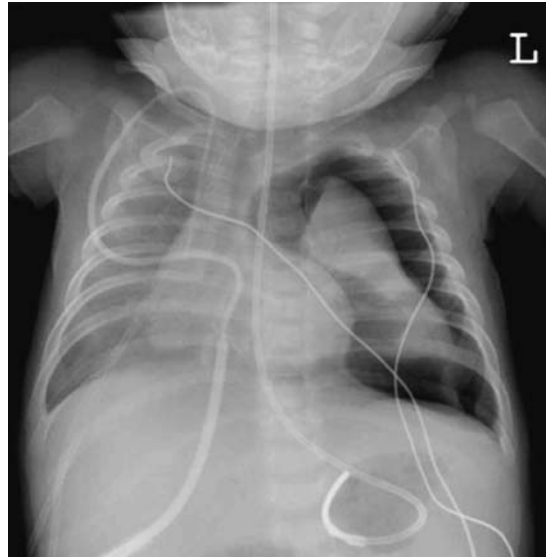


FIG. 10.13 Left tension pneumothorax

Respiratory Failure

- **Definition:** It is a decline in the respiratory function leading to $PO_2 < 60$ and $PCO_2 > 50$.
- **Types and causes:**
 1. Type I: Hypoxic normocapnic (low O_2 , normal CO_2): Caused by emphysema, pneumonia, and pulmonary edema
 2. Type II: Hypoxic hypercapnic (low O_2 , high CO_2): Caused by asthma and COPD
- **Clinical picture:**
 1. Hypoxia: Cyanosis and tachycardia
 2. Hypercapnia: Headache, full bounding pulse, and lethargy (CO_2 narcosis)
- **Treatment:**
 1. Type I: O_2 with *high* concentrations
 2. Type II: O_2 with *low* concentrations to maintain the respiratory center stimulation. *This is one case in which high oxygen flow can kill somebody.*

Pneumothorax

- **Types:** It is air in the pleural sac, which could be:
 1. Closed, e.g., due to ruptured blebs or bullae
 2. Open: Air enters and leaves without trapping
 3. Tension pneumothorax: Air enters and only partially leaves the pleural sac due to *check valve* mechanism (Fig. 10.13)

- **Causes:**
 1. Primary: Suspect in *tall, thin, middle-aged smoker*
 2. Secondary: COPD or cystic fibrosis
- **Clinical picture:** *Sudden* respiratory distress and chest pain on inspiration due to *severe pleurisy*
- **On exam:** *Hyperresonance* on chest percussion, and decreased/absent breath sounds on auscultation of the affected lung.
- **Diagnosis:** Chest x-ray (CXR) shows *hyperinflation and shift of the mediastinum to the opposite side.*
- **Treatment:** *Chest tube insertion;* however, if not immediately available and the patient is unstable, insert a wide-bore needle into the second intercostal space in the midclavicular line to allow the trapped air out until the chest tube is inserted.

Lung Cancer

- It is the second most common malignancy in men after prostate, and the third in women after breast and colon; however, *it is the number one cause of death from cancer in both genders.*
- *It is also the most common cause of pleural effusion.*
- Smoking increases the lung cancer risk by *10 times more than normal.*
- **Types:** See Table 10.5
- **Clinical picture:** Cough, hemoptysis, weight loss, and pleural effusion or sometimes completely asymptomatic
- **Diagnosis:** *Biopsy;* peripheral ones by *CT-guided biopsy*, and central ones by *bronchoscopy-guided biopsy or mediastinoscopy*

TABLE 10.5 Types of lung cancer.

Type	Location	Paraneoplasia	Miscellaneous
Adenocarcinoma	Peripheral	None	<ul style="list-style-type: none"> • Most common lung cancer • Early metastases
Squamous cell carcinoma	Central	Hypercalcemia: due to release of parathormone (PTH)-related peptide	<ul style="list-style-type: none"> • Second most common lung cancer • Causes lung cavitations • Squamous cells are eosinophilic with hyperchromatic nuclei
Small cell carcinoma	Central	<ul style="list-style-type: none"> • Adrenocorticotrophic hormone (ACTH): Cushing syndrome • Antidiuretic hormone (ADH): syndrome of inappropriate ADH (SIADH) • Muscle weakness: Eaton-Lambert, due to calcium channel antibodies • Sensory neuropathy: due to antineuronal antibodies (ANNA-1) 	<ul style="list-style-type: none"> • Eaton-Lambert is just like myasthenia gravis, except: <ol style="list-style-type: none"> 1. Activity makes symptoms better 2. Activity makes EMG waves stronger • Small cells are basophilic and lymphocyte sized
Large cell carcinoma	Peripheral	Gynecomastia	

- *Workup for metastases: Bone scan, CT of abdomen and pelvis, and CT of the head to rule out metastases*
- *Treatment: Surgery if operable, radiation, and chemotherapy for all types, except for small cell, where surgery is not an option*
- *Remember: Central tumors are Squamous and Small cell (SS), and the rest are peripheral.*
- *Notes:*

1. Any type of lung cancer infiltrating the sympathetic chain will cause Horner syndrome and it can be called Pancoast tumor. Horner syndrome presentation:
 - *Ptosis:* Due to paralysis of superior tarsal muscle
 - *Miosis:* Due to paralysis of dilator pupillae muscle
 - *Anhydrosis*
2. A bronchopulmonary segment is formed histologically of a bronchus with its supplying artery and vein, plus the lung segment that they all supply.
3. Mesothelioma is a pleura-based malignancy that occurs on exposure to asbestos for long duration, at least 10 years.
4. Bronchial adenoma is a benign tumor arising from bronchial mucosa. Patient presents with recurrent hemoptysis and carcinoid syndrome (diarrhea, flushing, bronchospasm, right heart valve lesions, high urinary 5-hydroxyindoleacetic acid [HIAA]).

Pleural Diseases

Pleurisy

- *Causes:* Any nearby infection or irritation, e.g., pneumonia, pneumothorax

- *Clinical picture:* Stitching chest pain increased with deep inspiration and cough
- *On exam:* Pleural rub
- *Treatment:* Treat the cause and prescribe NSAIDs.

Pleural Effusion

- *Causes:* Transudative (e.g., CHF), exudative (e.g., pneumonia), chylous (e.g., thoracic duct obstruction), or hemorrhagic (e.g., malignancy)
- *Clinical picture:* Dyspnea and pleuritic chest pain (increased with inspiration)
- *On exam:* Decreased everything, i.e., decreased chest movement on inspiration, decreased tactile vocal fremitus (TVF), dullness on percussion and decreased air entry on auscultation
- *Diagnosis:* CXR shows leveling of fluid filling the costophrenic angle. Large effusion pushes the mediastinum toward the opposite lung (Fig. 10.14).

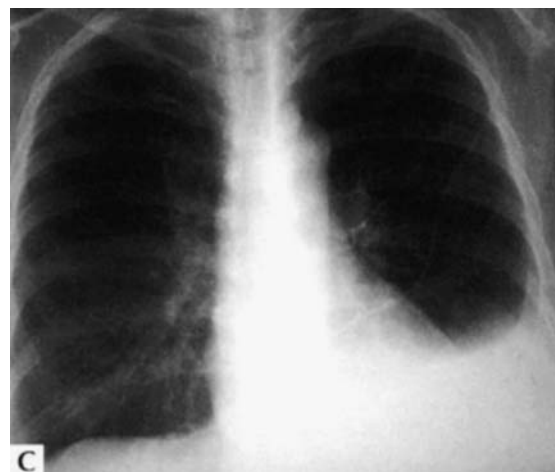


FIG. 10.14 Left pleural effusion

- **Treatment:**
 1. Thoracocentesis is diagnostic and therapeutic. Fluid is sent to the lab for analysis to diagnose its nature, e.g., exudate, transudate, etc. (Same numbers as in Table 10.4)
 2. If fluid reaccumulated after thoracocentesis, *chest tube should be inserted.*
 3. If fluid reaccumulated after removal of chest tube, *pleurodesis should be done.*
- **Notes:**
 1. Malignant effusions reaccumulate rapidly and pleurodesis is indicated.
 2. Empyema is accumulation of pus in the pleural cavity. Treatment: *Antibiotics and intercostal tube drainage.* If failed: open drainage and removal of the pleura (decortication).
 3. Lung collapse and lung fibrosis are two other diseases with “*decreased everything*” on exam, but the mediastinal shift is *toward the opacified lung, not toward the opposite side.*

Interstitial Lung Disease (ILD)

- **Mechanism:** Infiltration of the lung tissue with inflammatory cells leading to restrictive lung disease
- **Causes:** Silicosis, asbestosis, sarcoidosis, drugs, e.g., amiodarone
- **Clinical picture:** (5 Cs) Cough, cyanosis, clubbing, crackles, and cor pulmonale
- **CXR:** Diffuse reticulonodular infiltrate
- **Diagnosis:** Lung biopsy
- **Treatment:** Steroids
- **Notes on some ILDs:**
 1. Idiopathic pulmonary fibrosis (IPF): Rapidly progressive ILD with bad prognosis. Most patients end up on steroids and O₂ at all times.
 2. Eosinophilic granuloma (Langerhans’ cell granulomatosis, formerly histiocytosis X): More common in male smokers. **Diagnosis:** Langerhans’ cells on lung biopsy or bronchioalveolar lavage. **Complication:** Pneumothorax. **Hand-Schüller-Christian disease** = eosinophilic granuloma + lytic bone lesions + diabetes insipidus + exophthalmia.
 3. Aspergillosis: Immune complex mediated ILD. **Brownish** sputum with *branching hyphae* under microscope.

Silicosis and Asbestosis

- **Silica:** Exposure occurs in *glass* and *sand* industries. Clinical picture: *Upper lung zone injury* and *hilar egg shell calcifications.*

- **Asbestos:** Exposure occurs in *brakes* and *shipyard* industries. Clinical picture: *Lower lung zone injury* and *pleural calcifications.* Unique feature: *Ferruginous bodies* in lungs (asbestos and hemosiderin) with *clubbed ends.* Complications: *Mesothelioma* and bronchogenic carcinoma.

Pneumonia

- **Definition:** It is *infection* and *consolidation* of the pulmonary tissue.
- **Types:** It is usually community acquired, unless the patient has been in a hospital or a nursing home for more than *72 hours* before symptoms started; then it is called *nosocomial pneumonia.*
- **Forms:** *Lobar pneumonia* is the most common form and is caused by *Streptococcus pneumoniae*; however, pneumonia could be interstitial or bronchopneumonia.
- **Phases:**
 1. Congestion
 2. Red hepatization (2–4 days): *Mediated mainly by neutrophils*
 3. Gray hepatization (4–8 days): *Characterized by high fibrin content*
 4. Resolution: After 8 to 10 days from the initial phase
 - **Clinical picture:** Cough and expectoration, fever, and shortness of breath
 - **On exam:** The area with pneumonia is *dull to percussion, has high tactile vocal fremitus (TVF), rhonchi and crackles, bronchial sounds, and egophony* (“e” to “a” changes on auscultation).
 - **Diagnosis:** Chest x-ray (Fig. 10.15) and sputum culture



FIG. 10.15 Right lower lobe pneumonia

- **Treatment:** Community acquired pneumonia is best treated by quinolones (e.g., levofloxacin) or a combination of macrolide (e.g., azithromycin) and third-generation cephalosporins.

- **Notes:**

1. Atypical pneumonia:

- If the chest x-ray looks worse than the patient's clinical presentation, think of atypical pneumonia, especially if the patient also has diarrhea or change in mental status. The most common causes are:

a. *Legionella*: Diagnosed by direct immunofluorescence and culture on charcoal agar, or detecting the legionella antigen in the urine. Typical sources are shower heads and air conditioners.

b. *Mycoplasma*: Diagnosed by high mycoplasma IgM titers.

- Treatment of atypical pneumonia: Macrolides, e.g., erythromycin

2. Aspiration pneumonia: It is usually in the right lung due to the large right main bronchus that is more in line with the trachea. Suspect aspiration in patients with gastrostomy feeding tubes, alcoholics, and after coma or seizure. Most common organism: *Pseudomonas aeruginosa*.

3. Key facts:

- *Staphylococcus aureus*: Causes lung cavitation and hemoptysis. It is also the most common cause of pneumonia following an influenza infection.
- *Klebsiella*: Causes apical (Friedländer's) pneumonia and red current jelly sputum
- *H. influenzae* is a common cause of pneumonia in patients with COPD.

Bronchiectasis

- **Mechanism:** It is a combination of airway obstruction and infection, leading to abnormal persistent dilatation of the bronchi.
- **Most common sites:** Bases of the lungs
- **Clinical picture:** Cough and expectoration more on stooping forward. Also hemoptysis due to mucosal ulceration.
- **On exam:**

1. Lung bases: Dull to percussion with high TVF
2. Lung apices: Resonant to percussion with low TVF, due to compensatory emphysema

- **Diagnosis:** CXR or CT chest shows honeycomb appearance.
- **Treatment:** Postural drainage and antibiotics

Pulmonary Embolism (PE)

- Most common source is deep venous thrombosis (DVT) in the lower extremities.
- **Clinical picture:** Sudden dyspnea, hyperventilation, and pleuritic chest pain. Usually asked on the USMLE as a hospitalized patient who suddenly develops unexplained respiratory distress a few days after surgery.
- **Diagnosis:**
 1. Gold standard for diagnosis: Pulmonary angiography
 2. In practice, we use the V/Q scan, which will show ventilation/perfusion mismatch.
 3. If the CXR is not clear, V/Q will not be accurate, so a CT of the chest is done.
 4. Right ventricular strain on electrocardiogram (ECG)
- **Note:** Patients with PE have normal chest x-ray.
- **Treatment:** Heparin is the first step, followed by warfarin for 3 to 6 months.
- **Fat pulmonary embolism:** Occurs after long bone fractures, e.g., femur; patients have dyspnea and skin petechiae. Treatment is mainly supportive.

Tuberculosis (TB)

- **Causes:** *Mycobacterium tuberculosis* (acid-fast bacillus) is the most common cause; however, in immunocompromised patients atypical mycobacteria are involved, e.g., *M. avium*.
- **Primary complex:** Ghon's focus in the upper lung lobe
- **Pathology:** *M. tuberculosis* lives inside macrophages, after inhibiting the phagosome-lysosome fusion process.
- **Clinical picture:**
 1. Helpful to remember: Two "nights" and two "losses": Night fever, night sweats, loss of weight, and loss of appetite
 2. Cough and expectoration and hemoptysis due to erosion of a blood vessel or oozing from friable granulation tissue
- **Diagnosis:**
 1. Isolation of the organism on a culture is the diagnostic test of choice. Sample is obtained from the sputum or gastric aspirate.
 2. CXR: Apical infiltrate or cavitations
 3. Tuberculin test: Purified protein derivative (PPD) is injected intradermally in the forearm, and the induration (not erythema) is measured in 48 to 72 hours. Note: PPD test becomes positive 3 to 10 weeks after infection, and not immediately afterwards.

- *PPD interpretation:*
 1. Induration less than 10 mm in immunocompetent person: Normal
 2. Induration more than 10 mm in immunocompetent person: Next step is to obtain a chest x-ray:
 - Normal CXR (latent TB): *Isoniazid (INH) therapy for 9 months*
 - Abnormal CXR: TB treatment
 3. Induration less than 5 mm in immunocompromised patient: Normal
 4. Induration more than 5 mm in immunocompromised patient: Next step is to obtain a CXR:
 - Normal CXR (Latent TB): *INH therapy for 12 months*
 - Abnormal CXR: TB treatment
- *Treatment: 6-month course:* 2 months of INH, rifampin, pyrazinamide, and *ethambutol (or streptomycin)*, followed by 4 months of INH and rifampin.

Sleep Apnea

- *Definition:* It is cessation of breathing during sleep.
- *Types and causes:*
 1. Central: Respiratory center depression, e.g., alcohol, benzodiazepine (BDZ)
 2. Obstructive: Narrow airway, e.g., large tongue, large palate, big neck
 3. Pickwickian syndrome: Obstructive sleep apnea, obesity, and CO₂ retention
- *Clinical picture:* Loud snoring during sleep along with episodes of apnea followed by waking up gasping for air, plus *daytime sleepiness and fatigue*
- *Diagnosis:* Sleep study (polysomnography)
- *Complications:* Pulmonary hypertension (>20), core pulmonale, and sudden death
- *Treatment:*
 1. Continuous positive airway pressure (CPAP) during sleep and *weight loss*
 2. Avoidance of alcohol and BDZ before bedtime
 3. For resistant cases: Uvulopalatopharyngoplasty (UPPP)

Solitary Lung Nodule

- It is any nodule that is *less than 5 cm* in diameter that is discovered accidentally on a CXR or CT without any related symptoms.
- *Characteristics:*
 1. Benign: Central, round, regular border, uniform calcification

2. Malignant: Peripheral, irregular shape, speculated, irregular calcification

- *Management:*

1. High-risk patient (old, smoker, family history of cancer): *Biopsy*
2. Low-risk patient (young, nonsmoker, no family history): *Repeat CXR every 3 months for 2 years:*
 - If any change in characteristics mentioned above: Biopsy.
 - If stable: Follow up on symptoms

Cough

- Cough is a protective reflex in cases of infection and in postoperative patients.
- *Most common cause:* *Smoking*
- *Causes of chronic cough:* Chronic sinusitis, GERD, and asthma
- *Antitussives:* Decrease cough by two mechanisms:
 1. Peripheral: Anesthetize peripheral receptors; best is *benzonatate*
 2. Central: Increase threshold of cough center; best is *dextromethorphan*
- *Note:* One of the complications of lack of cough, deep breaths, and using incentive spirometry in postoperative patients is *atelectasis*. *Suspect atelectasis in a patient developing fever 1 to 2 days after surgery.*

Renal System

- *Function:* Kidneys filter the blood, secrete erythropoietin, activate vitamin D by adding the 1-hydroxyl group, and regulate the renin-angiotensin-aldosterone system.
- *Renal blood flow:* It constitutes around 25% of the cardiac output.
- *Autoregulation:* Usually between 80 and 200 mm Hg, and is accomplished by changing the renal vascular resistance, which is regulated by the *juxtaglomerular apparatus* in the ascending limb of loop of Henle.
- *Glomerular basement membrane:* Formed as follows ("FFF"):
 1. Foot processes of podocytes
 2. Fenestrated endothelium of glomerular capillaries
 3. Fused basement membrane: *This is the charged part of the membrane.*
- *Total body water:* It constitutes 50% to 60% of total body weight; *intracellular fluid constitutes 40% of total body water and extracellular fluid 20%.*
- *Threshold of glucosuria:* It is the plasma concentration of glucose at which it starts to appear in the urine. It is equal to 250 mg.

- *Tubular maximum (T_m) for glucosuria*: It represents the full nephron saturation for glucose. It is equal to 350 mg.
- *Renal clearance*: It is the volume of plasma from which a certain substance is cleared in a certain period of time. *If clearance of a substance is less than the glomerular filtration rate (GFR), there is net reabsorption of that substance and vice versa.*
- *GFR depends on four factors*: High glomerular hydrostatic pressure, high Bowman's oncotic pressure, normal renal blood flow, and normal capillary permeability.
- *Loop of Henle*:
 1. Proximal convoluted tubule (PCT): Performs *obligatory water absorption*; it also absorbs two thirds of sodium, and most of the glucose and amino acids in the tubular fluid.
 2. Descending limb of loop of Henle: *Countercurrent effect* leading to increased concentration of the fluid by at least *three times*.
 3. Ascending limb of loop of Henle: *Na/K/2Cl cotransport* takes place. *Loop diuretics act here.*
 4. Distal convoluted tubule (DCT):
 - a. *Na/Cl cotransport. Thiazide diuretics act here.*
 - b. Calcium excretion through the action of *parathyroid hormone*
 5. Collecting duct:
 - a. *Principal cells*: Na/K exchange through action of *aldosterone*
 - b. *Intercalated cells*: H/K exchange through action of *ADH on V2 receptors*
- Fluid measurements:
 1. Extracellular fluid: Measured using *mannitol*
 2. Plasma: Measured using *Evans blue*
 3. Glomerular filtration rate (GFR) (normal =90–125: Using *creatinine or inulin clearance*; calculated by the famous equation $C = U \times V/P$ (C = clearance of a substance, U = urine concentration of a substance, V = urine volume per time, P = arterial plasma concentration).
 4. Effective renal plasma flow: Using *para-aminohippuric acid*, which normally has a very high clearance

Acid-Base Balance

- Main acid-base buffers are:
 1. Carbonic acid–bicarbonate system
 2. Chloride shift phenomenon: K-HCO₃ exchange

3. Lungs: Acidosis causes hyperventilation (to wash away CO₂) and vice versa
 4. Kidneys: Control absorption and excretion of H and HCO₃
- K and H follow each other, so hypokalemia causes alkalosis and vice versa.
 - Major extracellular buffer is HCO₃, while the major intracellular one is *hemoglobin*
 - *Anion gap = Na - (Cl + HCO₃) = 8 to 16 normal range*
 - $pH = HCO_3/CO_2$

Metabolic Acidosis (Low pH, Low HCO₃, Low CO₂)

- *Normal anion gap*: Caused by:
 1. Diarrhea
 2. Renal tubular acidosis
- *High anion gap*: Caused by:
 1. Salicylate toxicity: Starts with *respiratory alkalosis first*
 2. Alcohol toxicity: Mainly ethylene glycol (antifreeze) and methanol (wood alcohol). The former is converted to *oxalate crystals* in the kidneys, while the latter is converted to *formaldehyde and formic acid*.
 3. Renal failure
 4. Ketosis: Diabetic ketoacidosis (DKA), alcoholic ketoacidosis, and lactic acidosis
- *Clinical picture*: Hyperventilation and *hyperkalemia*
- *Treatment*: HCO₃ and treatment of the cause. Note that in DKA, fluids and insulin therapy are enough to correct the pH; the only indication to give HCO₃ is $pH < 7$.
- *Note*: Oil of wintergreen is a rich source of salicylates.

Metabolic Alkalosis (High pH, High HCO₃, High CO₂)

- *Causes*:
 1. Loss of fluids to the point of dehydration, i.e., *contraction alkalosis*
 2. Loss of acid, e.g., vomiting, or ingestion of excessive HCO₃
- *Clinical picture*: Hypokalemic alkalosis, which results in *tetany*
- *Treatment*: *Normal saline* and treatment of the cause. In resistant cases, acetazolamide could be used (*causes metabolic acidosis and alkaline urine*).

Respiratory Acidosis (Low pH, High HCO_3^- , High CO_2)

- *Cause:* Slow breathing, e.g., respiratory failure, COPD
- *Clinical picture:* High CO_2 causes lethargy, full bounding pulse, and tremors
- *Treatment:* O_2 and CO_2 , as pure O_2 will cause further respiratory center depression

Respiratory Alkalosis (High pH, Low HCO_3^- , Low CO_2)

- *Causes:* Fast breathing, e.g., salicylate poisoning, midbrain lesion
- *Clinical picture:* Hyperventilation leading to tetany and seizures
- *Treatment:* Rebreathing mask, e.g., paper bag

Nephrotic Syndrome

- *Pathology:* Heavy proteinuria (>3.5 g/day), hyperlipidemia, and hyperlipiduria
- *Causes:* DM, HTN, and amyloidosis
- *Clinical picture:* Generalized edema that starts from the face downward
- *Types of nephrotic syndrome:*
 1. Minimal change disease (lipoid nephrosis): *Foot processes effacement*. Responds to steroids. It is the most common form of idiopathic nephrotic syndrome in *children and young adults*.
 2. Membranous glomerulonephritis (GN): *Spike and dome* appearance. High risk of malignancy and DVT, so if you are asked on the USMLE about a nephrotic patient having DVT, *renal vein thrombosis*, or malignancy, it is most likely membranous GN. It is the most common form of idiopathic nephrotic syndrome in *Caucasians*.
 3. Focal segmental sclerosis: Common in *HIV*. It is the most common form of idiopathic nephrotic syndrome in *African-Americans*.
 4. DM: Kimmelstiel-Wilson syndrome. First sign of diabetic nephropathy is glomerulosclerosis, which is detected by checking for *microalbuminuria*.
 5. SLE: *Wire loop lesions with subendothelial deposits*
 6. Amyloidosis: Diagnosed by *Congo red staining of abdominal pad of fat*. Treatment: *Colchicine*.
 7. Familial Mediterranean fever (fever, serositis, and nephrosis): Treatment: *Colchicine*.

Nephritic Syndrome

- *Clinical picture and pathology:* Proteinuria (<3 g/day), hematuria, and HTN

- *Causes:* Mostly infectious, e.g., group A beta-hemolytic streptococcus
- *Types of glomerulonephritis:*
 1. Acute poststreptococcal: *Lumpy bump deposits and subepithelial humps*
 2. Goodpasture's syndrome (discussed later): *Linear deposits*
 3. Rapidly progressive GN: *Crescent moon-shaped deposits*
 4. Membranoproliferative: *Train-track deposits*
 5. IgA nephropathy (Berger disease): *Mesangial IgA deposits*
- *Note:* GN with low complement levels are post-streptococcal, membranoproliferative GN, and SLE (helpful to remember "PMS").
- *Note:* One of the markers of any GN is the presence of *RBC casts* in the urine.

Urinary Tract Infection (UTI)

- *Causes:* Most commonly caused by *E. Coli* and *Klebsiella*
- *Clinical picture:* *Dysuria, frequency, urgency*, and even *hematuria*
- *On exam:* *Costovertebral angle tenderness* is alarming for pyelonephritis.
- *Diagnosis:* Urinalysis showing more than 5 white blood cells (WBCs) per high-power field (hpf) with bacteria is diagnostic of UTI; however, if it shows more than 5 WBCs/hpf without any bacteria, this is known as *sterile pyuria*. Causes of sterile pyuria: interstitial nephritis, TB, or nephrolithiasis.
- *Treatment:*
 1. Complicated UTI, e.g., pyelonephritis: IV *ampicillin and gentamicin*
 2. Uncomplicated UTI: Oral ciprofloxacin or sulfamethoxazole/trimethoprim (SMX/TMP) (Bactrim)
- *Notes:*
 1. UTI in polycystic kidney is best treated by SMX/TMP or tetracycline due to their *high lipid solubility*.
 2. Long-term UTI in females could occur due to colonization of the vaginal introitus by fecal material.
 3. UTI during pregnancy can occur without symptoms; however, it must be treated or pyelonephritis would be a sequel in 40% of cases.
 4. UTI in diabetic patients can trigger *acute papillary necrosis*.
 5. Upper UTI (pyelonephritis) could be differentiated from lower UTI (cystitis, urethritis) by

the presence of *WBC casts in the urine in the former*.

6. Treatment duration: Lower UTI, 3 days; upper UTI, 10 to 14 days
7. Treatment failure of UTI: Caused by noncompliance or resistance to treatment. *Next thing to do: Urine culture and sensitivity.*

Interstitial Nephritis

- Inflammatory-mediated infiltration of interstitial tissues with *neutrophils*
- *Causes:* Mostly drugs, e.g., ampicillin, methicillin, cephalosporins
- *Clinical picture:* Fever, rash, and acute renal insufficiency
- *Diagnosis:* Elevated creatinine, sterile pyuria, and most importantly *eosinophiluria*
- *Treatment:* Stop the offending drug

Acute Renal Failure

- *Pre-renal*, e.g., hypovolemia, congestive heart failure: *blood urea nitrogen (BUN)/creatinine (Cr) ratio of more than 20 and fractional excretion of sodium (FeNa) <1%*
- *Renal*, e.g., intravenous contrast, rhabdomyolysis, or toxic drugs like aminoglycosides: *BUN/Cr <20 and FeNa >1%. Urine shows epithelial or granular, muddy casts indicating acute tubular necrosis (ATN).*
- *Postrenal*, e.g., obstructive uropathy: *Note that post-obstructive diuresis results in dilute and alkaline urine.*
- *Note:*
 1. ATN starts with an oliguric phase for 2 to 4 weeks, followed by polyuric phase (*low serum Na and K*) and finally a postdiuretic phase.
 2. Rhabdomyolysis is diagnosed by elevated serum creatine phosphokinase (CPK) (in thousands) and elevated *urine myoglobin*. Treatment: *Fluids and bicarbonate drip.*

Chronic Kidney Disease (CKD)

- *Causes:* Most common in the United States are *DM* and *HTN*
- *Clinical picture:*
 1. Anemia, increased capillary fragility, platelet and lymphocyte dysfunction
 2. Nausea, vomiting, and *ammonia-like odor* in the breath
 3. CVS: Hypertension, cardiomyopathy, and uremic pericarditis

4. Endocrine: Hypothyroidism, hypocalcemia, and hyperkalemia
5. Renal osteodystrophy: Osteitis fibrosa cystica, osteomalacia, and osteoporosis
6. CNS: Motor, sensory, and autonomic neuropathy
7. Skin: Itching, and *earth-colored skin*. Due to calcium deposition in skin
8. Urine: Oliguria (<400 cc/day) or anuria (<100 cc/day) and low fixed urine specific gravity (isosthenuria)

- *Pathology:* Urine shows *waxy casts*

- *Treatment:*

1. Treat the cause and electrolyte and hormone imbalances.
2. Calcium replacement
3. Prepare the patient for hemodialysis once the GFR is *less than 15*. Peritoneal dialysis is not preferred due to high risk of infection and visceral injury.

Renal Cell Carcinoma

- *Anatomic hint:* Most common renal malignancy, originates from *renal tubules*
- *Clinical picture:*
 1. *Painless hematuria:* Due to invasion of renal pelvis
 2. *Polycythemia:* Due to *erythropoietin* secretion by the tumor
 3. Metastases: Multiple, but *cannonball metastases* to the lung are common
- *Diagnosis:* Biopsy is the gold standard. Intravenous pyelogram (IVP) shows *irregular spider leg deformity*.
- *Pathology:* *Golden yellow tumor* with polygonal clear cells (Fig. 10.16)
- *Treatment:* Surgical resection.

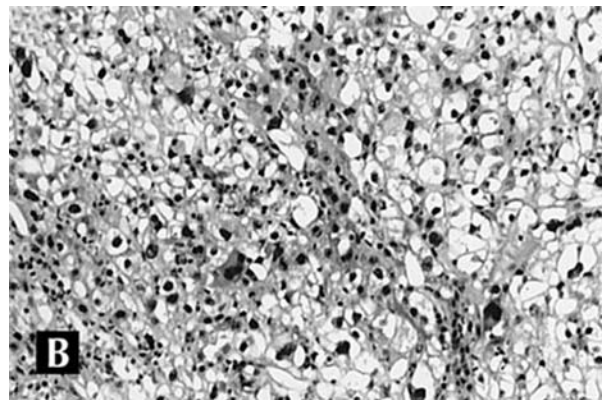


FIG. 10.16 Renal cell carcinoma

Nephro- and Ureterolithiasis

- *Types:*
 1. The most common are *calcium oxalate stones*, which are *radiopaque*.
 2. Magnesium ammonium phosphate stones, also called *struvite* stones, are common in females with recurrent UTI secondary to urea-splitting organisms, e.g., *Proteus mirabilis*.
- *Clinical picture:* Colicky flank pain radiating to the groin and inner thigh, dysuria, and even hematuria
- *Diagnosis:*
 1. Test of choice: *Spiral CT of the abdomen and pelvis*
 2. Most renal stones are radiopaque and seen on x-ray (Fig. 10.17)
- *Treatment:*
 1. Stone <4 mm: Increase fluid intake and stone will pass spontaneously.
 2. Stone ≥ 4 mm: Admit to the hospital and consult urology for possible extraction or extracorporeal shock-wave lithotripsy (ESWL).
 3. Recurrent calcium stones: Treat with *thiazide diuretics*.
 4. Recurrent oxalate stones: Treat with *cholestyramine* (oxalate chelator), and *magnesium citrate* (decreases intestinal oxalate absorption).
 5. Alkalinization of the urine with NaHCO_3 is used to manage all types of stones, except *phosphate stones* (*acidify urine with vitamin C*).



FIG. 10.17 Nephrolithiasis

- *Notes:*
 1. Stone in the ureterovesical junction is the most common cause for ureteral dilatation.
 2. Uric acid stones are common after the use of uricosuric drugs or in case of tumor lysis syndrome. They are *radiolucent*.
 3. Cystine stones can form in cystinuria, a disease diagnosed by nitroprusside test and treated with *penicillamine*.

Renal Artery Stenosis (RAS)

- *Causes:* *Fibromuscular dysplasia* in young, and *atherosclerosis* in elderly
- *Clinical picture:* *Hypokalemia-resistant hypertension*
- *On exam:* Continuous systolic and diastolic bruit on auscultation to epigastrium
- *Screening:* Captopril provocation test
- *Diagnosis:* Test of choice is *angiography*; however, in practice we use magnetic resonance angiography (MRA) or duplex ultrasound
- *Treatment:* Significant stenosis is corrected by stent placement.
- *Notes:*
 1. An ACE inhibitor (ACEI) is absolutely contraindicated in bilateral RAS; however, it is the drug of choice to treat HTN in cases of unilateral RAS.
 2. The kidney whose artery is stenosed is smaller in size than the healthy kidney.
 3. Renal vein of the stenosed side has *higher renin* level than the healthy side.
 4. Fibromuscular dysplasia mainly affects the *media* of the blood vessel.

Nephrology Notes

- *Causes of hematuria:* Helpful to remember “SHITTT”: *Stones, Hematologic disease, Infection, Tumor, Trauma, Treatment* (e.g., anticoagulants, cyclophosphamide)
- *Blood urea nitrogen:* Not as specific as creatinine for kidney function. BUN is also elevated due to upper GI bleeding, steroids, or after a high-protein diet.
- *DM:* The first indicator of diabetic nephropathy is *microalbuminuria*, representing *glomerulosclerosis*. This could be treated with an *ACEI*. If you see a patient on the USMLE who is on ACEI, and the urine microalbumin is still high, increase the ACEI dose. If the patient cannot tolerate the ACEI, switch to an angiotensin receptor blocker (ARB).
- *Bartter’s syndrome:* Also known as *juxtaglomerular hyperplasia*. There is resistance to angiotensin, and

accordingly hyponatremia ensues. The low Na stimulates the renin-angiotensin-aldosterone system, which leads to hypokalemia. Treatment: Prostaglandin (PG) blockage, e.g., indomethacin (PG stimulates renin).

- *Urethral diverticulum*: Suspect it in any female patient presenting with a *DDD* triad: Dysuria, Dribbling, and Dyspareunia.
- *Indications for urgent hemodialysis*: Fluid overload, resistant hyperkalemia, resistant metabolic acidosis, and uremic pericarditis

Cardiovascular System

- *Arteries*: Contain the high-pressure volume of the circulation, and *arterioles are the location of maximal resistance to blood flow*.
- *Veins*: Contain the low-pressure volume of the circulation, and *most of our blood is contained within the venous system*.
- *Capillaries*: They have the largest surface area of the entire vascular system, and blood flow through them is regulated by *precapillary sphincters*.
- *The lower the surface area of a blood vessel, the faster the blood flow and vice versa*; e.g., capillary blood flow is slow due to the large surface area.
- Adding resistance in parallel decreases the peripheral resistance, and increases blood flow.
- *Turbulence*: Highest in big vessels with high blood velocity, e.g., aorta
- *Local autoregulation*: Done by the heart, brain, and muscles. The most important vasodilator of cerebral circulation is CO_2 .
- *Active hyperemia*: Blood flow to an organ is *directly proportional* to its metabolic activity.
- *Reactive hyperemia*: Increased blood flow to an organ after temporary occlusion of its circulation.
- *Pulse pressure*: It is the difference between systolic and diastolic blood pressure. It is determined by *stroke volume* and *compliance* of large arteries; that is the reason atherosclerosis causes a wide pulse pressure.

Electrocardiogram Waves (Fig. 10.18)

- *P wave*: Atrial depolarization
- *P-R interval*: Atrioventricular conduction
- *QRS*: Ventricular depolarization
- *Q-T interval*: Ventricular depolarization and repolarization
- *S-T interval*: Isoelectric
- *T wave*: Ventricular repolarization

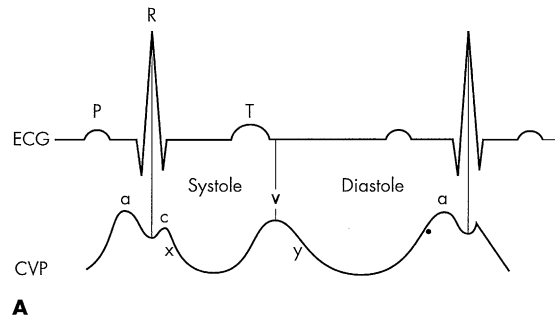


FIG. 10.18 Normal electrocardiogram (ECG) and jugular vein waves. CVP, Central venous pressure

- *Note*: Conduction is *fastest in Purkinje fibers*, and is *slowest across the AV node*.

Action Potentials

- *Action potential of Purkinje fibers* (Fig. 10.19)
 1. Phase 0 (depolarization): Due to *Na influx*. Inhibited by *Quinidine*.
 2. Phase 1 (partial repolarization): Due to *K efflux*
 3. Phase 2 (plateau): Due to *K efflux* and *Ca influx*
 4. Phase 3 (repolarization): Due to *K efflux*
 5. Phase 4 (forward current): Due to *Na influx*
- *Action potential of the sinoatrial node (pacemaker)* (Fig. 10.19):
 1. Stage 4: Mediated by *Na influx*
 2. Stage 0: Mediated by *Ca influx*
 3. Stage 3: Mediated by *K efflux*

Cardiac Cycle

- *Phases* (Figs. 10.20 and 10.21)
- *Increased preload*, i.e., venous return: Causes *right shift* of curve
- *Increased afterload*, i.e., peripheral resistance: Causes *upward shift* of curve

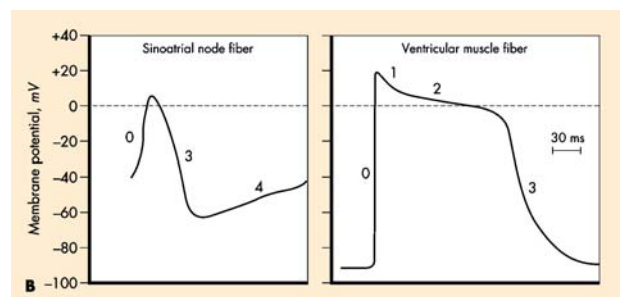


FIG. 10.19 Action potential of sinoatrial (SA) and Purkinje

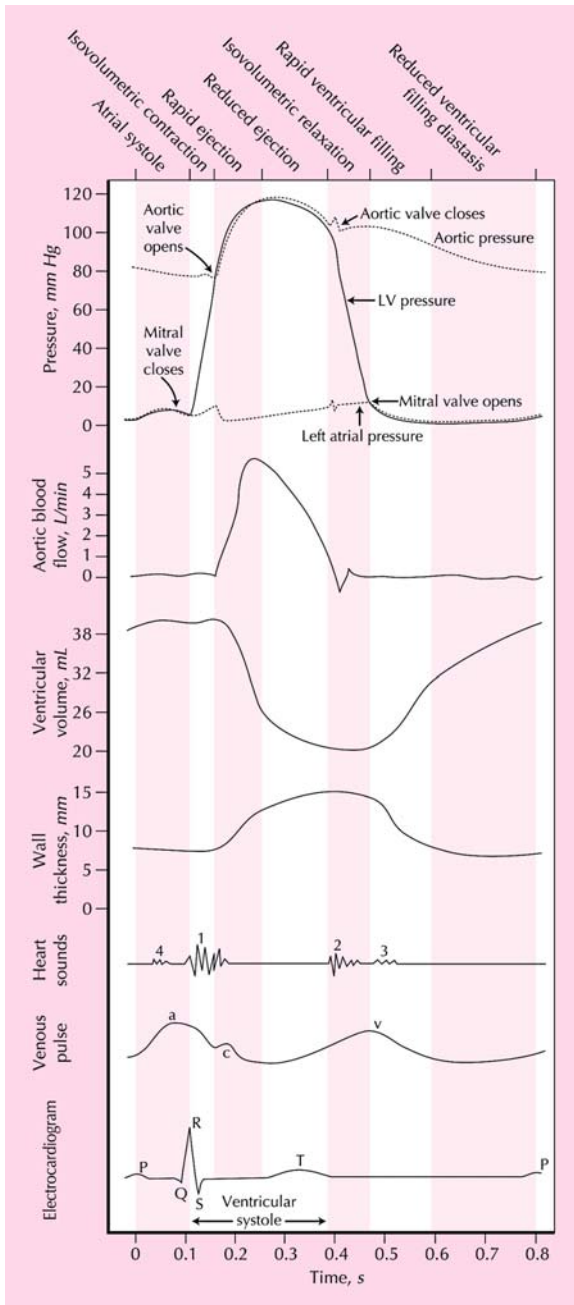


FIG. 10.20 Cardiac cycle

- *Increased contractility*, i.e., inotropy: Causes *left shift* of curve
- *Note*: Preload = End diastolic volume, and After-load = Diastolic BP

Heart Sounds

- *S1*: Due to closure of AV valves, i.e., mitral and tricuspid

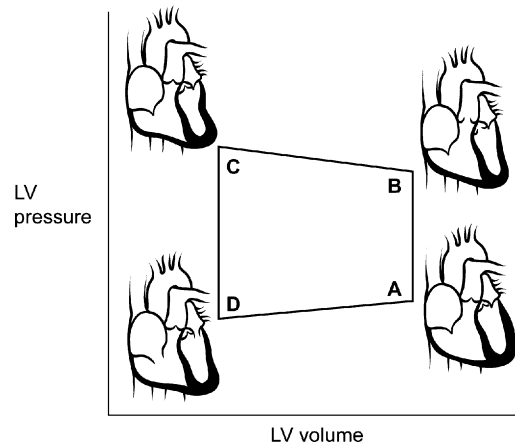


FIG. 10.21 Cardiac cycle. **A-B**, isovolumetric contraction phase; **B**, aortic and pulmonary valves open; **B-C**, ventricular ejection phase, i.e., stroke volume; **C**, aortic and pulmonary valves close; **C-D**, isovolumetric relaxation phase. **D**, atrioventricular (AV) valves open; **D-A**, ventricular filling phase; **A**, AV valves close. LV, left ventricular

- *S2*: Due to closure of semilunar valves, i.e., aortic and pulmonary
- *S3*: Due to ventricular filling; prominent in *CHF*
- *S4*: Due to high atrial pressure caused by atrial contraction; prominent in *ventricular diastolic dysfunction*

Heart Murmurs

- *Aortic stenosis*: Systolic *ejection* diamond-shaped murmur on the base, *radiating to the carotids*
- *Aortic regurgitation*: *Blowing diastolic* murmur on base, along with *wide pulse pressure, water hammer pulse, and strong carotid and capillary pulsations*
- *Mitral stenosis*: *Diastolic rumbling* murmur on the apex with *opening snap*
- *Mitral regurgitation*: *Pansystolic* murmur on the apex; most common murmur
- *Mitral prolapse*: *Midsystolic click* with *late systolic* murmur
- *Notes*:

1. A mitral stenosis murmur that *changes with position* in a female patient who also has *positional syncope* suggests *left atrial myxoma*.
2. *Most common cause of valve lesions* is wear and tear.
3. *Valve replacement* is done using *tissue valves* in elderly (*side effect: calcification*), and *mechanical valves* otherwise (*side effect: thrombosis and hemolysis*). Only patients with *mechanical valves* require *lifelong anticoagulation* with *warfarin* to a *target international normalized ratio (INR)* of 2.5 to 3.5

Jugular Vein Waves (Fig. 10.18)

- *A*: Due to atrial contraction
- *C*: Due to right ventricle contraction, causing mitral bulge inside the atrium
- *V*: Due to high atrial pressure
- *Y descent*: Drop in atrial pressure during ventricular filling
- *X descent*: Ventricular ejection phase

Important Equations

- *Stroke volume (SV)* = End diastolic volume (EDV) – End systolic volume (ESV)
- *Ejection fraction (EF)* = SV/EDV (normal >50%)
- *Cardiac output (CO)* = Stroke volume (SV) × Heart rate (HR)
- *Fick's equation*: $CO = \text{Rate of oxygen consumption} / \text{Difference between arterial and venous oxygen contents}$
- *Mean arterial pressure* = $CO \times \text{Peripheral resistance}$

Congestive Heart Failure (CHF)

- *Mechanism*: It is failure of the heart to pump out enough blood.
- *Starling's law*: Force of contraction is directly proportional to length of muscle fiber, until a certain limit, at which point muscles undergo dilatation and failure.
- *Types*:
 1. Systolic: Low EF; caused by myocardial infarction, alcohol, and illicit drugs
 2. Diastolic: Normal EF and decreased ventricular compliance; caused by long-standing hypertension and characterized by S4 on exam
 3. High output CHF, e.g., thyrotoxicosis
 4. Low output CHF: Most cases of CHF fall in this category.
- *Clinical picture*: See Table 10.6
- *Diagnosis*: Clinically, with butterfly shaped pulmonary venous congestion on CXR, Kerley A and B lines on CXR, and $EF < 50\%$ on echocardiogram (Fig. 10.22)
- *Treatment*: See Chapter 9, Pharmacology

Atherosclerosis

- *Mechanism*: It is a disease of the large and midsized arteries.
- *Predisposing factors*: Smoking, old age, and DM
- *Complications*: Myocardial infarction (MI), cerebrovascular accidents (CVAs)

TABLE 10.6 Congestive heart failure.

	Left ventricular failure	Right ventricular failure
Symptoms	<ul style="list-style-type: none"> • Dyspnea • Orthopnea • Paroxysmal nocturnal dyspnea (PND) • Frothy blood tinged sputum 	<ul style="list-style-type: none"> • Lower extremities edema • Right hypochondrial pain
Signs	<ul style="list-style-type: none"> • Bilateral basal crackles • Pulsus alternans • S3 gallop 	<ul style="list-style-type: none"> • Jugular venous distention • Hepatomegaly • Positive hepatojugular reflux • Pitting edema of lower extremities • Pulsus paradoxus • S3 gallop



FIG. 10.22 Pulmonary edema and Kerley B lines in congestive heart failure

- *Pathology*: Starts with *fatty streaks* and *foam cell* formation (where macrophages phagocytose oxidized low-density lipoprotein [LDL]), and then a *plaque* is formed. The end point is interfering with blood flow to an organ and causing an infarct, which is of two types:

1. Red: Made of *blood*, e.g., *lungs*, *GI system*
2. Pale: e.g., as in *MI* and *CVA*

Myocardial Infarction (MI)

- *Clinical picture*: Crushing substernal chest pain or heaviness radiating to left shoulder, along with diaphoresis, nausea, and dizziness

- **Risk factors:** Age (men ≥ 55 , women ≥ 65), smoking, dyslipidemia, and family history; *age* is the most important risk factor.
- **Diagnosis:**
 1. Electrocardiogram shows changes in the ST segments or T waves (*first sign of MI*).
 2. Elevated troponin and isoenzyme of creatine kinase with muscle and brain units (CK-MB), and lactate dehydrogenase fraction 1 (LDH₁) $>$ LDH₂ flip ratio. Myoglobin is the first to rise (*after 1 hour*) and troponin is the last to disappear (*rises after 3 hours and lasts for 10 days*).
- **Treatment:**
 1. First step: Morphine, Oxygen, Nitroglycerin, Aspirin (MONA)
 2. Non-ST elevation MI (NSTEMI): Heparin IV drip, nitroglycerin, aspirin, beta-blockers, ACEI, and statins
 3. STEMI: As with NSTEMI, except that the mainstay of treatment here is *urgent heart catheterization (within 90 minutes)*
- **Note:** Glycoprotein IIb/IIIa inhibitors are also used in acute MI and after stent placement, as they *inhibit platelet aggregation and fibrinogen production*.
- **Pathologically:** Coagulative necrosis in the myocardium starts within hours:
 1. Day 1: Neutrophil migration occurs.
 2. Week 1: Granulation tissue formation
 3. Week 3 after the MI: Myocardial scar is complete.
- **Angina:** Chest pain due to myocardial ischemia, and it has three types:
 1. Stable angina: Due to *uncomplicated atheroma*
 2. Unstable angina: Due to *a complicated plaque, i.e., rupture*
 3. Prinzmetal angina: Caused by *coronary vasospasm*, shows *ST elevations*. *Beta-blockers are contraindicated, as it allows full uninhibited alpha action on blood vessels and more vasospasm.*
- **Complications:**
 1. Arrhythmia and heart failure
 2. Rupture of interventricular septum or papillary muscles: On the USMLE, an MI is followed by the appearance of new mitral regurgitation murmur. Note: *Papillary muscles attach posteriorly in the myocardium and are supplied by right coronary artery.*
 3. Ventricular aneurysm: Suspected by persistent ST elevation after resolution of MI. A thrombus can form inside the aneurysm and embolism can ensue.
 4. Dressler syndrome: It is pericarditis that might occur few weeks after resolution of the MI, and is treated with *steroids*.
- **Notes:**
 1. Chest pain that starts days after the MI indicates *pericarditis or re-infarction*.
 2. MI is the most common complication after *carotid endarterectomy*.
 3. Most common cause of death in MI is *arrhythmia*
 4. Cessation of smoking for *5 years* decreases risk of MI by *50%*.
 5. Indications for bypass surgery: Left main coronary artery involvement, or 3+ vessel disease. Anything else could be treated with *stenting*.

Pericarditis

- **Causes:** Multiple, but mostly *viral*
- **Clinical picture:** Chest pain, *worse on lying flat and relieved by sitting up or leaning forward*
- **On exam:** *Friction rub*
- **ECG:** *Diffuse PR depressions and ST elevations* and normal troponins (Fig. 10.23)
- **Treatment:** Nonsteroidal antiinflammatory drugs (NSAIDs)

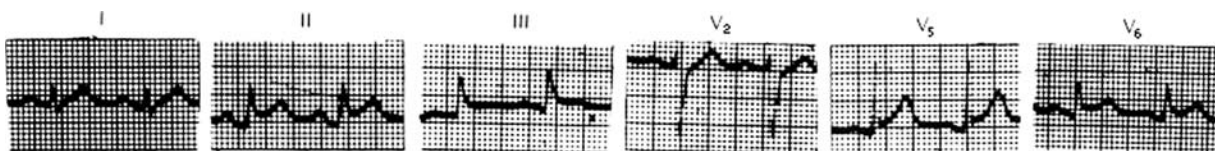


FIG. 10.23 Electrocardiogram changes in pericarditis

Pericardial Effusion and Tamponade

- **Mechanism:** If *any amount of fluid* collects rapidly between the visceral and parietal layers, tamponade occurs.
- **Clinical picture:**
 1. Hypotension
 2. Distant heart sounds
 3. Inspiratory drop of blood pressure (“*pulsus paradoxus*”)
 4. Inspiratory filling of jugular veins (“*Kussmaul’s sign*”)
- **Diagnosis:** Echocardiogram
- **Treatment:** Urgent pericardiocentesis
- **Notes:**
 1. During pericardiocentesis, the *internal mammary artery* is at risk of injury.
 2. In tamponade, the left atrial pressure (LAP) is equal to right atrial pressure (RAP) and is equal to right ventricular end diastolic pressure (RVEDP): LAP = RAP = RVEDP
 3. *Malignant effusions are hemorrhagic, and uremic effusions are serous.*

Rheumatic Fever

- **Mechanism:** Post-group *A beta-hemolytic streptococcal* infection, due to cross-sensitivity between streptococcal antigen and cardiac tissue
- **Clinical picture:** This is a “CCASE” that you never forget once you see a patient with fever and two or more of the *Jones criteria (CCASE)*:
 1. Chorea: Known as Sydenham’s chorea
 2. Carditis: Valve lesions, *mitral being most common*
 3. Arthritis: Migratory and fleeting
 4. Subcutaneous nodules
 5. Erythema marginatum on the trunk and proximal extremities
- **Diagnosis:** High erythrocyte sedimentation rate (ESR) and antistreptolysin O titers (ASO)
- **Complication:** Most common is *mitral stenosis*
- **Pathology:**
 1. *Aschoff bodies; central fibrinoid necrosis surrounded by fibrosis*
 2. *Anitschkow cells*
- **Treatment:** *Penicillin (PCN)*. If allergic to PCN, give *erythromycin*.

Endocarditis

- **Causes**
 1. *Streptococcus viridans*: *Most common cause*; responsible for subacute cases

2. *Staphylococcus aureus*: Has rapid onset, more aggressive and common in *IV drug users*
3. Abacterial (marantic endocarditis): Secondary to renal failure, cancer

- **Valves involved:**

1. Most common is mitral valve, just like rheumatic fever
2. Tricuspid valve is more commonly involved in IV drug users

- **Clinical picture:**

1. Fever and sepsis in a patient with a *new murmur*
2. Osler nodes: Tender nodular lesions on fingers
3. Janeway lesions: Erythematous lesions on palms
4. Roth spots: White spots in the retina
5. Splinter hemorrhages: Linear hemorrhage under the nails

- **Diagnosis:**

1. Positive blood cultures: *First thing to order* when you suspect this disease
2. Transesophageal echocardiogram: To diagnose valvular vegetations

- **Treatment:** Broad-spectrum antibiotics for 4–6 weeks

- **Note:** *Antibiotic prophylaxis before procedures aims to decrease the risk of endocarditis. Amoxicillin (2 g orally 1 hour before most procedures) is given to any patient with heart murmur. Clindamycin or azithromycin are given in case of a penicillin allergy.*

Hypertrophic Obstructive Cardiomyopathy (HOCM)

- **Mechanism:** It is a familial disease (AD) characterized by *disproportionate thickening of the interventricular septum* leading to *subaortic stenosis*.
- **Clinical picture:**

1. Syncope or sudden death on exertion. *Always think of this on the USMLE for a young patient who suddenly collapses during exercise.*
2. Aortic stenosis murmur: Decreased by anything that increases the venous return, e.g., squatting, lying supine, hand grip

- **On exam:** *Pulsus bisferious*

- **Diagnosis:** Echocardiogram

- **Treatment:** Beta-blockers and vasodilators

- **Contraindication:** Inotropic agents, e.g., digoxin

- **What to advise your patient:** All family members should be evaluated for HOCM.

Hematology

Red Blood Cells (RBCs)

- Normally *biconcave* with *no nucleus* and their half-life is *120 days*; normal RBC count is 5-6 million/mm³ in males, and 4-5 million/mm³ in females
- *Hemoglobin*: In adults is HbA (2 alpha and 2 beta chains) and its normal values are 13 to 17 g/dL in males, and 12 to 16 g/dL in females.
- *Hematocrit (packed cell volume)*: It is the volume of packed RBCs in 100 cc of blood and is around 40% to 50% on average, and slightly less in females.
- *Erythrocyte sedimentation rate (ESR)*: It is the rate of deposition of RBCs in a tube due to rouleaux formation. It is normally below 20 mm/hr. Elevation above 100 mm/hr suggests *severe infection, malignancy, or connective tissue disease or multiple myeloma*.
- *Mean corpuscular volume (MCV)*: Volume of a red blood cell (normal = 78–100 fL)
- *Mean corpuscular hemoglobin (MCH)*: Amount of Hb per cell (normal = 27 to 32 pg)
- *Mean corpuscular hemoglobin concentration (MCHC)* = Hb concentration/Hematocrit (normal = 33%)
- *Anemia*: Hb <13 in males, <12 in females, <11 in pregnancy
- *Abnormal forms of hemoglobin*: Detected by *multiple wavelength co-oximetry*. The most common toxicities:
 1. *Carboxyhemoglobin*: Carbon monoxide bound to Hb; *common in old houses with a fireplace* and is treated with *100% or hyperbaric oxygen*
 2. *Methemoglobinemia*: Iron is converted from Fe₂ to Fe₃ and bound O₂ is useless; *common in lidocaine toxicity* and is treated with *methylene blue*
- *Abnormal cell forms*:
 1. Reticulocytes: 0.2% to 2% of RBCs. They are the immature form of RBCs and *the first cell to rise after starting iron therapy in iron-deficiency anemia*.
 2. Microcytosis: MCV <78 fL; common in *iron-deficiency anemia*
 3. Macrocytosis: MCV >100 fL; common in *megaloblastic anemia*
 4. Basophilic stippling: Common in *lead poisoning* (Fig. 10.24)
 5. Teardrop RBCs: Common in *myelofibrosis*
 6. Burr cells: Common in *renal diseases*
 7. Schistocytes: Common in *hemolysis* (Fig. 10.25)
 8. Acanthocytes: Common in *abetalipoproteinemia*

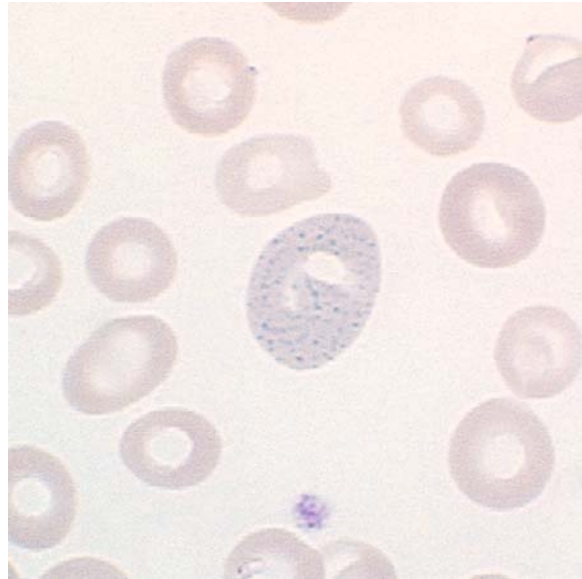


FIG. 10.24 Basophilic stippling of red blood cells (RBCs)

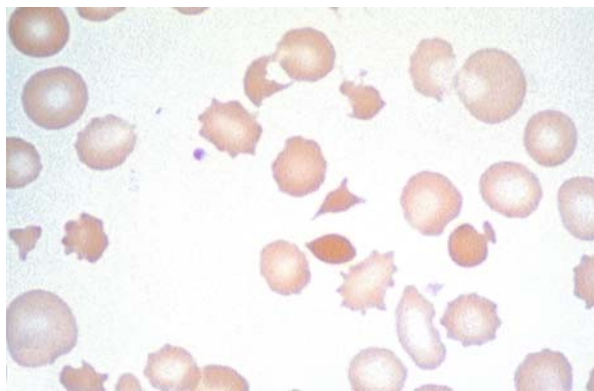


FIG. 10.25 Schistocytes

9. Auer rods: Seen on peripheral smear in *acute myelogenous leukemia (AML)* (Fig. 10.26)
10. Howell-Jolly bodies: Common in patients with *absent or nonfunctioning spleen*

White Blood Cells (WBCs)

- *Normal count*: 4000 to 11,000 /mm³; discussed in Chapter 4, Histology
- *Embryology*: They develop from blast cells, which normally do not exceed 3% in the blood.

Platelets

- *Normal count*: 150,000 to 400,000 /mm³
- *Embryology*: Develop from *megakaryocytes* in the bone marrow

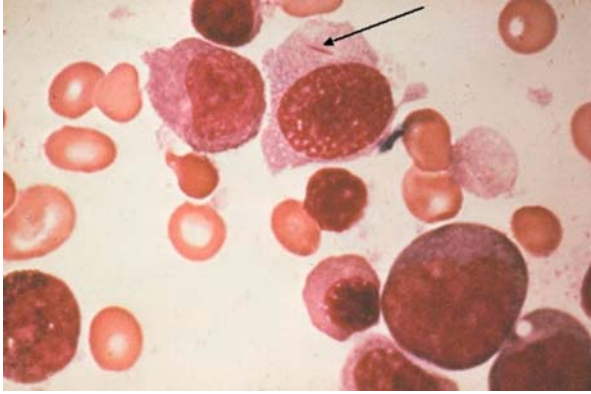


FIG. 10.26 Auer rods of acute myelogenous leukemia (AML) (arrow)

- **Function:** Coagulation
- **Hemostasis:** Upon blood vessel injury, vasoconstriction occurs due to the effect of *thromboxane A₂*. Release of von Willebrand factor also causes *platelet adhesion*. Platelets release *adenosine diphosphate (ADP)* to induce *platelet aggregation* and a platelet plug is formed.
- **Notes:**
 1. The first thing to do about a low platelet count is to *repeat the test*, and then examine a peripheral smear.
 2. Alcohol inhibits thrombopoietin in the liver and causes transient thrombocytopenia that lasts about 7 days. However, alcoholism can also cause hypersplenism, which causes permanent *pancytopenia*.

Coagulation Cascade

- **Extrinsic:** Rapid, starts with tissue injury and release of tissue thromboplastin (factor VII), which activates factor X in the presence of calcium. Reflected by prothrombin time (PT) (normal = 10–15 seconds).
- **Intrinsic:** Starts with contact with a foreign object. Factors activated in order are: XII → XI → IX → X. Reflected by activated partial thromboplastin time (APTT) (normal = 30–40 seconds).
- **Common pathway:** Starts with factor X activating conversion of prothrombin to thrombin. Thrombin converts fibrinogen to fibrin and platelet plug forms.
- **Platelet abnormalities:** Lead to petechiae and purpura
- **Clotting factors abnormalities:** Lead to big bleeds, e.g., joints, intracranial, etc.
- **Causes of isolated high PT:** Warfarin

- **Causes of isolated high PTT:** Hemophilia, von Willebrand disease, and antiphospholipid antibody syndrome
- **Causes of elevated PT and PTT:** DIC, liver disease, and vitamin K deficiency.
- **Note:** When blood clots inside a test tube, the supernatant contains plasma rich in vitamin K-dependent clotting factors (*II, VII, IX, and X*).

Iron-Deficiency Anemia

- It is the most common form of anemia in females.
- **Normal iron requirement:** 10 mg/day, of which only 1 mg is absorbed in the *ferrous* form. Absorption occurs in the *duodenum* and is stimulated by *vitamin C* and inhibited by *phosphates*.
- **Causes:** Decreased intake or increased loss, e.g., bleeding or *Ankylostoma* (hookworm) infection
- **Clinical picture:** Fatigue, pallor, and craving for ice (*pica*)
- **On exam:** Spooning of the nails (*“koilonychia”*)
- **Diagnosis:** Low iron, ferritin, MCV and MCH; total iron-binding capacity (TIBC) is high (Fig. 10.27) for microcytic hypochromic RBCs.
- **Treatment:** Iron therapy
- **Follow-up on response:** *Reticulocytes* are the first cells to be elevated and are a marker of response to therapy, which should be continued for *at least 6 months*.
- **Notes:**
 1. Side effects of iron therapy: *GI upset, constipation, and black stools*
 2. *Any elderly patient with iron-deficiency anemia must get a colonoscopy to rule out colon cancer.*
 3. Ferritin is an acute-phase reactant, so in inflammatory conditions it will be elevated, *even in patients with iron-deficiency anemia.*

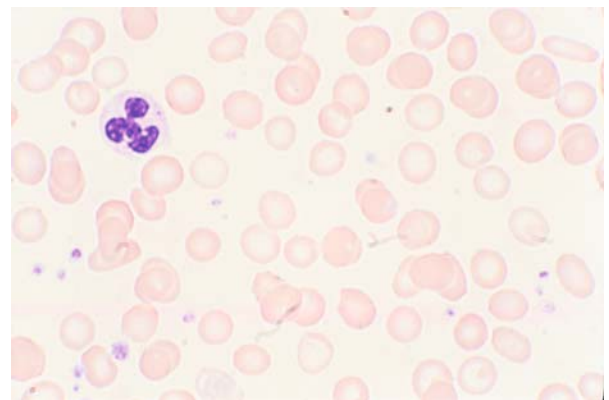


FIG. 10.27 Microcytic hypochromic anemia

4. *Anemia of chronic disease: Normocytic, normochromic, with low iron and normal ferritin. However, 25% of cases have microcytic hypochromic picture.*
5. Sideroblastic anemia is an *X-linked recessive, microcytic hypochromic anemia* that leads to deposition of iron-studded cells in the bone marrow. Diagnosis: *Prussian blue stain of bone marrow*. Treatment: *Vitamin B₆*.

Megaloblastic Anemia

- **Mechanism:** Folic acid or vitamin B₁₂ deficiency. Normal requirement of folic acid is 50 µg/day, while that of B₁₂ is 1 µg/day
- **Causes:** Decreased intake, intrinsic factor deficiency, or *Diphyllobothrium latum* (fish tapeworm) infection (*D. latum* causes B12 deficiency).
- **Clinical picture:** Fatigue, pallor, and possibly neurologic symptoms (subacute combined degeneration [SCD])
- **Diagnosis:**
 1. High MCV and MCH, low B₁₂ and folic acid
 2. Folic acid deficiency: Positive *formiminoglutamic acid (FIGLU) test*, done using histidine
 3. B₁₂ deficiency: Positive *Schilling test*, *hypersegmented neutrophils* on peripheral smear (Fig. 10.28), and elevated serum *homocysteine and methylmalonic acid*
- **Treatment:** Replacement therapy
- **Notes:**
 1. Liver stores of B₁₂ last for 3 to 5 years, so B₁₂ deficiency is not common.
 2. Vitamin B₁₂ is abundant in meat products, so deficiency of B₁₂ is more commonly seen in *vegetarians*. Meat eaters (who eat no vegetables), on the other hand, are more likely to suffer *vitamin C deficiency*.

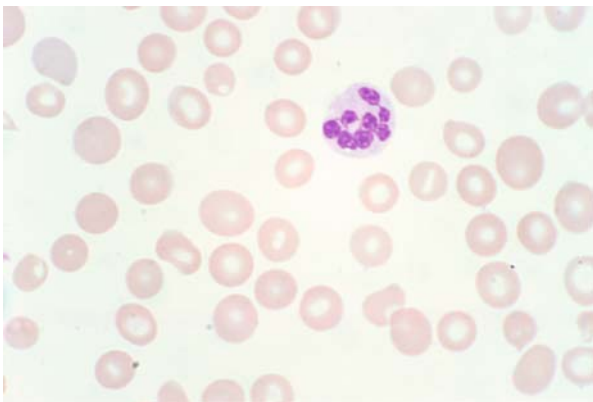


FIG. 10.28 Hypersegmented neutrophils

3. B₁₂ deficiency can lead to *pancytopenia* and *neurologic manifestations*. See Subacute Combined Degeneration in Chapter 3, Neuroanatomy.
4. *Pernicious anemia* is a form of B₁₂ deficiency that occurs due to antibodies against intrinsic factor and gastric parietal cells; it is associated with other immunologic diseases.
5. *Folic acid deficiency is the most common type of anemia in the U.S.*

Hemolytic Anemia

- **Clinical picture:** Fatigue, jaundice of skin and sclera, and normal colored urine
- **Diagnosis:**
 1. High *indirect bilirubin* and low haptoglobin
 2. Peripheral smear: *Schistocytes*
 3. Coombs test: Positive in *autoimmune hemolytic anemia*
- **Note:** Drugs such as amphotericin B and penicillin can cause hemolysis

Aplastic Anemia

- **Causes:** Bone marrow destruction, e.g., benzene, chemotherapy, radiation, or infection with *parvovirus B19*
- **Clinical picture:**
 1. Anemia: Fatigue and pallor
 2. Leukopenia: Recurrent infections
 3. Thrombocytopenia: Bleeding
- **Diagnosis:** Bone marrow biopsy reveals *empty marrow*
- **Treatment:** Treat the cause, *bone marrow transplantation*, and rule out two diseases that present similarly:
 1. B₁₂ deficiency: Severe cases lead to pancytopenia
 2. Hypersplenism: Occurs with liver cirrhosis and leads to pancytopenia
- **Note:** Antilymphocyte or antithymocyte globulins could be used to treat aplastic anemia; however, *serum sickness* is always a concern during therapy.

Hypersplenism

- **Definition:** It is a pancytopenia that is reversible by splenectomy.
- **Clinical picture:** Fatigue, infections, and bleeding

- **Diagnosis:** Low hemoglobin, WBCs, and platelets. *Chromium 51-labeled RBCs* shows excessive spleen uptake.
- **Treatment:** Splenectomy

Thalassemia

- **Mechanism:** Absent alpha or beta chains of hemoglobin, and is common in *Mediterranean* populations; that is a key question on the USMLE.
 1. **Defect in alpha chain:** Alpha-thalassemia could be due to a defect in one locus causing alpha-thalassemia trait, two loci (alpha-thalassemia minor), three loci (hemoglobin H), or all four loci (hemoglobin Bart's), which causes *hydrops fetalis*. *Common in Asians*.
 2. **Defect in beta chain** causes beta-thalassemia minor or major, also called *Cooley's anemia*.
- **Clinical picture and diagnosis:**
 1. *Microcytic hypochromic anemia*
 2. *Target cells* on peripheral blood smear (Fig. 10.29)
 3. Hb electrophoresis: Hemoglobin F in Cooley's anemia (*Hgb A2 in Beta thalassemia minor*)
 4. *Chipmunk facies* and *hair-on-end appearance* on skull x-rays due to extramedullary hematopoiesis
- **Treatment:** Blood transfusion, folic acid, and bone marrow transplantation

Sickle Cell Disease

- **Mechanism:** Replacement of *glutamic acid* with *valine* in *beta chain of Hb*
- **Clinical picture:**
 1. Diffuse dactylitis, abdominal pain, and shortness of breath, mostly due to *microinfarctions by sickle cells*

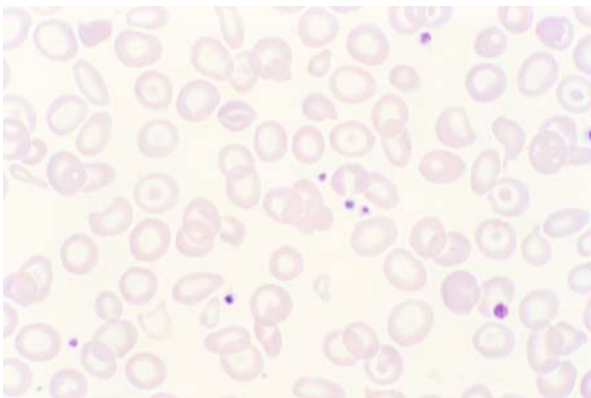


FIG. 10.29 Target cells

2. Multiple infections: Due to functional asplenia; therefore, these patients have to be vaccinated against *Haemophilus influenzae* type B (HiB), *Streptococcus pneumoniae*, and *Neisseria meningitidis*.
3. Normocytic normochromic anemia
4. *Sickle cells* on peripheral smear (Fig. 10.30)
5. Hb electrophoresis: *Hemoglobin S*

- **Complications:**

1. Aplastic anemia: Due to *parvovirus B19* infection
2. Osteomyelitis: *Salmonella* is more common in this population, but the most common organism is still *Staphylococcus aureus*.

- **Treatment:**

1. Supportive: Warming, fluids, analgesics, and oxygen if needed
2. Exchange transfusion: Only if there is severe *dyspnea* or *priapism*
3. Hydroxyurea: It increases HbF and decreases HbS

- **Notes:**

1. Sickle cell anemia is a predisposing factor for *follic acid deficiency*.
2. Patients present in sickle cell crisis *usually due to infections* or hypoxia.
3. Sickle cell patients are resistant to infection by *Plasmodium falciparum*.

Spherocytosis

- **Mechanism:** Defect in the RBC membrane; namely *spectrin*
- **Clinical picture and diagnosis:**
 1. *Extravascular hemolysis:* Normocytic normochromic anemia

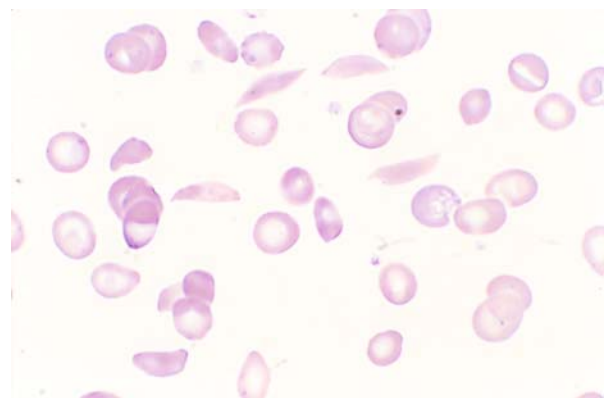


FIG. 10.30 Sickle cells

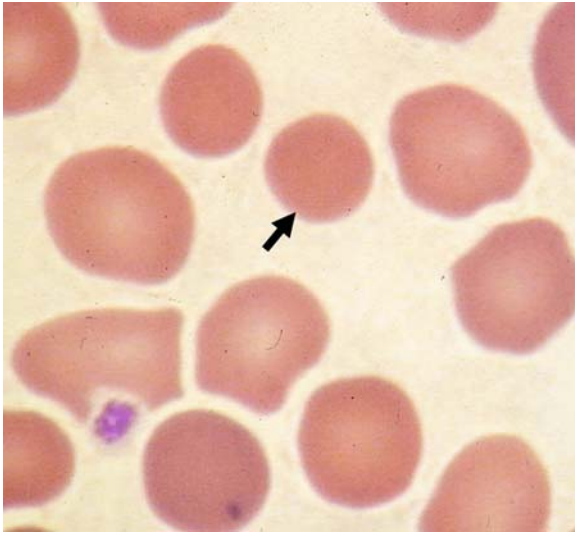


FIG. 10.31 Spherocytes (arrow)

2. Spherocytes on peripheral smear ($MCHC > 33\%$) (Fig. 10.31)
3. Positive *osmotic fragility test*
4. Gallstones and splenomegaly

- **Treatment:** Splenectomy
- Remember three vaccines before surgery: *H. influenzae* B, pneumococci, and meningococci. Also remember that pneumococcus is the most fatal infection.
- **Note:** Postsplenectomy patients have chronic low *IgM* levels.

Glucose-6-Phosphate Dehydrogenase (G-6-PD) Deficiency

- **Mechanism:** Absent RBC membrane enzyme; more common in African-Americans
- **Clinical picture and diagnosis:**
 1. Hemolysis after ingestion of fava beans, sulfa, or antimalarial medications
 2. Low G-6-PD levels in RBCs occur a few days after the hemolysis episode.
 3. *Heinz bodies* and *bite cells* in the peripheral smear
- **Treatment:** Supportive and avoiding the inducing agent

Paroxysmal Nocturnal Hemoglobinuria (PNH)

- **Mechanism:** Absent decay accelerating factor (*DAF*) in the RBC membrane; this in turn leads to activation of complement *C3* to attack the RBCs, causing *intravascular hemolysis*

- **Clinical picture:**

1. Blood in the urine *only upon waking in the morning*, but not throughout the day (*that is the key to the whole case*).
2. Leukopenia: Recurrent infections
3. Platelets: Decreased count, yet increased aggregation leading to thromboembolic events

- **Diagnosis:** *Ham test* and *sucrose lysis test*: Hemolysis occurs at pH of 6.2. Recently, we check for *CD55* and *CD59* levels.
- **Treatment:** Steroids

Hemophilia

- **Mechanism:** *X-linked recessive* disease due to deficiency of clotting factors *VIII* (type A) or *IX* (type B)
- **Clinical picture:**
 1. Bleeding since birth, e.g., cephalhematoma
 2. Multiple ecchymosis and large joint hemorrhagic effusions
 3. Retroperitoneal hematoma: Patients can only present with femoral neuropathy (*unilateral leg pain, weakness and numbness*)
- **Diagnosis:** Prolonged PTT, normal PT, and low factor VIII or IX
- **Treatment:** Desmopressin (DDAVP) as a factor VIII-rich substance

Idiopathic Thrombocytopenic Purpura (ITP)

- **Mechanism:** Immunologically generated antibodies (*IgG*) against platelets, mostly following a recent viral illness
- **Clinical picture:** Repeated, prolonged bleeding episodes
- **Diagnosis:** Low platelet count and high serum *IgG* against platelets
- **Treatment:** Steroids. If that fails, splenectomy. Usually self-resolving in children.
- **Notes:**
 1. *Evans syndrome:* ITP and autoimmune hemolytic anemia
 2. Most cases in children, unlike in adults, resolve spontaneously.

Von Willebrand Disease (VWD)

- **Mechanism:** Autosomal dominant disease that affects the platelet *adhesion* process, while the platelet count and aggregation are both normal

- *Clinical picture*: Repeated *easy bruising* and prolonged bleeding after injuries
- *Diagnosis*: Prolonged PTT, normal PT, prolonged bleeding time, low von Willebrand factor (vWF) and defective vWF activity on ristocetin platelet study
- *Treatment*: Desmopressin (DDAVP) or factor VIII (both rich in vWF)

Disseminated Intravascular Coagulopathy (DIC)

- *Mechanism*: It is a process that involves *consumption of the clotting factors* to end up with bleeding or thrombosis.
- *Causes*: Sepsis, malignancy, leukemia, or pulmonary embolism. Most common DIC associated leukemia is *acute promyelocytic leukemia*.
- *Clinical picture*: Extensive bleeding or thrombosis
- *Diagnosis*:
 1. Low platelets and elevated LDH
 2. Prolonged PT and PTT
 3. Low fibrinogen and elevated fibrin degradation products (FDP)
- *Treatment*: Treat the cause. If patient is bleeding, transfuse with *fresh frozen plasma*.

Antiphospholipid Antibody Syndrome

- *Mechanism*: Immunologically derived antibodies against enzymes of the coagulation pathways
- *Clinical picture*:
 1. Multiple unprovoked thromboembolic events, e.g., deep venous thrombosis, myocardial infarction, cerebrovascular accidents
 2. *Recurrent unprovoked abortions (this is the key to the case)*
 3. Livedo reticularis: *Net-shaped violaceous rash*
- *Diagnosis*:
 1. Prolonged PTT, normal PT
 2. Elevated antibodies: Lupus anticoagulant, anticardiolipin, glycoprotein B1
- *Treatment*: Lifelong anticoagulation

Thrombotic Thrombocytopenic Purpura (TTP)

- *Mechanism*: Lack of ADAM-TS13, a vWF cleaving factor
- *Clinical picture*: Pentad:

1. Microangiopathic hemolytic anemia: Diagnosed by presence of schistocytes in a peripheral blood smear
2. Thrombocytopenia
3. Renal failure
4. Neurologic symptoms
5. Fever

- *Diagnosis*: Schistocytes on the peripheral blood smear
- *Treatment*: Life-threatening disease; *urgent plasmapheresis* is required
- *Note*: Hemolytic uremic syndrome (HUS): It is caused by *E. coli 0157-H7*, which causes *bloody diarrhea* followed by a TTP-like picture *without the fever and neurologic symptoms*. Diagnosis and treatment is the same as for TTP. *Chemotherapy combinations containing mitomycin can also induce HUS*.

Myeloproliferative Disorders

- Biggest complication of these disorders is transformation into *leukemia*

Polycythemia

- It entails excessive RBCs causing *hyperviscosity syndrome*.
- *Causes*: Primary (*polycythemia vera*), or secondary to smoking or erythropoietin-secreting tumor, e.g., renal cell cancer
- *Clinical picture*:
 1. Plethora, facial flushing, and itching: *Gets worse after warm showers*
 2. Elevated B₁₂, basophils, and uric acid levels
 3. Splenomegaly
- *Diagnosis*:
 1. High RBC mass and hematocrit (>48 in females and >52 in males)
 2. Erythropoietin level: *Low in primary cases and high in secondary ones*
- *Treatment*: Phlebotomy, hydroxyurea, and treat the cause

Myelofibrosis

- It is fibrosis of the bone marrow.
- *Clinical picture*: Pancytopenia and hepatosplenomegaly
- *Diagnosis*: *Dry bone marrow tap*, and *teardrop RBCs*
- *Treatment*: Hydroxyurea and bone marrow transplant

Thrombocytosis

- Could be primary (count $\geq 1,000,000$) or reactive to iron-deficiency or infection (count $< 1,000,000$)
- *Clinical picture:* Thrombosis or bleeding
- *Treatment:* Hydroxyurea and treat the cause

Henoch-Schönlein Purpura

- *Mechanism:* Poststreptococcal vasculitis that is more common in children
- *Clinical picture:*
 1. Abdominal pain
 2. Hematuria: Due to glomerulonephritis
 3. Purpuric rash on buttocks and lower extremities (Fig. 10.32)
- *Diagnosis:* Skin biopsy shows IgA deposits
- *Treatment:* Self-resolving

Multiple Myeloma

- *Mechanism:* A plasma cell malignancy leading to a single immunoglobulin spike on protein electrophoresis



FIG. 10.32 Henoch-Schönlein purpura

- *Clinical picture:*

1. Bone pain: It is the key symptom. If on the USMLE you see an elderly patient complaining of bone pains, look for multiple myeloma. It occurs due to lytic “punched out” bone lesions that develop due to the release of osteoclast activating factor (OAF).
2. Anemia and thrombocytopenia
3. Hypercalcemia and renal failure resulting in nitrogen retention

- *Diagnosis:*

1. High serum protein, mainly IgG (monoclonal)
2. High urine protein (“Bence Jones proteinuria”)
3. High serum calcium
4. Rouleaux formation of RBCs on peripheral smear
5. Plasma cell content of the bone marrow $> 10\%$. Plasma cells have a “cartwheel” or “clockface” nucleus, and are basophilic due to their high content of rough endoplasmic reticulum and Golgi apparatus (Fig. 10.33)

- *Treatment:* Chemotherapy (melphalan) or bone marrow transplant

Leukemia

- It is abnormal uncontrolled proliferation of WBCs.
- *Causes:* Genetic, benzene, alkylating agents, and human T-cell leukemia virus (HTLV)
- *Clinical picture:*
 1. Low RBCs and Hb: Fatigue and pallor
 2. Low platelets: Bleeding
 3. High WBCs:
 - Hepatosplenomegaly and lymphadenopathy: Through infiltration of white pulp in all types, except hairy cell leukemia targeting the red pulp

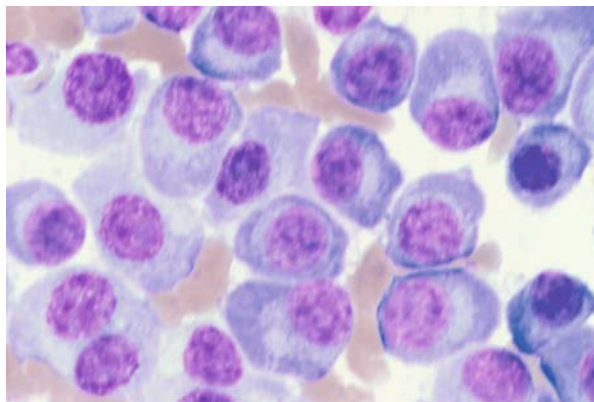


FIG. 10.33 Plasma cells

- Skin: *Greenish nodules* in acute myeloid leukemia (AML)
- Bones: Fractures
- CVS: Cardiomyopathy and effusion
- Renal: Acute tubular necrosis (ATN)
- *Diagnosis:*
 1. High WBC count with *>90% blasts*
 2. Low RBCs and low platelets
- *Treatment:*
 1. Acute myeloid leukemia (AML): Cytosine arabinoside (ara-c) and doxorubicin
 2. Acute lymphatic leukemia (ALL): Prednisone, vincristine, and doxorubicin
 3. Chronic myeloid leukemia (CML): Imatinib (tyrosine kinase inhibitor)
 4. Chronic lymphatic leukemia (CLL): *No need to treat unless symptomatic*; fludarabine
 5. Hairy cell leukemia: 2-chlorodeoxyadenosine (2-CdA)
- *Notes:*
 1. *Auer rods* are specific to AML; *t15:17* is associated with a good prognosis in AML (M3 subtype).
 2. Positive common acute lymphocytic leukemia antigen (CALLA) and positive terminal deoxynucleotidyl transferase (TdT) favor the prognosis of ALL and vice versa.
 3. Philadelphia chromosome *t9:22* is a poor prognostic indicator for ALL and is a good one for CML
 4. CML is associated with *high basophil, uric acid, and B₁₂ levels*, and low leukocyte alkaline phosphatase levels.
 5. *Smudge (smear) cells* can be seen on the peripheral smear of CLL (Fig. 10.34).
 6. CLL is associated with high incidence of *auto-immune hemolytic anemia*.

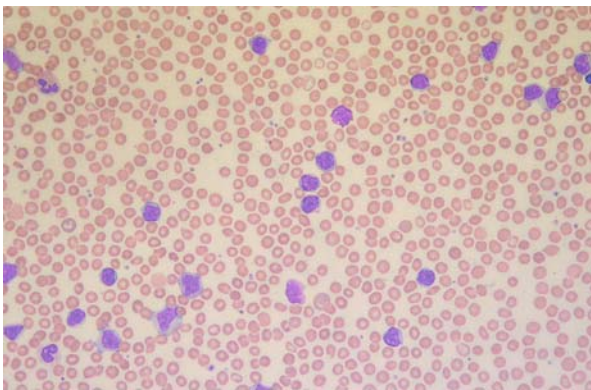


FIG. 10.34 Smudge (smear) cells of chronic lymphatic leukemia (CLL)

7. Bone marrow in hairy cell leukemia shows *fried egg-shaped cells*.
8. Leukemoid reaction: High WBC count due to a severe infection; it is not leukemia because blast cells are less than 5% and there is elevated leukocyte alkaline phosphatase.

Lymphoma

- *Clinical picture:*
 1. Painless enlargement of lymph nodes (discrete and rubbery), hepatosplenomegaly, fever, and pruritus
 2. *B symptoms* (helpful to remember: Two “nights” and two “losses”): *Night fever, night sweats, loss of weight, and loss of appetite*
- *Types:*
 1. Hodgkin’s:
 - *Bimodal* age distribution (20s and 60s)
 - Best prognosis is *lymphocyte predominance* and worst is *lymphocyte depletion lymphoma*. The latter has the highest amount of Reed-Sternberg cells.
 - *Diagnosis:* Lymph node biopsy; *Reed-Sternberg cell* is diagnostic (Fig. 10.35)
 - *Treatment:* Adriamycin, bleomycin, vinblastine, dacarbazine (ABVD)
 - *Note:* Treatment of lymphomas can cause tumor lysis syndrome characterized by high serum (“KUP”): *K, uric acid, and phosphorus* and low calcium. Aggressive fluid and bicarbonate infusion and allopurinol during therapy is essential to prevent renal failure.

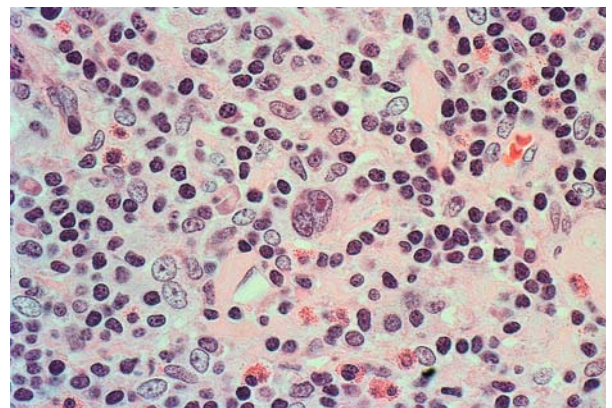


FIG. 10.35 Reed-Sternberg cell (in the center of this picture)

2. Non-Hodgkin’s:

- More common in the elderly
- Most common type is *large B-cell lymphoma*
- Burkitt lymphoma is a non-Hodgkin’s lymphoma caused by Epstein-Barr virus (*EBV*) and it causes *mandibular tumor* in African children. *American Burkitt’s lymphoma (t8:14) presents with intestinal obstruction especially in young women with breast cancer.*
- Treatment: Cyclophosphamide, hydroxydaunomycin (“doxorubicin”), Oncovin (“vincristine”), and prednisone (CHOP)
- Note: Hemorrhagic cystitis caused by cyclophosphamide can be prevented by *MESNA*.

phosphatase. Bone x-ray in these patients show *pseudofractures (Looser’s zones)*

- Treatment: Calcium and vitamin D, calcitonin and bisphosphonates, which act by *inhibiting the osteoclasts*, e.g., pamidronate
- Note:
 1. Smoking and alcohol increase the risk of osteoporosis by *twofold*.
 2. Most common side effect of bisphosphonates is *erosive esophagitis*
 3. Raloxifene is a Selective Estrogen Receptor Modulator (*SERM*) that acts like estrogen on bones (*prevents osteoporosis*) and act as an estrogen blocker on breast and endometrium (decreases risk of cancer). Ideal for *postmenopausal woman*.
 4. Osteopetrosis: Occurs due to *defective osteoclasts*. Patient presents with *bone fractures and facial nerve palsy*. Treatment: Steroids and low calcium diet.

Common Blood Transfusion Reactions

- *Hemolysis*: Due to ABO incompatibility
- *Febrile, nonhemolytic reaction*: Due to antibodies against WBCs or HLA
- *Treatment*: Stop the transfusion and send the blood to the lab for typing and cross-matching.

Bones and Joints

Bone Tumors

- See Table 10.7

Osteoporosis and Osteomalacia

- *Osteoporosis*: Loss of bone mass, with the remaining bone being of normal density. It could be postmenopausal (type 1) or senile (type 2), and it puts the patient at risk of fracture, e.g., compression vertebral fracture, fracture of the neck of femur. *These patients have normal serum calcium and alkaline phosphatase.*
- *Osteomalacia*: Normal bone mass, but the bone density is significantly decreased. *These patients have low serum calcium and high alkaline*

Paget’s Disease of the Bone

- *Mechanism*: Rapid bone turnover, mostly due to infection, e.g., paramyxovirus
- *Clinical picture*: On the USMLE, a patient has frequent bone fractures and deformities and his *hat recently does not fit anymore* (due to frontal bossing)
- *Diagnosis*:
 1. X-ray of bones: Thick bone cortex and trabeculae
 2. High *serum alkaline phosphatase* and *urinary hydroxyproline*; everything else is within normal limits.
- *Treatment*: Bisphosphonates, e.g., alendronate

Septic Arthritis

- *Causes*: Staphylococci (*most common*), streptococci, or *H. influenzae B*
- *Clinical picture*: Red, warm, tender, and swollen joint

TABLE 10.7 Bone tumors.

	Ewing sarcoma	Osteogenic sarcoma	Giant cell tumor
Target	Diaphysis of long bones	Metaphysis of long bones	Epiphyseal end of long bones
Unique feature	Onion skin appearance on x-ray	Codman triangle on x-ray due to elevation of the periosteum	Soap bubble appearance on x-ray
Notes	Translocation t11;22	Most common malignant bone tumor	Benign tumor with spindle shaped and multinucleated giant cells

- *Diagnosis:*
 1. Arthrocentesis should be the first step
 2. High WBC in serum and synovial fluid, elevated ESR and C-reactive protein (CRP)
- *Treatment:* Arthrocentesis and systemic antibiotics

Rheumatoid Arthritis (RA)

- *Mechanism:* Immunologically mediated *T lymphocyte* inflammatory synovitis. Linkage to *HLA-DR4* has been suggested.
- *Clinical picture:*
 1. *Symmetric small joint* arthritis: Mainly metacarpophalangeal (MCP) and proximal interphalangeal (PIP), *never the distal ones*
 2. *Morning stiffness* for at least 1 hour, which gets better toward the end of the day (osteoarthritis gets worse with exercise, not better)
 3. Systemic: Serositis, fever, pulmonary rheumatoid nodules
- *Diagnostic criteria (at least four criteria for at least 6 weeks):*
 1. Morning stiffness for at least 1 hour
 2. Symmetrical involvement of arthritis
 3. Arthritis of three or more joints
 4. Arthritis of the hand joints
 5. Positive rheumatoid factor
 6. Rheumatoid nodules
 7. X-ray changes, e.g., erosions, loss of joint space
- *Complications:*
 1. Joint deformities: *Ulnar deviation* and *swan neck deformity* (Fig. 10.36)
 2. Joint subluxation: Most dangerous is *atlantoaxial joint*. On the USMLE, when you get a patient with RA who has any neurologic issue in his neck or upper extremities, think of this.



FIG. 10.36 Swan-neck deformity

- *Diagnosis:*
 1. Positive rheumatoid factor: It is an *IgM* directed against serum *IgG*.
 2. Positive *antinuclear antibody (ANA)* and anti-cyclic citrullinated peptide antibody (Anti-CCP)
 3. Low *synovial complement* with normal serum complement levels
- *Treatment:* See Chapter 9, Pharmacology
- *Notes:*
 1. Psoriatic arthritis occurs in patients with psoriasis; is characterized by *distal interphalangeal joint (DIP) involvement* (sausage digits) and *pencil in cup appearance* on hand x-rays
 2. Sjögren's syndrome is a subtype of RA in which patients have arthritis, plus *dry secretions*, i.e., dry eyes, dry mouth. Diagnosis: *Anti-Ro (anti-SSA)*, *anti-La (anti-SSB)*, and *antisalivary duct antibodies*.
 3. Juvenile rheumatoid arthritis occurs in children and is associated with fever, rash, iritis, pericarditis, and negative rheumatoid factor.
 4. Felty's syndrome: RA and hypersplenism due to lymphocyte infiltration. Suspect it on the USMLE when you see a patient with RA and pancytopenia.

Osteoarthritis

- *Mechanism:* *Wear and tear*
- *Clinical picture:*
 1. Morning stiffness: Lasts *less than 30 minutes*
 2. Arthritis gets *worse after* exercise and toward the end of the day.
 3. The DIPs *are commonly involved*.
 4. Deformities: Proximal interphalangeal joints can swell up and form *Bouchard's nodes*, while the DIP can form *Heberden's nodes (genetically mediated)*.
- *Diagnosis:* X-ray shows *subchondral bone formation* and *osteophytes*.
- *Treatment:* Physical therapy, NSAIDs, glucosamine, and chondroitin sulfate

Systemic Lupus Erythematosus (SLE)

- *Mechanism:* It is a systemic connective tissue disease, mainly in females (*F:M = 9:1*). It is more common in females due to alleles existing on *class II major histocompatibility complex (MHC)*
- *Clinical picture*
 1. Photosensitivity and rash: Could be discoid or the famous *butterfly malar rash* (Fig. 10.37)
 2. Painless oral ulcers



FIG. 10.37 Butterfly rash of systemic lupus erythematosus (SLE)

3. -itis: Serositis, arthritis, and *wire loop glomerulonephritis due to immune complex deposition*
 4. *Anemia, lymphopenia, and thrombocytopenia (RA does not cause that!)*
- **Complications:**
 1. Libman-Sacks endocarditis: Where vegetations *do not embolize*
 2. Lupus nephritis: It has five types; the most aggressive is type IV (diffuse proliferative GN). Treatment: Steroids and cyclophosphamide
 - **Diagnosis:**
 1. Positive ANA, *anti-double-stranded DNA (ds-DNA)* and *anti-Smith antibodies*
 2. Low serum complement factors, *C3* and *C4*
 3. *False-positive workup for syphilis*, e.g., Venereal Disease Research Laboratory (VDRL) and rapid plasma reagent (RPR)
 - **Notes:**
 1. Markers of SLE activity: *Elevated ESR and CRP*, and *low C3 and C4*
 2. Most common cardiac manifestation of SLE is *pericarditis*.
 3. Most specific ocular manifestation of SLE is *retinal cytoid bodies*.
 4. Drugs (e.g., INH, hydralazine, and procainamide) can cause a *lupus-like syndrome*, which is diagnosed by *positive antihistone antibodies*.
 5. Neonatal lupus can cause *heart block* and is diagnosed by positive *anti-Ro* antibodies. Keep your eyes open on the USMLE for a neonate with heart block whose mother has been having a weird rash and joint pains.

6. Kidney biopsy for lupus nephritis shows *C3* and *fibrinogen* deposits.

- **Treatment:** NSAIDs and steroids

Ankylosing Spondylitis

- **Mechanism:** An inflammatory arthropathy that is linked to *HLA-B27*, usually following a prostate infection, especially with *Klebsiella*.
- **Clinical picture:** *Sacroiliitis*, *uveitis*, and *pulmonary fibrosis*
- **X-ray of the back:** *Bamboo spine*
- If you hear a murmur in this patient, it is most likely a diastolic murmur of *aortic regurgitation*.
- **Treatment:** Similar to RA

Polyarteritis Nodosa (PAN)

- **Mechanism:** *Necrotizing vasculitis* affecting *medium-sized vessels*, causing *fibrinoid necrosis* and *tiny aneurysms* formation
- **Causes:** Multiple, most common being *hepatitis B infection*
- **Clinical picture:**
 1. Skin: Purpura and skin ulcers
 2. Joints: Arthralgias and arthritis
 3. Renal: Renal hypertension due to involvement of *arcuate artery*, and *crescentic necrotizing glomerulonephritis*
 4. CVS: Coronary artery disease (CAD)
 5. CNS: Cerebrovascular accidents (CVAs)
- **Diagnosis:** Kidney biopsy and positive perinuclear antineutrophil cytoplasmic antibodies (p-ANCA)
- **Treatment:** *Steroids*
- **Notes:**
 1. Suspect PAN if you see a *young patient* on the USMLE with *hepatitis B* and multiple elderly diseases (CAD, CVA, renal failure).
 2. Churg-Strauss vasculitis is another necrotizing vasculitis characterized by asthma, allergic rhinitis, and eosinophilia

Reiter's Syndrome

- **Mechanism:** A rheumatologic disease that follows *nongonococcal infections*
- **Clinical picture:** *Uveitis*, *circinate balanitis*, and large joint *arthritis*
- **Diagnosis:** Elevated ESR, negative rheumatoid factor, and positive HLA-B27

- *Notes:*
 1. These patients might also have an *aortic regurgitation murmur* and *lung fibrosis*.
 2. Reactive arthritis: Common after infection with *Salmonella*, *Shigella*, *Campylobacter*, gonococci, and *Chlamydia*. It affects large joints, is *migrating (fleeting)* in nature, and is associated with tenosynovitis, e.g., DeQuervain tenosynovitis.

Temporal Arteritis (Giant Cell Arteritis)

- *Mechanism:* A *giant cell vasculitis* that mainly affects the elderly
- *Clinical picture*
 1. *Temporal headache* with a *palpable pulseless* temporal artery
 2. *Jaw claudications*, especially upon eating
- *Complications:* *Blindness* due to *ischemic optic neuropathy* secondary to the involvement of posterior ciliary branches of ophthalmic artery
- *Diagnosis:* *Elevated ESR (>40)*. *Temporal artery biopsy* showing infiltration with *plasma cells* and *giant macrophages*.
- *Treatment:* *High-dose systemic steroids* are the first step (even before biopsy).

Wegener's Granulomatosis

- *Mechanism:* *Focal necrotizing vasculitis* and *granuloma* formation
- *Clinical picture:*
 1. Upper airway involvement, e.g., sinusitis, epistaxis, and saddle nose
 2. Lower airway involvement, e.g., cough, hemoptysis, and lung cavitations
 3. Renal involvement, e.g., proteinuria and hematuria
- *Diagnosis:* Positive cytoplasmic-staining antineutrophil cytoplasmic antibodies (*c-ANCA*s)
- *Treatment:* Steroids and cyclophosphamide
- *Note:* *Goodpasture's syndrome* is a *type II hypersensitivity disease* that involves *antiglomerular basement membrane antibodies* causing *HH: Hematuria and Hemoptysis*.

Takayasu Disease

- *Mechanism:* Vasculitis affecting the big vessels, e.g., aorta and its major branches
- *Clinical picture:* *Decreased pulse on one extremity* plus claudications

- *Diagnosis:* Angiography
- *Treatment:* Steroids
- *Note:* Do not confuse this with Kawasaki disease, where patients have mucocutaneous lesions, cervical lymphadenopathy, and aneurysms of the coronary arteries. Treatment here is aspirin and immunoglobulin therapy.

Behcet Syndrome

- It is a disease of unknown etiology.
- *Clinical picture:* Recurrent iritis, recurrent painful oral ulcers, and recurrent painful genital ulcers
- *Treatment:* Steroids

Dermatomyositis

- *Mechanism:* Immune-mediated infiltration of the connective tissue with inflammatory cells
- *Clinical picture:*
 1. Dermato-: *Heliotrope eyelids* (purple rash) and *Gottron papules* over MCP and PIP joints. *Gottron papules* are the most specific sign of dermatomyositis.
 2. -myositis: Proximal bilateral symmetrical muscle weakness and tenderness
 3. Others: Arthralgia, cardiomyopathy, and *malignancy* If you see a patient on the USMLE with muscle pains, the rash described above, and any kind of cancer, think of dermatomyositis.
- *Diagnosis:* Elevated CPK, electromyogram (EMG), and muscle biopsy are diagnostic.
- *Treatment:* Steroids, *plus careful malignancy screening*
- *Notes:*
 1. Polymyositis could exist alone and is diagnosed by high *anti-Jo-1 antibodies*.
 2. Dermatomyositis is well known to be highly associated with malignancy, so when you see any patient with this disease, *you must screen him/her for malignancy*.

Gout and Pseudogout

- Normally, two thirds of the uric acid is excreted by the kidneys and one third by the GI tract.
- Hypouricemia can occur in pregnancy and in patients with Fanconi's syndrome, i.e., glucosuria, aminoaciduria, and uricosuria.

Gout

- **Mechanism:** Deposition of *monosodium urate* crystals. This could be idiopathic or secondary, e.g., Lesch-Nyhan syndrome (hypoxanthine-guanine phosphoribosyltransferase [HGPRT] deficiency) or renal failure.
- **Clinical picture:**
 1. Arthritis is *asymmetric*, painful, warm joints. The first metatarsophalangeal joint is a classic site, also called *podagra*.
 2. Chronic cases are associated with formation of tophi and renal failure.
- **Diagnosis:**
 1. Joint aspiration shows *needle-shaped, strongly negative birefringent crystals*.
 2. Serum uric acid more than 7 mg%. *Joint aspiration remains the test of choice*.
- **Prevention:** Low purine diet and avoidance of alcohol
- **Treatment:** See Chapter 9, Pharmacology

Pseudogout

- **Mechanism:** Deposition of *calcium pyrophosphate* crystals
- **Clinical picture:** Same as for gout
- **Diagnosis:** Joint aspiration. Crystals are *rhomboid-shaped with weakly positive birefringence*
- **Treatment:** NSAIDs

Scleroderma

- **Limited:** CREST: Calcinosis of the skin, Raynaud's phenomenon, Esophageal diverticulae and dysmotility, Sclerodactyly, and Telangiectasia.
- **Diffuse:** Involves all systems
- **Diagnosis:** Positive *anti-Scl 70* and *anticentromere antibodies*
- **Treatment:** Supportive
- **Notes:**
 1. *Suspect it on the USMLE when you see a patient with shiny tight skin and bad uncontrollable GERD and dysphagia.*
 2. Scleroderma renal crisis: If you see a patient on the USMLE with scleroderma and renal failure, *ACEI* is the treatment of choice.

Polymyalgia Rheumatica

- **Mechanism:** Giant cell vasculitis

- **Clinical picture:** A disease of the elderly, who present with early morning pain and stiffness of shoulders and hips
- **Diagnosis:** Elevated ESR (>40 mm/hr)
- **Treatment:** Steroids

Sarcoidosis

- **Mechanism:** A disease of noncaseating granulomas, more common in African-Americans. *Remember that granuloma is a type IV hypersensitivity reaction.*
- **Clinical picture:**
 1. Uveitis, lacrimal and parotid glands swelling
 2. CVS: Cardiomyopathy
 3. CNS: *Bilateral* facial nerve palsy (*Lyme disease also causes that!*)
 4. Lungs: Hilar lymphadenopathy and restrictive lung disease
 5. Metabolic:
 - Hypercalcemia: Due to secretion of activated vitamin D by macrophages
 - Diabetes insipidus: Due to posterior pituitary dysfunction
- **Diagnosis:**
 1. High serum angiotensin-converting enzyme (*ACE*) level
 2. Transbronchial biopsy showing noncaseating granuloma is diagnostic; microscopy shows *Schumann* and *asteroid* bodies
- **Treatment:** Self-resolving; however, severe and non-resolving cases are treated with systemic *steroids*.
- **Notes:**
 1. In sarcoidosis, there is *low albumin* and *high gamma globulin* levels.
 2. Mucocutaneous forms of sarcoidosis are treated with *chloroquine*.

Fibromyalgia

- It is a syndrome of unclear etiology.
- **Clinical picture:** Pain and tenderness in at least 11 of the following 18 points (the following nine are *all bilateral*):
 1. Occiput: At insertion site of suboccipital muscles
 2. Lower neck: At the level of C7
 3. Trapezius muscle: At the center of superior border of the muscle
 4. Supraspinatus muscle: On the midscapular region
 5. Second rib: At the costochondral junction

6. Lateral epicondyle: Just distal to it
 7. Upper outer quadrants of the buttocks
 8. Greater trochanters
 9. Knees: On the medial aspect just proximal to the joint
- *Treatment:* Tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitor (SSRI). Currently, drug of choice is Duloxetine

Breast and Genitalia

Breast Cancer

- *Location:* Most common in the *upper outer quadrant*
- *Risk factors:* Age, early menarche, late menopause, and positive family history
- *Types:*
 1. Ductal carcinoma: The most common type is the *infiltrating adenocarcinoma*
 2. Medullary carcinoma: *Soft and vascular* tumor that occurs at young age, and is characterized microscopically by patches of hemorrhage and necrosis
 3. Colloid carcinoma: Cystic tumor with *honeycomb appearance* and *signet ring cells*
 4. Lobular carcinoma: Arises from the *terminal lobular ducts*, and is notorious for being *bilateral*
 5. Paget's disease: It is a slow-growing tumor characterized by epidermal hyperplasia, multinucleated vacuolated Paget cells, and round cell infiltration of the dermis. Paget's disease might be confused with eczema of the nipple and areola; however, Paget's disease, unlike eczema, is *unilateral, well defined, and not itchy*.
 6. Mastitis carcinomatosis: Aggressive cancer with bad prognosis, common during pregnancy and lactation. It might be confused with lactational mastitis; however, mastitis carcinomatosis, unlike lactational mastitis, affects *more than just one quadrant of the breast, is associated with painless lymphadenopathy, and does not respond to antibiotics*.
- *Metastases:*
 1. Direct: To breast tissue and skin
 2. Blood and transperitoneal e.g., *Krukenberg tumor of the ovaries (now thought to occur via retrograde lymphatic permeation)*
 3. Lymphatic: Subareolar plexus and deep pectoral plexus, which both drain to axillary and supraclavicular lymph nodes. Note that medial quadrants' lymphatics cross to the opposite breast. Also the lower quadrants can send metastases to umbilicus (*Sister Joseph nodule*).
- *Clinical picture:*
 1. Hard irregular breast mass with ill-defined edge, and lymphadenopathy
 2. Dimpling and puckering: Due to *contraction of ligaments of Cooper*
 3. Nipple retraction or inversion
 4. Peau d'orange: Edema of the breast skin with pitting at the sites of hair follicles and sweat glands, which looks like an orange
- *Prevention:*
 1. Annual breast exam by a physician starting at the age of 20
 2. Monthly breast self-exam by the patient starting at the age of 20 (*controversial*)
 3. Annual mammogram starting at the age of 40
- *Diagnosis:* Gold standard is *biopsy*. Mammogram shows *irregular ill-defined microcalcifications* are suggestive of malignancy, and vice versa.
- *Treatment:* Surgery, radiotherapy, chemotherapy, and hormonal therapy
- *Notes:*
 1. Most important risk factor in breast cancer is *age*
 2. Most important prognostic factor in breast cancer is *the tumor size* and *lymph node involvement*
 3. One of the common complications of mastectomy is injury of the *long thoracic nerve*, which supplies the *serratus anterior muscle*, and *winging of the scapula is the resulting deformity*.
 4. Surgeries of the breast: Make sure you know levels of axillary lymph nodes:
 - Level 1: *On the lateral border* of pectoralis minor
 - Level 2: *Underneath* the pectoralis minor muscle
 - Level 3: *Medial to* the pectoralis minor muscle

Fibrocystic Disease (Fibroadenosis)

- *Definition:* Changes in the breast that occur due to *evolution and involution*
- *Pathology:* A combination of *fibrotic and cystic* changes. Straw-colored fluid is contained within the cysts.
- *Clinical picture:*
 1. Breast pain and tenderness, *more pronounced around menstruation dates*
 2. Breast *nodules* and nipple discharge, *more pronounced around menstruation*
 3. *Nodular breast diffusely* on palpation

- **Diagnosis:** Excisional biopsy is the gold standard
- **Complication:** Breast cancer
- **Treatment:** Supportive except for large lesions, e.g., cysts or lumps, which can be excised
- **Notes:**
 1. Do not confuse this with *fibroadenoma*. **Clinical picture:** Young nulliparous female with firm smooth mobile breast mass. **Complications:** Increase in size, malignancy, and myxomatous degeneration. **Treatment:** Inoculation. If large in size, simple mastectomy can be done.
 2. Intraductal papilloma: Most common cause of bloody nipple discharge

Genital Infections

- As a rule, know that the normal vaginal pH is 3.5 to 4.5, which is achieved by vaginal flora, namely the *lactobacilli*.
- All the infections discussed here can cause vulvovaginitis, i.e., painful, red and itchy female genitalia.
- **Fact:** Most common sexually transmitted disease (STD) is *Chlamydia*, while the most common genital infection is candidiasis. Always make sure that the patient's sexual partners are treated.

Pelvic Inflammatory Disease (PID)

- Ascending genital infection that may include endometritis, salpingitis, hydrosalpinx, or tubo-ovarian abscesses
- **Organism:** Most commonly caused by *Chlamydia trachomatis* chlamydia D and K serotypes and *Neisseria gonorrhoea*. Any organism mentioned in this chapter may cause PID.
- **Clinical picture:**
 1. Lower abdominal and bilateral groin pain
 2. Purulent vaginal discharge
 3. Systemic symptoms: Fever, nausea, and vomiting
- **On exam:**
 1. Lower abdominal and bilateral inguinal tenderness.
 2. Pelvic exam: Cervical motion tenderness (*chandelier sign*)
- **Treatment:** Ceftriaxone or cefoxitin plus doxycycline for 2 to 3 weeks
- **Indications for hospitalization:** Pregnancy, pelvic abscess, or failure of outpatient therapy
- **Note:** Barrier contraception and oral contraceptive pills (OCPs) decrease the risk of acquiring PID.

Haemophilus ducreyi

- **Clinical picture:** Chancroid; a painful genital ulcer with an irregular shape, associated with painful lymphadenopathy
- **Diagnosis:** Gram-negative bacilli arranged in a school-of-fish pattern
- **Treatment:** Ceftriaxone
- **Note:** Chancre and lymphadenopathy in syphilis are painless.

Human Papillomavirus (HPV)

- **Clinical picture:** Lesion starts as a flat wart that later progress to a verrucous cauliflower-like lesion (*condyloma acuminatum*).
- **On exam:** Cobblestoning of the vaginal mucosa
- **Diagnosis:** Vacuolated cells with perinuclear halos known as *koilocytes*
- **Prevention:** Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine (GAR-DASIL). Currently approved for females between 9 and 26 years of age.
- **Treatment:** Cauterization of the lesions

Polycystic Ovarian Syndrome (PCOS)

- Also known as *Stein-Leventhal syndrome*
- **Mechanism:** High LH levels cause increased androgen and estrogen formation, which in turn leads to feedback inhibition of FSH. This leads to arrest of follicular development in various stages, plus the following:
 1. High androgens: Hirsutism and acne
 2. High estrogen: Endometrial and myometrial hyperplasia
- **Clinical picture:**
 1. Anovulation and infertility: Patient complains of long periods of amenorrhea interrupted by periods of prolonged bleeding
 2. Hirsutism and acne
- **Diagnosis:**
 1. Serum LH:FSH ratio >3:1
 2. Elevated serum androgen and estrogen levels, with low or no progesterone
 3. Laparoscopy: Pearly white ovaries with thick smooth capsules
 4. Ultrasound: Small ovarian subcortical cysts giving necklace appearance
- **Treatment:**
 1. If the patient desires pregnancy: Induce ovulation by *clomiphene citrate*.

2. If the patient does not desire pregnancy:
 - Progesterone supplementation
 - For hirsutism: Estrogen plus antiandrogen, e.g., cyproterone acetate
3. Resistant cases: Bilateral wedge resection of ovaries

Endometriosis

- It is the presence of *endometrial tissue outside the uterus*.
- *Locations:*
 1. Ovaries: Most common site. Forms *chocolate cysts*.
 2. Myometrium: Either diffuse (*adenomyosis*) or localized (*adenomyoma*)
 3. Extrauterine: Could be anywhere in or outside the pelvis. Nodules could be in a closed organ (*endometrioma*).
- *Pathology:* Implants are either *black active* or *gray fibrosed* lesions.
- *Clinical picture:*
 1. Infertility: *Endometriosis is the most common cause of female infertility*.
 2. *Perimenstrual* lower abdominal and back pain
- *Diagnosis:* Ultrasound (US) of the pelvis is suggestive, but diagnosis is confirmed only by visualizing the *powder burn implants* and *chocolate cysts* during *laparoscopy*.
- *Treatment:*
 1. Create a *pseudo-pregnancy* state: Using progesterone.
 2. Create a *pseudo-menopause* state: Using combined antiestrogen and antiprogestosterone
 3. High dose *GnRH* analogue: To downregulate gonadotrophin receptors
 4. *Androgens*, e.g., Danazol: Acts as an antigonadotrophin
 5. *Surgery:* Reserved for resistant complicated cases.

Ovarian Tumors

- *Types:*
 1. *Functional cysts:* Most common cysts during reproductive age; they are benign, and never exceed 6 cm in diameter. Treatment: Observe, as they usually regress spontaneously. *Note:* RLQ or LLQ abdominal pain in a female patient in child-bearing age is suggestive of *corpus luteum cyst*.

2. Epithelial tumors:

- *Serous tumors:* Show *psammoma* bodies. *Note:* *Psammoma bodies* could be seen in *Papillary carcinoma of thyroid, Meningioma, and Serous ovarian cyst (PMS)*.
- *Mucinous tumors:* Rupture into peritoneum causes *pseudomyxoma peritonei*.

3. Sex cord–stromal tumors:

- *Granulosa–theca cell tumors:* *Feminizing* tumors, causing precocious puberty, and irregular uterine bleeding
- *Sertoli–Leydig cell tumors:* *Virilizing* tumors, causing hirsutism, clitoromegaly, and deepening of voice

4. *Germ cell tumors:* Occur mainly in *children and young adults*. They are *highly malignant, except mature teratoma*; however, they are *very sensitive to radiotherapy and chemotherapy*. That leaves germ cell tumors with a better prognosis than epithelial tumors. *Dermoid cyst (mature cystic teratoma):* A thick-walled cyst containing ectodermal, endodermal and mesodermal structures plus a *Rokitansky protuberance*, so *suspect it on the exam in any question describing an ovarian tumor containing hair and teeth*.

5. Others:

- *Krukenberg tumors:* Bilateral in 50% of cases, they metastasize from *stomach cancer* and reach the ovary by retrograde lymphatic spread. Microscopy: *Signet ring cells* in fibrous or myxomatous stroma.
- *Ovarian fibroma:* Solitary or as a part of *Meigs syndrome* (ovarian fibroma [benign], ascites, and right-sided pleural effusion)
- *Clinical picture:* Most common presentation is being asymptomatic. Symptoms are mainly non-specific abdominal symptoms, e.g., Dyspepsia, bloating or pain.
- *Diagnosis:*

1. Gold standard: *Excisional biopsy*.

2. Tumor markers:

- CA-125: Ovarian tumors, *except mucinous cysts*
- Carcinoembryonic antigen (CEA): *Mucinous cyst*
- Human chorionic gonadotropin (HCG) and alpha-fetoprotein: *Germ cell tumors*
- Estrogen and progesterone: *Functioning tumors*

3. Transvaginal ultrasound: Excellent in confirming ovarian tumors. Relies on showing tumors and cysts through their *neovascularization*.
- *Treatment*: Debulking surgery, chemotherapy, and radiotherapy.
 - *Notes*:
 1. *BRCA1* and *BRCA2* gene mutations and *nulliparity* are associated with high risk of *ovarian and breast cancer*.
 2. Most common ovarian tumor in children: *Germ cell tumor*
 3. Most common ovarian tumor in reproductive age: *Functional cyst*
 4. Most common ovarian tumor in menopause: *Epithelial tumor*
 5. Benign ovarian swellings: Unilateral, cystic, mobile, and painless
 6. Malignant ovarian swellings: Bilateral, solid, fixed, and painful
 7. Decreased ovulation, e.g., OCPs use, *decreases* risk of ovarian cancer
 8. *Peutz-Jeghers syndrome*: A triad of ovarian cancer, familial adenomatous polyposis (FAP), and circumoral/circumanal pigmentation

Leiomyoma (Fibroids)

- A *benign* tumor arising from the uterine *myometrium*
- It is an *estrogen-dependent* tumor, so it is more common in *child-bearing age* and *rare before puberty or after menopause*.
- Fibroids may *grow quickly during pregnancy* and in patients on OCPs, due to *high estrogen levels*.
- *Race*: Fibroids are more common in *African-Americans*.
- *Pathology*: Tumor consists mainly of *smooth muscles* and *fibroblasts*.
- *Clinical picture*:
 1. *The most common presentation is being asymptomatic*.
 2. *Prolonged painful heavy periods are one of the hallmarks of fibroids*. So when you see an African-American female in child-bearing age on the USMLE with very painful heavy periods that last days long, you know what to think!
 3. Pressure symptoms, mainly in cervical fibroids, e.g., urinary frequency, dysuria, dyschezia, and dyspareunia
- *Diagnosis*: *Ultrasound* of the uterus/pelvis
- *Complications*:

1. Degeneration:

- Most dangerous is *red degeneration*, a hemorrhagic necrosis secondary to acute infarction. *Clinical picture*: *Severe abdominal pain, fever, and vomiting*. *Treatment*: Rest, analgesics, and antipyretics.
- A uterus containing fibroids receives a huge blood supply due to *release of angiogenic factors*; however, the fibroid itself is usually pale and susceptible to degeneration as follows:
 1. *Central part*: *Hyaline* and *cystic degeneration*
 2. *Peripheral parts*: *Fatty degeneration* and *calcification*
- 2. Sarcomatous change: The incidence is low, approximately *0.5%*; however, the coincidence of endometrial cancer is around *2%* (*both are estrogen-dependent tumors*). Sarcomatous change is confirmed microscopically by presence of *more than 10 mitotic figures* per high power field (normal *<5*).
- 3. Torsion and inflammation: Severe abdominal pain, nausea, and vomiting
- *Treatment*:
 1. Supportive: Indicated in mild cases, pregnant, or near-menopause patients
 2. Surgical: Indicated only in severe cases:
 - *Polypectomy and dilation and curettage (D&C)*: For submucous fibroids
 - *Myomectomy*: A very bloody operation even after ligating the uterine vessels (*at the base of the round ligament*) and ovarian vessels (*in the infundibulopelvic ligament*)
 - *Hysterectomy*: Most common and successful surgery for leiomyoma removal

Endometrial Cancer

- *It is the most common malignancy of the female genital tract*.
- *Predisposing factors*: *Old age, postmenopausal, low parity, obesity, DM, and hypertension*
- *Pathology*: It is mainly an *adenocarcinoma*.
- *Clinical picture*:
 1. The key symptom is *postmenopausal bleeding*. So when you see a postmenopausal patient on the USMLE with uterine bleeding, she mostly has endometrial cancer until proven otherwise.
 2. Intermittent lower abdominal colicky pain at night (*Simpson pain*)

- **Metastases:**
 1. Direct: To surroundings; the *most common metastases of endometrial cancer*
 2. Blood: Lung, liver, bone, brain, kidneys, and suprarenal glands
 3. Lymphatic: *Paraaortic lymph nodes*
- **Diagnosis:** *Endometrial biopsy or fractional curettage*: The best next step in any postmenopausal patient with uterine bleeding.
- **Treatment:** Surgery, radiation, chemotherapy, and hormonal therapy
- **Notes:**
 1. Most common cause of death in endometrial cancer patients is *metastases*
 2. Most common complication of radical hysterectomy: *Denervation of the urinary bladder, leading to residual urine*

Cervical Cancer

- It is mostly *ectocervical*, and is of type *squamous cell*.
- **Predisposing factors:** *HPV infection* (strains 16, 18, 33, 45, and 56), *early sexual intercourse*, multiple sexual partners, and *multiparity*
- **Clinical picture:**
 1. The key symptom is *contact bleeding*, e.g., cervical bleeding after intercourse.
 2. Pain, discharge, and metastatic symptoms
- **Metastases:**
 1. Direct: Surrounding structures
 2. Blood: Lung, liver, bone, brain, kidney and suprarenal glands
 3. Lymphatic: Paracervical, iliac, and paraaortic lymph node
- **Diagnosis:**
 1. If lesion is grossly visible: *Excisional biopsy*
 2. If no visible lesion: Cytology (Pap smear), followed by colposcopy and biopsy
- **Prevention:**
 1. *Annual Pap smears starting the onset of sexual intercourse until three successive normal smears, then perform the Pap smear every 3 years*
 2. GARDASIL: HPV vaccine. Note that even in immunized patients, Pap smear recommendations should still be followed.
- **Treatment:** Surgery, radiation, and chemotherapy, depending on stage
- **Notes:** Most common cause of death in cervical cancer patients is *uremia*.

Ectopic Pregnancy

- It is any pregnancy that implants outside the uterine cavity.
- **Most common site:** *Ampulla* of the fallopian tube
- **Risk factors:** STDs (*PID is the most common cause*), tubal surgery, and some contraceptives, e.g., *progesterone pills and intrauterine devices (IUDs)*
- **Pathology:** During ectopic pregnancy, regardless of the site, the following occurs:
 1. Ovaries: *Corpus luteum* of pregnancy
 2. Uterus: Increases in size and the endometrium thickens, showing
 - *Decidual reaction (without villi)*
 - *Arias-Stella reaction:* Adenomatous hyperplasia
- **Complications:** Tubal rupture causing intraperitoneal hemorrhage or pelvic hematocele
- **Clinical picture:**
 1. Amenorrhea: Due to hormones secreted from corpus luteum. *Rarely exceeds 8 weeks in duration.*
 2. Severe lower unilateral abdominal pain: If radiates to shoulders, think of perforation and diaphragmatic irritation by intraperitoneal blood.
 3. Vaginal bleeding: Mild in amount, and rarely *decidual casts* too
 4. Pressure symptoms (dysuria, dyschezia, dyspareunia): Suspect pelvic hematocele.
- **On exam:**
 1. Cervical motion tenderness (*jumping sign*).
 2. Tender boggy swelling in cul-de-sac in cases of pelvic hematocele
- **Diagnosis:**
 1. Positive pregnancy test (urine or serum B-HCG)
 2. Absence of intrauterine pregnancy by ultrasound
- **Treatment:**
 1. *Resuscitation* is the best next step.
 2. If ectopic mass <3.5 cm and *stable*: Abortifacient medications could be used in these cases, e.g., methotrexate, prostaglandins, or mifepristone (RU-486; antiprogesterone)
 3. If ectopic mass >3.5 cm or *unstable* (e.g., *rupture or bleeding*):
 - Laparotomy or laparoscopy: Evacuation of fetal sac and membranes
 - Salpingectomy (total or partial): If the fallopian tube is ruptured

- *Note: Any female in reproductive age who presents with abdominal pain must have a pregnancy test to rule out ectopic pregnancy, even if she insists that she is not pregnant.*

Abortion

- **Definition:** It is the termination of pregnancy *before 20 weeks' gestation*.
- **Causes:**
 1. Fetal: Chromosomal or placental abnormalities. *It is the most common cause of first trimester abortions.*
 2. Maternal: General (e.g., infections/hormonal), or structural (e.g., patulous os or hypoplastic uterus)
- **Clinical picture:** Amenorrhea, followed by abdominal pain and vaginal bleeding *before 20 weeks of gestation*.
- **Types of abortion:**
 1. **Threatened abortion:** Slight hemorrhage into the *choriodecidual space*. Stops spontaneously in most cases. Pelvic exam: *Closed cervix*. Next best step: *B-HCG measurement and monitoring* (should double every 2 days. If no doubling, consider *missed abortion*). Treatment: Bed rest.
 2. **Inevitable abortion:** The fundal level corresponds to the period of amenorrhea (correct height), but the pelvic exam reveals an *open cervix*, and products of conception protruding through the os. Treatment: Resuscitation and uterine evacuation.
 3. **Incomplete abortion:** Presents in the same manner as an inevitable abortion; however, in the latter case, the uterus already expelled some of its contents, so the fundal height will be less than period of amenorrhea. In complete abortion, the uterus already expelled all products of conception.
 4. **Septic abortion:** Caused by *group B Streptococcus*, but also consider anaerobes or *Staphylococcus*. **Clinical picture:** Abortion plus fever, lower abdominal pain, and malodorous vaginal discharge. Treatment: Resuscitation, uterine evacuation, and broad-spectrum antibiotics, e.g., penicillin (gram positive) plus aminoglycoside (gram negative) plus metronidazole or clindamycin (anaerobes).
 5. **Missed abortion:** It is retained products of conception which are no longer viable, also called *fleshy mole* or *bloody mole*. On exam: Fundal level is *lower* than the period of amenorrhea, cervix is *closed*, while the vagina contains *small*

amount of dark blood. Complications: Septic abortion, and DIC (common after 3 to 4 weeks). **Diagnosis:** Elevated B-HCG, *but it does not double every 2 days*. **Treatment:** Uterine evacuation.

- **Notes:**

1. Most common fetal genetic disease to cause abortion: *Trisomy 16*.
2. Most common infection to cause abortion in early pregnancy: *Mycoplasma hominis*.

Placenta Previa

- **Definition:** A placenta that is situated in the lower uterine segment
- **Clinical picture:** *Bright red vaginal bleeding* after the time of fetal viability (20 weeks) but before full maturation of the fetus (37 weeks). Bleeding is usually related to sexual intercourse or pelvic exam. It is *painless*, recurrent, and stops spontaneously. This is a pathognomonic presentation.
- **On exam:**
 1. Fundal level and uterine external palpation are normal.
 2. *Pelvic examination is absolutely contraindicated (fatal bleeding)*.
- **Diagnosis:** Transabdominal (*not transvaginal*) ultrasound
- **Treatment:**
 1. *Resuscitation is the best next step*.
 2. Bed rest and sexual abstinence
 3. US follow-up: The unequal rate of growth of the upper and lower uterine segments can cause the placenta to migrate upward throughout pregnancy.
- **Indications for immediate termination:** Uncontrolled bleeding or fetal distress

Abruptio Placenta

- **Mechanism:** It is separation of a normally situated placenta.
- **Risk factors:** *Hypertension* and *cocaine abuse*. So when you see a pregnant patient on the USMLE who just had cocaine and is now presenting with sudden abdominal pain, you know what to think!
- **Clinical picture:** *Scanty dark and painful vaginal bleeding* (20 to 37 weeks' gestation) (*it is bright red and painless in placenta previa*).
- **On exam:** *Board-like abdominal rigidity*, and pelvic exam is still contraindicated.

- **Complications:**
 1. Fetal death
 2. Hemorrhagic shock
 3. *Couvelaire uterus*: Blood dissects its way through uterus to the peritoneum
 4. DIC and renal failure
 5. Postpartum hemorrhage: Might lead to Sheehan's syndrome (hypopituitarism)
- **Diagnosis:** Transabdominal (*not transvaginal*) ultrasound
- **Treatment:** Immediate termination by C-section.

Hydatidiform Mole (Vesicular) Mole

- **Definition:** It is a *trophoblastic disease* characterized by benign hyperplasia of trophoblast, along with hydropic degeneration of chorionic villi.
- **Risk factors:** Ages >40 or <15, and vitamin A deficiency
- **Pathology:**
 1. Uterus: Studded with *fluid-filled vesicles* up to 1 cm in diameter
 2. Ovaries: *Theca-lutein cysts* (due to HCG production by trophoblast)
- **Clinical picture:**
 1. Amenorrhea and symptoms of pregnancy
 2. Uterine bleeding, which might contain *vesicles*: Mainly in *first* trimester
- **On exam:** *Large doughy uterus* with absent fetal heart sounds
- **Complications:** *Choriocarcinoma*: Malignant transformation
- **Diagnosis:**
 1. *B-HCG* will be positive even in the highest dilutions.
 2. US of uterus: *Snowstorm* appearance
 3. Doppler: Absent fetal heart sounds
- **Treatment:** Suction followed by D&C in 2 weeks (*cluster of grapes inside uterus*)
- **Follow-up:**
 1. Monitoring the HCG levels *weekly for the first 12 weeks* after evacuation (12 weeks is the time HCG needs to fall back to normal values), and *then monthly for 12 months*, to make sure that level of HCG does not rise.
 2. If HCG level does not normalize or starts rising, this suggests choriocarcinoma.
- **Note:** During the follow-up period, *pregnancy is contraindicated*, as that will raise the HCG level and make the follow up difficult.

Preeclampsia

- **Definition:** Pregnancy-related *Edema*, *Proteinuria*, and *Hypertension* (EPH)
- **Pathology:** Vasospasm and *subintimal edema*
- **Cause:** Unknown, but most likely due to *prostaglandin imbalance causing endothelial damage*
- **Risk factors:** *Nulliparity*, extremes of age, and obese patients
- **Timing:** It is a disease of the *second half of pregnancy* (*20 to 40 weeks*). The only conditions in which you suspect this disease in the first half of pregnancy are:
 1. Hydatidiform mole
 2. Diabetes mellitus
 3. Twin pregnancy
 4. Polyhydramnios
- **Clinical picture and exam findings:**
 1. Diffuse body edema
 2. Elevated blood pressure: More than 140/90 mm Hg on *more than two occasions*
- **Diagnosis:** Clinical diagnosis, plus elevated urinary protein levels
- **Complications:**
 1. Eclampsia: *Seizures* associated with a high rate of organ failure and mortality. **Treatment:** Magnesium sulfate IV and immediate stabilization of the mother with subsequent delivery (Mg sulfate is continued for 24 hours postpartum). **Signs of magnesium toxicity:** Loss of deep tendon reflexes (*first sign*), and respiratory depression. **Antidote for magnesium:** Calcium gluconate IV.
 2. Placenta: Abruption placenta
 3. Cerebral edema or hemorrhage: Headache, blurry vision, nausea, and vomiting
 4. Periportal hepatic necrosis: Jaundice, and elevated bilirubin and transaminases
 5. Hepatic subcapsular hemorrhage: *Epigastric pain*
 6. Renal failure: Oliguria (<500 cc urine output/day), or anuria (<100 cc)
 7. Congestive heart failure and pulmonary edema: Dyspnea, orthopnea, and (paroxysmal nocturnal dyspnea (PND))
 8. HELLP syndrome: Microangiopathic hemolysis (H), elevated liver enzymes (EL), and low platelets (LP). It carries a very poor prognosis.
- **Treatment of preeclampsia:**
 1. Mild cases:
 - Control of blood pressure: Best is alpha-methyldopa or hydralazine

- Betamethasone for 48 hours: To accelerate fetal lung maturity
 - Once fetal lung maturity is achieved, delivery is induced.
2. Severe cases, or any signs of organ damage (see Complications):
- Immediate termination of pregnancy
 - Prophylactic magnesium sulfate should be given, and continued until 24 hours postpartum
- *Note:* The one and only definitive cure for preeclampsia/eclampsia is *delivery*.

Puerperal Sepsis

- *Definition:* It is infection of the female genital tract after labor.
- *Most common organism:* *Group B hemolytic streptococci*
- *Clinical picture:*
 1. Fever and leukocytosis
 2. Lower abdominal pain and tenderness
 3. Malodorous vaginal discharge. If you see any patient on the USMLE who gave birth very recently, and now having fever and lower abdominal pain, you know what to think! *If puerperal sepsis is ruled out, think pelvic thrombophlebitis.*
- *Diagnosis:* Culture of discharge, blood, and endocervix
- *Treatment:*
 1. Broad-spectrum antibiotics: Penicillin, aminoglycosides, and metronidazole
 2. Evacuation of the uterus

Varicocele

- *Mechanism:* Dilatation of *pampiniform* and *cremasteric* venous plexuses
- *Causes:* High venous pressure mostly due to compression, e.g., pelvic colon compressing the left testicular vein, superior mesenteric vessels compressing left renal vein
- *Clinical picture:* *Dragging pain* in the scrotum, more toward the left side
- *On exam:* *Bag-of-worms* sensation on palpation of scrotal neck. *Gives a thrill* on cough and disappears on scrotal elevation.
- *Complications:*
 1. Infertility: Due to thermal and *chemical effects of glucocorticoids*

2. Thrombosis and hydrocele

- *Treatment:* Varicosectomy
- *Notes:*
 1. Retroperitoneal diseases, e.g., tumor or fibrosis, can compress on testicular veins and present as varicocele.
 2. With unexplained left-sided varicocele, *suspect a renal tumor compressing the left testicular or left renal veins.*

Hydrocele

- *Mechanism:* It is fluid collection in the *processus vaginalis*.
- *Causes:* Patent processus vaginalis, varicocele, or lymphatic obstruction
- *Clinical picture:* *Painless cystic translucent* scrotal swelling, more pronounced on standing up and decreased by lying down and scrotal elevation
- *On exam:* *Positive transillumination test*
- *Complications:* Hematocele, pyocele, or testicular atrophy
- *Treatment:* Eversion or plication of tunica vaginalis
- *Notes:*
 1. Congenital hydrocele: Occurs due to patent processus vaginalis, and the mother will complain of the infant's scrotal swelling getting bigger toward the end of the day
 2. Encysted hydrocele of the cord: Due to nonobliteration of a small segment of processus vaginalis. Presents as small cystic translucent swelling on the cord. It is freely mobile, but its mobility is decreased by pulling down on the testicles.

Testicular Torsion

- It occurs due to the high attachment of the tunica vaginalis around the distal end of the cord, *also called bell-clapper deformity*.
- *Clinical picture:* Sudden severe scrotal pain, especially after trauma or straining, e.g., *heavy weight lifting*
- *On exam:* The testicle is situated *high and horizontally* on the scrotum and *extremely tender to touch*
- *Diagnosis:* Clinical, and *venous duplex* should also be done
- *Complication:* Strangulation and ischemic necrosis of testicle
- *Treatment:* *Manual detorsion and orchiopexy within 6 hours of presentation*
- *Note:* Right testicle torsion is usually *clockwise*, left is *counterclockwise*.

Epididymorchitis

- *Causes:* UTI, STDs, and straining, e.g., heavy weight lifting
- *Clinical picture:* Fever and unilateral pain in the scrotum
- *On exam:* Red, warm, tender and swollen testicle and epididymis
- *Diagnosis:*
 1. CBC: Leukocytosis
 2. Urine analysis and intraurethral swab for STDs
- *Treatment:* Bed rest, scrotal elevation, and antibiotics

Testicular Cancer

- *Types:* See Table 10.8
- *Clinical picture:*
 1. Firm and painless testicular swelling
 2. Loss of testicular sensation
- *Metastases:* Local, blood and lymphatic, mainly *paraaortic lymph nodes*. Seminoma is famous for causing *cannonball metastases* in the lungs.
- *Diagnosis:*
 1. Gold standard is *biopsy*; the trick here is that *needle biopsy is contraindicated in the testes and thyroid gland*, so *open biopsy* is done after an inguinal incision.
 2. Seminoma: Elevated serum human chorionic gonadotrophins (HCG)
 3. Teratoma: Elevated serum *alpha-fetoprotein*
- *Treatment:* Orchiectomy, chemotherapy, and radiation (for seminoma)

Benign Prostatic Hypertrophy (BPH)

- *Mechanism:* A disease of the elderly involving *adenomatous hyperplasia* of the *periurethral zone of the prostate*

- *Pathology:* *Hyperplastic acini* and *corpora amylacea*
- *Clinical picture:* *Nocturia, urinary frequency, hesitancy, and terminal dribbling*
- *Complications:* Urinary retention and hematuria
- *On exam:* Rectal exam reveals smooth painless *uniformly enlarged prostate*.
- *Diagnosis:*
 1. Transrectal ultrasound and biopsy is diagnostic.
 2. IVP: Smooth elevation at the base of urinary bladder
 3. Prostate-specific antigen (PSA) is slightly elevated *but does not exceed 10 ng/ml*
- *Treatment:*
 1. Dihydrotestosterone (DHT) antagonists, e.g., finasteride; a *5-alpha-reductase inhibitor*; prevents conversion of testosterone to DHT
 2. Surgery, i.e., transurethral resection of prostate (*TURP*) is reserved for severe resistant cases with complications.

Prostate Cancer

- *The most common cancer in males.*
- *Location:* *Posterior lobes of prostate*, which are rarely involved in benign prostatic hyperplasia (BPH)
- *Most common metastases:* *Spine*, mostly *osteoblastic lesions*
- *Clinical picture:* Similar to BPH, with *back pain and weight loss*
- *Diagnosis:*
 1. Transrectal ultrasound and prostate biopsy are diagnostic.
 2. IVP: Irregular elevation at the base of the urinary bladder
 3. PSA elevated more than 10 ng/ml
- *Prevention:* Screen by annual rectal exam and PSA starting at age 50
- *Treatment:*

TABLE 10.8 Types of testicular cancer.

	Seminoma	Teratoma	Leydig cell tumor	Sertoli cell tumor
Origin	Mediastinum testis; namely the seminiferous tubules	Totipotent cells of the rete testis	Leydig cells	Sertoli cells
Histopathology	Round cells with acidophilic nucleus and clear cytoplasm	Yellow colored cystic tumor engulfed by tunica albuginea	Polyhedral cells with hyaline bodies and cytoplasmic crystalloids of Reinke	Columnar cells with cleft nuclei
Clinical picture	See general clinical picture of testicular cancer; see above	See general clinical picture	See general clinical picture and virilization	See general clinical picture and feminization

1. Hormonal through blocking androgen:
 - Peripherally: Using cyproterone or flutamide
 - Centrally: Using *continuous* GnRH stimulation (secretion is normally pulsatile rather than continuous)
2. Surgery: TURP

Miscellaneous

Tumor Markers

- *Carcinoembryonic antigen (CEA)*: Colorectal cancer
- *CA 19-9*: Pancreatic cancer
- *CA 125*: Ovarian cancer
- *Alpha-fetoprotein (AFP)*: Hepatocellular cancer and teratoma
- *Prostate-specific antigen (PSA)*: Prostate cancer
- *Human chorionic gonadotrophin (HCG)*: Choriocarcinoma, vesicular mole, and seminoma
- *S-100*: Melanoma

Metastases

- Most common tumor to send metastases: *Breast cancer*
- Most common organ to receive metastases: *Adrenal medulla*
- Most common source of liver metastases: *Colon cancer*
- Most common sources of metastases to brain: *Breast, lungs, and prostate cancers*
- Most common sources of metastases to bone: *Breast, prostate, thyroid, and kidney cancers*

Carcinoid Syndrome

- It is the most common tumor of the appendix, but can arise from any GI organ. It is a very slow-growing tumor.
- *Clinical picture*:
 1. Diarrhea
 2. Flushing
 3. Bronchospasm
 4. Valvular heart disease: *Tricuspid regurgitation and pulmonary stenosis*
- *Diagnosis*: High levels of 5-hydroxyindoleacetic acid (5-HIAA) in urine
- *Treatment*: Surgical plus chemotherapy, as it can recur and metastasize

Healing and Regeneration

- *Primary intention*: Healing starts with a blood clot at the injury site, followed by neutrophil infiltration, and finally granulation tissue.
- *Secondary intention*: Healing is characterized by the presence of *myofibroblasts*.
- *Third-degree burns*: Heals by *keloid* formation
- *Liver injury*: Heals by regeneration, scar formation, or both
- *Lung injury*: Heals via *type II pneumocytes*
- *CNS injury*: Heals by *gliosis* performed by *astrocytes*
- *Peripheral nervous system injury*: Heals by *axonal regeneration*

Ophthalmology

- *Macular degeneration*: It is the most common cause of blindness in the elderly. Patients present with gradual, painless loss of vision. Treatment: Laser photocoagulation.
- *Central retinal artery (CRA) occlusion*: Patients present with sudden, unilateral, painless blindness. Retinal exam: *Cherry red fovea*. Treatment: Thrombolytics.
- *Central retinal vein (CRV) occlusion*: Presents in the same way as CRA occlusion. Retinal exam: Hemorrhage and exudates. Treatment: Laser photocoagulation.
- *Ischemic optic neuropathy*: Occurs due to involvement of *posterior ciliary artery*. Common in cases of giant cell arteritis.
- *Open-angle glaucoma*: Patients present with gradual loss of peripheral vision with an end result of complete blindness
- *Closed-angle glaucoma*: An *ophthalmologic emergency*. Patients present with sudden, severe eye pain, halos around light, nausea, and vomiting. Urgent treatment: *Topical pilocarpine, topical timolol, and systemic acetazolamide*.

Ear, Nose, and Throat (ENT)

- *Otitis externa*: Usually caused by *Pseudomonas aeruginosa*; patients present with a painful ear and tenderness on movement of the pinna. Treatment: *Antibacterial eardrops*.
- *Otitis media*: Usually caused by *Streptococcus pneumoniae*. Complication: Repeated infections lead to hearing loss. Treatment: *Amoxicillin*.
- *Inner ear infections*: e.g., *viral labyrinthitis, vestibular neuritis*. Patients present with vertigo, nausea, vomiting, and horizontal nystagmus. Treatment:

Meclizine. Vertical nystagmus indicates a central cause, e.g., verteobasilar CVA.

- *Sinusitis*: Usually caused by *S. pneumoniae*; patients present with facial pressure and postnasal drip. On exam: Oropharyngeal cobblestoning and opacification of sinuses on *transillumination*. Treatment: *Amoxicillin*.
- *Nasal meatuses*:
 1. Nasolacrimal duct opens into the *inferior meatus*.
 2. Sphenoid sinus opens into the *sphenoethmoidal recess*.
 3. Posterior ethmoid sinus opens into the *superior meatus*.
 4. All other sinuses open into the *middle meatus*.
- *Meniere's disease*: Due to *endolymphatic hydrops*. Patients present with recurrent episodes of *ear fullness*, *deafness* and *vertigo*. Treatment: Diuretics, e.g., *acetazolamide*.

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Cell Reactions

- *Nucleus*: DNA and RNA synthesis
- *Cytoplasm*: Glycolysis, hexose monophosphate (HMP) shunt, fatty acid synthesis
- *Mitochondria*: Tricarboxylic acid (TCA) cycle, fatty acid oxidation, pyruvate decarboxylation
- *Lysosomes*: Degradation

Receptors

- *Types*:
 1. Intracellular: Thyroid hormone, steroids, and vitamin D
 2. Ligand gated ion channel: Nicotine, gamma-aminobutyric acid (GABA), and glycine

3. Tyrosine kinase linked: Insulin
4. Adenylate cyclase linked: Epinephrine, alpha-2 and beta receptors
5. Phosphatidyl-inositol linked: Alpha-1 receptors and growth hormone

G-Protein Receptors

- *Examples:* Adenylate cyclase and phosphatidyl-inositol linked receptors
- *Mechanism:* The alpha subunit of G proteins activates protein kinase G. Protein kinase G synthesis is stimulated by the short-acting nitric oxide; however, they are always short acting due to the inhibitory effect of guanosine triphosphatase (GTPase).
- *Note:* Nitroglycerin, sodium nitroprusside, interleukin-1, and tumor necrosis factor (TNF) all stimulate nitric oxide synthesis, and accordingly protein kinase G. This leads to inhibition of the endothelial myosin light chain kinase (by phosphorylation); leading to vasodilatation. Note: Nitric oxide synthase converts oxygen to nitric oxide, and it requires calcium for activation in all cells *except macrophages*.

Adenyl Cyclase

- *Mechanism:*
 1. When the ligand binds to its receptor, adenylate cyclase converts adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP).
 2. cAMP converts to 5-AMP by the action of *phosphodiesterase*. Note that phosphodiesterase is inhibited by *methylxanthines*, e.g., coffee and theophylline.

Inositol System

- *Mechanism:* When a substance binds to the phosphatidyl-inositol receptor, phosphatidyl-inositol is hydrolyzed by the action of *phospholipase C* into:
 1. Inositol triphosphate: Stimulates calcium release from the endoplasmic reticulum
 2. Diacylglycerol: It uses the released calcium to stimulate *protein kinase C*, leading to the activation of cellular proteins (by phosphorylation).

Enzymes

- They are substances that regulate chemical reactions. They work best at an optimum temperature and pH. A cofactor can exist to help the enzyme do

its job; it is known as a *coenzyme*. *Holo-enzyme:* Enzyme + coenzyme.

- *Curve:* All enzymes show a *hyperbolic* curve of velocity, *except allosteric enzymes, which show a sigmoidal curve*.
- *Allosteric enzymes:* They have binding sites for effectors that act *immediately* and always *regulate an early step in the reaction*.
- *Modification:* All enzymes undergo *covalent modification*, where they get either phosphorylated by a kinase or dephosphorylated by a phosphatase.
- *Catalyst:* It *decreases the free energy needed for activation* of the reaction, hence speeding up the process.
- *Turnover number:* It is the number of substrate molecules converted to product molecules *every second*.

Lineweaver-Burk Plot

- Used to find the K_m (Michaelis' constant) and V_{max} (maximal velocity) of enzymes, based on the reaction ($V_0 = V_{max} \times S / K_m + S$). Note: V_0 = velocity, S = substrate concentration.
- K_m : It is the substrate concentration at which half V_{max} is achieved. *The lower the K_m , the higher is the enzyme affinity* (Fig. 11.1).

Kinetics

- *First-order kinetics:* Rate is *directly proportional* to substrate concentration. The value of S has to be *less than K_m* .
- *Zero-order kinetics:* Rate is constant at V_{max} , no matter what the substrate concentration is. The value of S has to be *more than K_m* .
- *Inhibition:* See Table 11.1

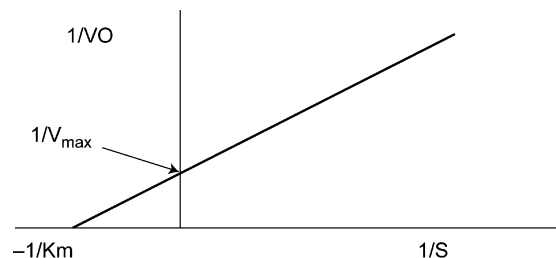


FIG. 11.1 Lineweaver-Burk blot

TABLE 11.1 Competitive and noncompetitive inhibition.

	Competitive inhibition	Noncompetitive inhibition
Action	Competition with substrate on same site	Inhibitor binds to a different site
V_{max}	Constant	Decreased
K_m	Increased	Constant
Example	Inhibition of succinate dehydrogenase by malonate	Lead poisoning

Graphs
The solid line is the norm; the dotted line is the effect of inhibition on the curve

• *Energy sources:*

- 1 g of carbohydrate = 4 kilocalories
- 1 g of proteins = 4 kilocalories
- 1 g of lipids = 9 kilocalories

Well-Fed State

• *Regulation:* Three enzymes, which are only active in the phosphorylated state:

1. Glycogen phosphorylase
2. Fructose 2-6-biphosphatase
3. Hormone sensitive lipase

• *Note:* Brain metabolism depends mainly on glucose derived from the TCA cycle.

Metabolism

- The most important regulator of metabolism is the *availability of substrate*.
- *Anabolism:* A building process that consumes energy
- *Catabolism:* A destructive process that releases energy in the form of ATP
- *Glucose:* The primary nutrient of brain and most organs. It enters the tissues by:
 1. Cotransport with sodium against a concentration gradient
 2. Glucose transporter (GLUT) receptors: There are five different receptors. Remember that *GLUT-1 is present in red blood cells (RBCs)*, while *GLUT-4 is present in muscles and fat*.
- *Requirement:* A 70-kg human requires around 2900 kilocalories/day.

Starvation

- *Mechanism:* The first reaction in starvation state is *liver glycogenolysis*, followed by gluconeogenesis if starvation is prolonged. Ketogenesis also plays a major role during starvation, mainly *beta-hydroxybutyrate*, which is consumed by the brain.
- *Sources of energy during starvation:*
 1. Brain: Glucose and beta-hydroxybutyrate
 2. Muscles: Free fatty acids and ketone bodies
 3. Adipose tissue: Free fatty acids

Respiratory Chain

- Also known as the *electron transport chain*. It takes place in the *inner mitochondrial membrane* (Fig. 11.2).
- *Mechanism:* Electrons flow from the negative-charged to the positive-charged poles, with the most negative molecule in the respiratory chain being reduced nicotinamide adenine dinucleotide (*NADH*).

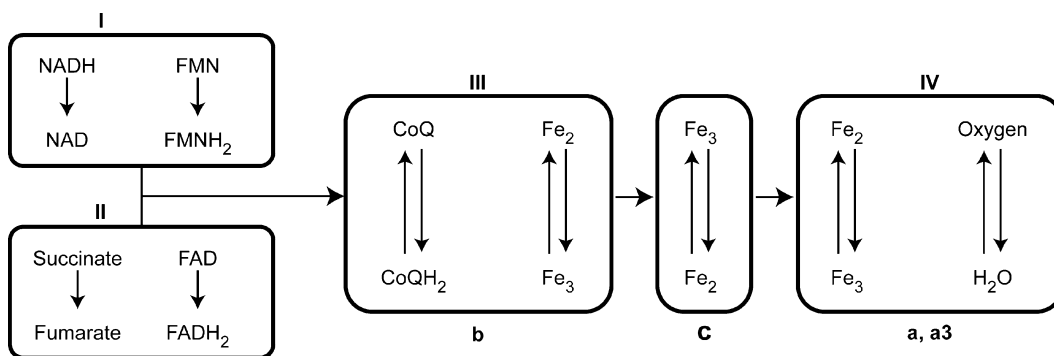


FIG. 11.2 Respiratory chain. FAD, flavin adenine dinucleotide; FADH, reduced flavin adenine dinucleotide; FMN, flavin mononucleotide; NAD, nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide

- *End result:* A total of three ATPs are produced from:
 1. Flavin mononucleotide (FMN)
 2. Cytochrome b: Regulates phase III
 3. Cytochromes a and a3: Regulate phase IV
- *Inhibitors of the chain:*
 1. Coenzyme Q: Inhibited by *Amytal* and *rotenone*
 2. Antimycin A: Inhibits iron conversion in phase III
 3. Sodium azide, cyanide, and carbon monoxide: Inhibit cytochromes a and a3 in phase IV
 4. Oligomycin: Blocks the ATP synthetase and prevents electron transfer
 5. 2,4-dinitrophenol: *Uncouples* the oxidative phosphorylation process. Uncoupling occurs through decreasing the number of protons in the inner mitochondrial membrane.
 6. High doses of aspirin: Leads to electron transfer *without ATP synthesis*
 7. Atractyloside: Inhibits adenosine diphosphate (ADP)/ATP pump
- *Note:* Disruption of the oxidative phosphorylation process can cause diseases, e.g., mitochondrially inherited Leber's optic atrophy.

Glycolysis (Fig. 11.3)

- *Important steps at a glance:*
 1. Glucose is converted to glucose-6-phosphate, by one of two mirror-image enzymes:
 - Hexokinase: It has *low* K_m and *low* V_{max} , and responds to the feedback inhibition of glucose-6-phosphate (G-6-P).
 - Glucokinase: It has *high* K_m and *high* V_{max} , and does *not* respond to the feedback inhibition of G-6-P. Glucokinase is abundant in the liver and beta cells of pancreas.
 2. G-6-P is converted to fructose-6-phosphate (F-6-P) by *isomerase* enzyme.
 3. F-6-P is converted to fructose 1,6-bisphosphate; the enzyme regulating this step is phosphofructokinase-1 (PFK1). *This is the rate-limiting step of glycolysis.* PFK1 is stimulated by *adenosine monophosphate (AMP)* and *fructose 2,6-bisphosphate*, and is inhibited by *ATP* and *citrate*.
 4. Note that the fructose 2,6-bisphosphate is formed by PFK2, and its level is increased in a well-fed state due to the stimulatory action of insulin. Fructose 2,6-bisphosphate maintains
- high levels of F-1,6-bisphosphate not only by stimulating the PFK1, but also by inhibiting the F-1,6-bisphosphatase.
- 5. 1,3-bisphosphoglycerate is converted by mutase to 2,3-bisphosphoglycerate, which is further converted to 3-phosphoglycerate by the action of phosphatase.
- 6. Pyruvate kinase enzyme converts phosphoenol pyruvate to pyruvate. This reaction is stimulated by F-1,6-bisphosphate.
- *Notes:*
 1. In starvation, high glucagon causes an increase in the cAMP levels, which inhibits the pyruvate kinase (*by phosphorylation*), so the phosphoenol pyruvate redirects itself toward gluconeogenesis.
 2. Pyruvate kinase deficiency is a genetic disorder that leads to weak RBC membrane and *hemolytic anemia*.
- *End result:*
 1. Anaerobic glycolysis: Lactate, which could be used by the heart muscle. It converts lactate to CO_2 and H_2O via the Krebs cycle.
 2. Aerobic glycolysis: *Two pyruvates, 2 NADH, and 6 ATPs*
- *Fate of pyruvate:* The pyruvate generated by glycolysis can be used by the cell in many ways, depending on the cell's needs:
 1. Acetyl coenzyme A (CoA): *Pyruvate dehydrogenase* converts pyruvate to acetyl CoA in the *mitochondria* in preparation for Krebs cycle. This process is regulated by thiamine pyrophosphate, flavin adenine dinucleotide (FAD), NAD, and acetyl CoA.
 2. Oxaloacetate: *Pyruvate carboxylase* converts pyruvate to oxaloacetate in the mitochondria in preparation for gluconeogenesis. This process is stimulated by biotin and acetyl CoA.
 3. Alanine: Pyruvate can undergo *transamination* (with glutamate) and be converted to alanine.
 4. Lactate: Pyruvate is reduced to lactate by *lactate dehydrogenase* in the cytoplasm.
 5. Lactate and acetaldehyde: Ethanol oxidation in the cytoplasm leads to pyruvate combining with EtOH and NAD to form lactate and acetaldehyde. This process is stimulated by thiamine pyrophosphate.
- *Regulation of glycolysis:* Regulatory enzymes of glycolysis are all stimulated by *insulin* and inhibited by *glucagons*. The three regulatory enzymes are glucokinase, PFK1 (*regulates the rate-limiting step*), and pyruvate kinase.

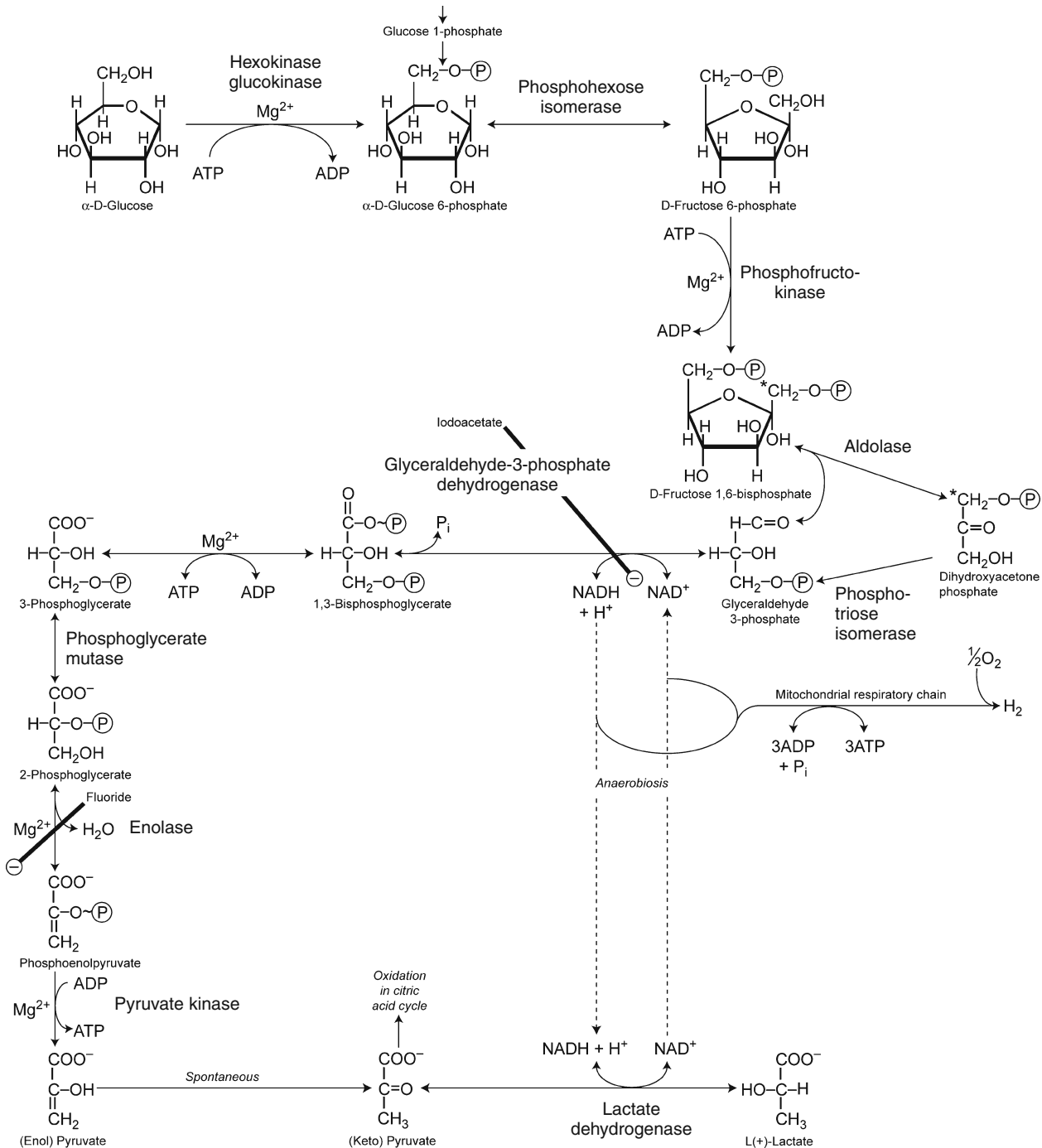


FIG. 11.3 Glycolysis. (From Robert K. Murray, Darryl K. Granner, Peter A. Mayes, Victor W. Rodwell, et al. Harper's Biochemistry, 27th ed. New York: McGraw-Hill, 2006, with permission.)

Gluconeogenesis

- A liver process, but might occur in the kidney to a lesser extent
- Precursors for gluconeogenesis:
 1. Carbon skeletons of amino acids
 2. Glycerol and alpha-ketoacids, e.g., pyruvate

3. Lactate from skeletal muscles and RBCs. It gets recycled in the liver to glucose and redistributed to these tissues again; this is known as the *Cori cycle*.

- Important steps at a glance:

1. Pyruvate carboxylase converts pyruvate to oxaloacetate. Note that pyruvate carboxylase exists

in the liver and kidneys, *but not in the muscle tissue*. It has a coenzyme derived from biotin known as *biocytin*. It also has an allosteric regulator, namely *acetyl CoA*.

- Fructose 1,6-bisphosphate is degraded by phosphatase to fructose 6-phosphate. This phosphatase is the mirror image of PFK1; it is *inhibited by AMP and F-2,6-bisphosphate*, and is *stimulated by ATP and citrate*.
 - Glucose 6-phosphate is degraded by phosphatase to glucose. *Von Gierke's disease (glycogen storage disease) occurs due to absence of this phosphatase*.
- Regulation of gluconeogenesis:** Glucagon has a magic touch on gluconeogenesis via two actions:
 - Inhibits pyruvate kinase enzyme (by phosphorylation)

2. Stimulates fructose 1,6-bisphosphatase

- Alcohol:** It is metabolized by *alcohol dehydrogenase*, then by *acetaldehyde dehydrogenase* to form *acetate*. Alcohol leads to excessive *NADH* production during its metabolism, which inhibits gluconeogenesis and causes hypoglycemia by converting pyruvate to *lactate* and converting oxaloacetate to *malate*.
- Note:** Disulfiram (Antabuse) inhibits *acetaldehyde dehydrogenase*.

Krebs Cycle (Fig. 11.4)

- Also known as tricarboxylic acid (TCA) cycle. It takes place in the *mitochondrial matrix*.
- Important steps at a glance:**

1. TCA cycle starts with oxidative decarboxylation of pyruvate to acetyl CoA; which is regulated by

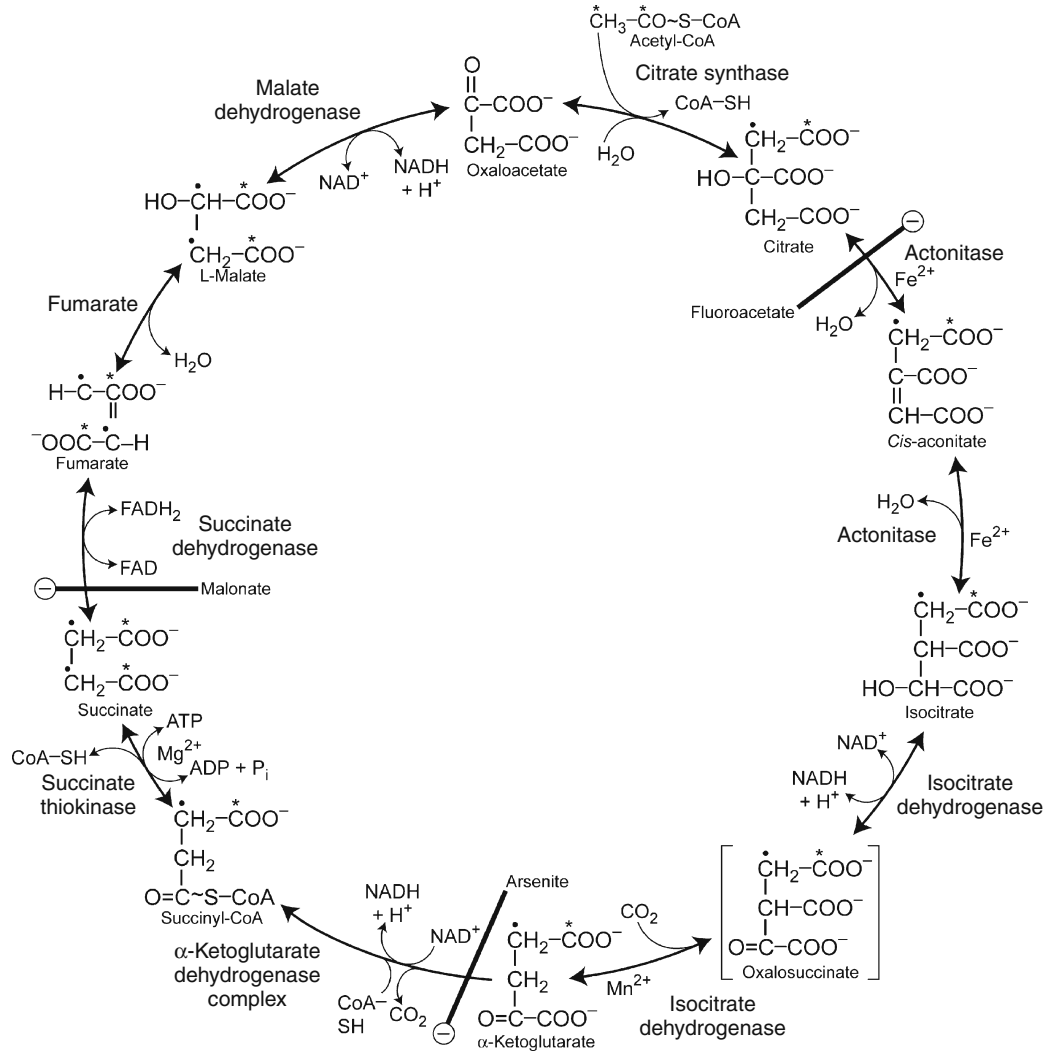


FIG. 11.4 Krebs cycle. (From Robert K. Murray, Darryl K. Granner, Peter A. Mayes, Victor W. Rodwell, et al. Harper's Biochemistry, 27th ed. New York: McGraw-Hill, 2006, with permission.)

pyruvate dehydrogenase. This reaction is inhibited by *acetyl CoA*, *ATP*, and *NADH*.

2. Citrate synthase regulates the reaction between acetyl CoA and oxaloacetate to form citrate. This reaction is inhibited by succinyl CoA, ATP, and NADH. Citrate is a major player in metabolism, as it *inhibits PFK1* of glycolysis, and *stimulates acetyl CoA carboxylase* of fatty acid synthesis.
 3. Isocitrate dehydrogenase converts isocitrate to alpha-ketoglutarate. *This is the rate-limiting step of the TCA cycle.*
 4. Alpha-ketoglutarate dehydrogenase converts alpha-ketoglutarate to succinyl CoA. *This reaction is stimulated by ADP and is inhibited by ATP.*
- *End result: 1 acetyl CoA → 12 ATP + 3 NADH + 2 CO₂ + 1 FADH₂.*
 - *Note: FADH₂ is produced by succinate dehydrogenase, which converts succinate to fumarate. This step is inhibited by malonate.*
 - *Regulation of the Krebs cycle: Citrate synthase, isocitrate dehydrogenase (regulates the rate-limiting step) and alpha-ketoglutarate dehydrogenase*

Hexose Monophosphate (HMP) Shunt

- Also known as pentose phosphate pathway. This cycle is not involved in the production of any ATP.
- *Rate-limiting step: Transformation of glucose 6-phosphate to 6-phosphogluconolactone by G-6-P-dehydrogenase (G6PD) enzyme. This step is inhibited by NADPH.*
- *End result: 1 glucose → 2 NADPH. Other end products are ribose 5-phosphate, xylulose 5-phosphate, and fructose 6-phosphate.*
- *Respiratory burst:*
 1. Macrophages and neutrophils capture oxygen from the surroundings by means of *NADPH oxidase*.
 2. They then convert the oxygen to superoxide, which further converts to peroxide (H₂O₂) by *dismutase*. (*Anaerobes are deficient in dismutase.*)
 3. Hydrogen peroxide is then fused to a chloride molecule by the *myeloperoxidase* enzyme, forming HOCL, which kills bacteria.
 4. *Absence of NADPH oxidase causes chronic granulomatous disease.* Discussed in Chapter 8, Immunology.
- *Notes:*
 1. The only coenzyme needed in HMP is *thiamine pyrophosphate* with *transketolase*.

2. *NADH function is oxidation*, while that of *NADPH is reduction* and *activation of the cytochrome P-450 system.*

Carbohydrates (CHO)

- *Lactose = glucose + galactose; maltose = glucose + glucose; sucrose = glucose + fructose; lactulose = fructose + galactose*
 - *Isomers: Glucose, galactose, and fructose are all isomers, i.e., they all have C6 H12 O6*
 - *Epimers: Glucose differs from galactose in the fourth carbon, so they are C-4 epimers. Similarly, glucose and mannose (C2 epimers) differ in the second carbon.*
 - *Forms:*
 1. Carbohydrates can be visualized in chain form (*Fischer projection formulas*), or cyclic form (*Haworth formulas*).
 2. All human sugars are in D-configuration, *except L-fucose and L-iduronic acid.*
 - *Groups: Carbohydrates can have their –OH group attached to different sites, and they can switch between forms through a process known as mutarotation, where the two forms are referred to as anomers. These two forms are:*
 1. Left of the ring: Known as beta-carbohydrate, e.g., glycogen
 2. Right of the ring: Known as alpha-carbohydrate, e.g., cellulose
 - *Glycoside: A sugar with an aglycone part attached to its –OH or –NH groups*
 - *Glycoprotein: Formed by addition of monosaccharides to the nonreducing end of the growing chain*
- ## Digestion of CHO
- CHO digestion starts in the mouth and is completed at the duodenojejunal junction.
 - *In the mouth: Salivary alpha amylase (ptyalin) destroys the alpha 1-4 bonds of CHO. Note that humans are incapable of destroying beta 1-4 bonds.*
 - *In the stomach and intestine: Acidity inhibits ptyalin, and then food passes to the duodenum where pancreatic amylase comes to action. Additionally, brush border enzymes of the upper jejunum act on lactose, mannose and sucrose.*
 - *Products of CHO digestion: Small molecules, e.g., glucose, galactose, fructose*

Fructose Metabolism

- *Important steps at a glance:*
 1. The process starts with one of two enzymes acting on *fructose*:
 - Hexokinase: It has *high* K_m for fructose, and converts it to *F-6-P*.
 - Fructokinase: It has *low* K_m for fructose, and converts it to *F-1-P*.
 2. Two important enzymes in fructose metabolism you have to know:
 - Aldolase A: Degrades F-1,6-bisphosphate into glyceraldehyde and dihydroxyacetone phosphate
 - Aldolase B: Degrades F-1-P into same products as aldolase A
- *End result: Acetyl CoA*, which joins the *lipogenesis* process
- *Fructokinase deficiency*: Results in high serum levels of fructose. The only result of that abnormality is *fructosuria*.
- *Aldolase B deficiency*: Results in high serum levels of F-1-P. This results in *fructose intolerance* and poisoning. Clinical picture: Hypoglycemia, vomiting, liver failure, jaundice, and hemorrhage after ingestion of fructose.
- *Glucose-fructose link*:
 1. Glucose is converted into sorbitol by the action of *aldolase reductase* enzyme, which is abundant in the *lens, retina and kidneys*.
 2. In the *liver* and *seminal vesicles*, the sorbitol is converted by *sorbitol dehydrogenase* into fructose.
 3. From that, you can conclude that glucose excess, e.g., diabetes mellitus (DM), leads to high sorbitol levels, which causes *cataracts, retinopathy and nephropathy*.

Glycogenesis

- Homopolysaccharides are formed of *alpha D-glucose* subunits attached together by *alpha 1-4 bonds*, with an *alpha 1-6 bond* every 10 positions.
- *Important steps at a glance*:
 1. Glucose 6-phosphate (G-6-P) undergoes conversion by *phosphoglucomutase* to glucose 1-phosphate (G-1-P).
 2. G-1-P then binds uridine diphosphate (UDP) pyrophosphorylase to form UDP-glucose.
 3. The glucose portion of UDP-glucose then detaches and binds to the -OH group of the

tyrosine side chain of glycogenin. This process is regulated by *glycogen initiator synthase*.

4. Glycogen synthase then adds more units to build up the glycogen molecules.
 5. The branching enzyme (*transferase*) is responsible for adding the *alpha 1-6 bonds*.
- *Note*: Glycogen synthase is inhibited by *phosphorylation*, and is stimulated by *G-6-P*.

Glycogenolysis

- Regulated by phosphorylase, debranching enzyme, phosphoglucomutase, and to a minimal extent lysosomal *alpha 1-4 glucosidase*
- *End result: G-6-P*, and its fate varies depending on the organ:
 1. Muscle tissue: G-6-P joins *glycolysis*
 2. Liver: G-6-P is degraded by glucose-6-phosphatase into *glucose*
- *Notes*:
 1. Glycogen phosphorylase is *stimulated* by *phosphorylation* through calcium and cAMP, and is *inhibited* by *glucose, G-6-P, and ATP*.
 2. Glucagon stimulates *liver glycogenolysis*, but does not affect the muscle's glycogenolysis.

Glycogen Storage Diseases (GSDs)

- *Type I: Von Gierke's disease*: Due to deficiency of *glucose-6-phosphatase*. Clinical picture: *Doll facies, hypoglycemia, high lactic acid and uric acid levels*.
- *Type II: Pompe's disease*: Due to deficiency of *lysosomal alpha 1-4 glucosidase*. Clinical picture: *Cardiomegaly*, due to deposition of glycogen in the cytoplasm. Note: Blood glucose in these patients is *normal, not hypoglycemic*.
- *Type V: McArdle's disease*: Due to deficiency of *skeletal muscle's glycogen phosphorylase*. Clinical picture: *Weak, crampy muscles and myoglobinuria*.

Glycosaminoglycans (GAGs)

- GAGs (*mucopolysaccharides*) are long carbohydrate chains that come together around a protein core to form *proteoglycans*. The only exception is *hyaluronic acid*, which functions without a protein core and does not have a sulfa group. Table 11.2 lists some important glycosaminoglycans.
- *Sulfur donor for GAGs: 3-phosphoadenosyl-5-phosphosulfate (PAPS)*
- *Mucopolysaccharidoses (MPS)*: Defective degradation leading to storage diseases:

TABLE 11.2 Glycosaminoglycans.

	Chondroitin sulfate: most common GAG	Dermatan sulfate	Keratan sulfate	Hyaluronic acid
Composition	N-acetyl- galactosamine + glucuronic acid	N-acetyl- galactosamine + L-iduronic acid	N-acetyl- glucosamine + galactose	N-acetyl- glucosamine + glucuronic acid
Half-life	10 days	10 days	120 days	3 days
Location and function	Cartilage and tendons	Skin and blood vessels	Cartilage and cornea	Joint lubricant and a shock absorber

1. Type I: *Autosomal recessive*, and has two subtypes:
 - Ia: *Hurler's syndrome*: Due to *iduronidase deficiency*. Clinical picture: Patient is short, mentally retarded, and suffers *gargoylism* (*coarse facial features*), corneal opacity, and coronary ischemia.
 - Ib: *Scheie's syndrome*: Just like Hurler's, *minus the mental retardation*
2. Type II: Hunter's syndrome: *X-linked recessive* disease. Mechanism: *Iduronate sulfatase* deficiency. Clinical picture: Mental retardation, *macroglossia*, and *deafness*.
3. Type IV: Sly syndrome: *Autosomal recessive disease*. Mechanism: *Glucuronidase* deficiency. Clinical picture: *Hepatosplenomegaly*.
- *Notes*:
 1. Cartilage: Formed of *chondroitin sulfate* and *keratan sulfate*
 2. Heparin: Intracellular GAG, formed of glucosamine and glucuronic or iduronic acid
- *Secretin*: Stimulates the secretion of pancreatic *bicarbonate*
- *Pancreatic lipases*: They degrade triglycerides into three separate molecules: two monoacylglycerols and one free fatty acid. These degradation products bind to bile salts in the jejunum and form *micelles*.
- Most fatty acids in the plasma are in the form of esters, and they are degraded by esterase.
- *Phospholipids*: They are degraded by *pancreatic phospholipase A₂* into lysophospholipids. This reaction is activated by the pancreatic enzyme *trypsin*.
- *Chylomicrons*:
 1. They are lipids manufactured by intestinal mucosal cells, and are released from cells by *apolipoprotein B48*. Deficiency of Apo-B48 leads to an increased intestinal cell triglyceride concentration and may lead to *congenital abetalipoproteinemia*.
 2. Chylomicrons are degraded in the blood by *lipoprotein lipase*, a process regulated by *Apo-CII*. Deficiency of lipoprotein lipase or Apo-CII is the cause of type I hyperlipoproteinemia.
- *Triglycerides*:
 1. The combination of glycerol and three fatty acyl CoA groups forms one triglyceride. *Glycerol* is supplied from *glycolysis*, while fatty acyl CoA groups are supplied from fatty acids.
 2. Triglycerides are stored in the adipose tissue, and when degraded by pancreatic lipase, the glycerol component is sequestered in the liver, while fatty acids bind to albumin.
- *Apolipoprotein E*: Cleanses the blood of chylomicrons. Deficiency leads to elevated blood chylomicrons concentration, a disease known as type III hyperlipoproteinemia (familial dysbetalipoproteinemia).
- *Low-density lipoprotein (LDL) receptors*:
 1. After LDL molecules attach to receptors, they are endocytosed inside the cell and packed into endosomes, which are then lysed by endosomal adenosine triphosphatase (ATPase).

Lipids

- *Types*: There are only two essential fatty acids: *Linoleic acid* and *linolenic acid*. Essential fatty acids are those that must come from the diet because the body cannot manufacture them. Fatty acids may be divided into two major groups:
 1. Saturated fatty acids, e.g., coconut and palm oil
 2. Unsaturated fatty acids, e.g., Corn and olive oil
- *Digestion*:
 1. Lipid digestion begins in the stomach with the activation of lingual lipases; however, gastric lipases do not play a major role in adults because they require a neutral environment.
 2. Lipids then pass into the duodenum stimulating the release of two enzymes:
 - *Cholecystokinin (CCK)*: Stimulates biliary and pancreatic *enzymes* secretion

2. LDL receptors are mediated by *Apo-B100*, and they contain *clathrin*. Disorder of receptor or *Apo-B100* leads to elevated LDL levels, also known as *type II hyperlipidemia (high LDL, cutaneous xanthomas, xanthelasmas on eyelids)*.
- *Very low density lipoprotein (VLDL)*: When circulating in the blood, triglycerides along with cholesterol and other lipids are all packaged into a molecule known as VLDL. The production of VLDL molecules is executed by *apolipoprotein B100*.
 - *Type IV dyslipidemia*: High *VLDL*, while type V has high *triglyceride* level
 - *Notes*:
 1. Oxidation of fatty acids ends up in unsaturated fatty acids, also called *rancids*.
 2. Neuro fatty acids are known as cerebrosides, e.g., *lignoceric* and *nervonic* acids.
 3. *Refsum disease*: Occurs due to failure to degrade *phytanic acid*. Patients with this *peroxisomal* disorder present with signs of central and peripheral nervous system damage, due to *faulty myelin sheaths formation*.

Fatty Acid (FA) Synthesis (Fig. 11.5)

- As we review fatty acid synthesis keep in mind:
 1. Fatty acids enter the cytoplasm via the *citrate shuttle*.
 2. Fatty acids enter the mitochondria via the *carnitine shuttle*.
- *Location*: Liver and breast tissue; ATP and NADPH are required for the process.
- *Important steps at a glance*:
 1. FA synthesis begins within the mitochondria, where acetyl CoA binds oxaloacetate to form citrate.
 2. Citrate crosses into the cytoplasm and re-converts to acetyl CoA.
 3. Acetyl CoA is converted to malonyl CoA by the enzyme *carboxylase*.
- *End result*: Palmitate (16 carbons)
- *Rate-limiting factor*: Fatty acid synthase enzyme
- *Notes*:
 1. Reduced nicotinamide adenine dinucleotide phosphate (NADPH) is an important product released when malate is converted to pyruvate via dehydrogenase enzyme.
 2. FAs are converted by *thiokinase* into fatty acyl CoA. Fatty acyl CoA is a building block of triglycerides as discussed above.

Beta-Oxidation

- It is the process of carbon removal from the long chain fatty acids in fatty acyl CoA, until it becomes *acetyl CoA*.
- *Location*: Mitochondria, and is regulated by the *carnitine shuttle*
- *The carnitine shuttle*: Regulated by the carnitine acyl transferase (CAT-2) on the *inner side of the inner mitochondrial membrane*. Note that CAT-1 is present on the outer side of the inner mitochondrial membrane, and is inhibited by malonyl CoA. A deficiency in the CAT proteins leads to *muscle weakness*.
- *End result*: B-oxidation of palmitoyl CoA yields 131 ATPs.

Arachidonic System

- *Mechanism*: The arachidonic acid system is composed of two important pathways, regulated by two distinct enzymes:
 1. Cyclooxygenase pathway (COX): COX converts arachidonic acid into either prostaglandins or thromboxanes. Prostaglandin (PG) G₂ and H₂ are the initial products, but may be further converted to thromboxane A₂ (TXA₂), PGI₂, PGE₂, or PGF₂ via *thromboxane synthase*.
 2. Lipooxygenase pathway (LOX): LOX converts arachidonic acid into leukotrienes. Leukotrienes regulate *vasoconstriction*, *bronchoconstriction*, and *chemotaxis*.
- *Notes*:
 1. Cyclooxygenase is *irreversibly inhibited* by aspirin, while thromboxane synthase is inhibited by *dipyridamole*.
 2. Omega-3-fatty acids in fish oil stimulate the formation of thromboxane A₃, which is a weak platelet aggregator compared to TXA₂.
 3. All prostaglandins have a short half-life and only act locally.

Ketogenesis (Fig. 11.6)

- *Important steps at a glance*:
 1. Two acetyl CoA molecules combine with a fatty acyl CoA to form acetoacetyl CoA.
 2. Acetoacetyl CoA converts to acetoacetate.
 3. Finally, acetoacetate differentiates into:
 - Acetone: A spontaneous reaction
 - Beta-hydroxy butyrate: Regulated by a *dehydrogenase enzyme*

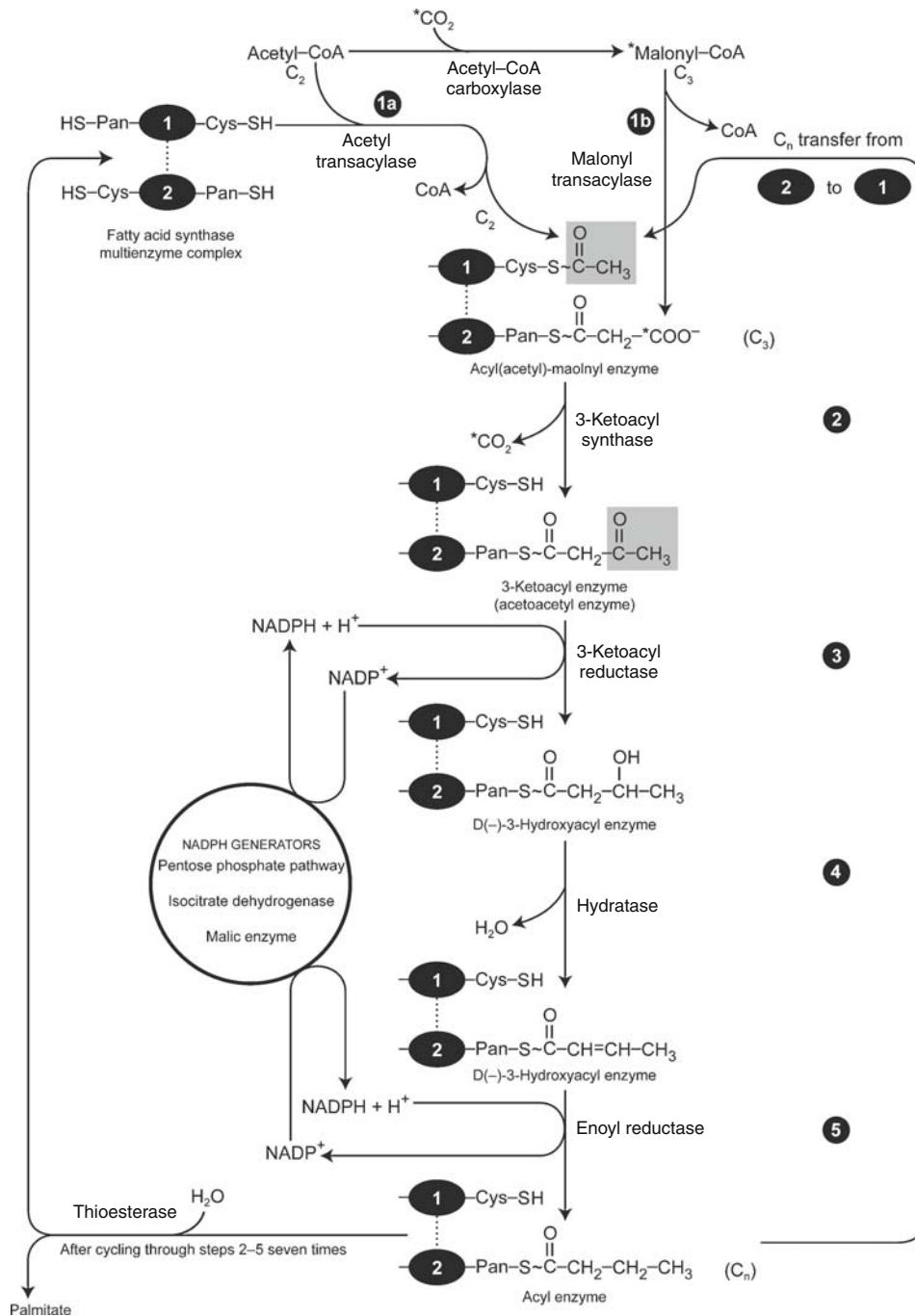


FIG. 11.5 Fatty acid synthesis. (From Robert K. Murray, Darryl K. Granner, Peter A. Mayes, Victor W. Rodwell, et al. Harper's Biochemistry, 27th ed. New York: McGraw-Hill, 2006, with permission.)

- *Note:* Ketone bodies cannot be utilized by the liver as a source of energy.

Phospholipids

- They all have a hydrophilic head and a hydrophobic tail, and are synthesized in the *smooth endoplasmic reticulum*.

- *Examples and composition:*

1. Lecithin: Phosphatidylcholine. Do not confuse this with phosphatidylcholine, a component of the *myocardium*.
2. Cephalin: Phosphatidylethanolamine
3. Plasmalogen: Phosphatidylethanolamine, present in myelin. Another example is platelet activation factor (PAF), which stimulates *platelet aggregation*.

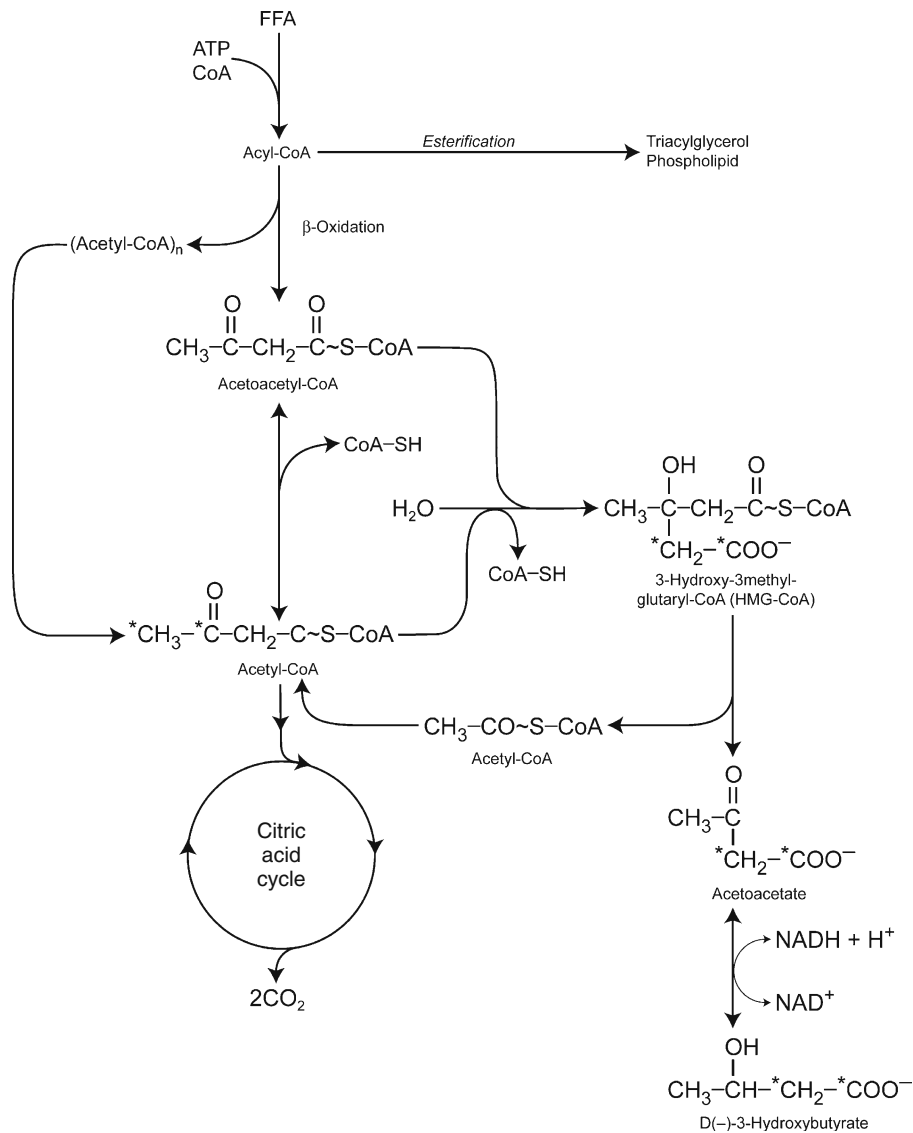


FIG. 11.6 Ketogenesis. (From Robert K. Murray, Darryl K. Granner, Peter A. Mayes, Victor W. Rodwell, et al. Harper's Biochemistry, 27th ed. New York: McGraw-Hill, 2006, with permission.)

4. Cardiolipin: Diphosphatidylglycerol, present in the inner mitochondrial membrane
 5. Choline: Phosphatidylserine and methionine
 6. Ceramide: Sphingomyelin and fatty acids, e.g., lignoceric, nervonic, palmitic, or stearic acids.
- *Phospholipases*:
 1. Phospholipase A_1 : Present in all mammals
 2. Phospholipase A_2 : Forms arachidonic acid, stimulated by trypsin and inhibited by cortisol
 3. Phospholipase C: Present in liver lysosomes and clostridia.
 - *Niemann-Pick disease*: Mechanism: autosomal recessive (AR) deficiency of *sphingomyelinase*; more common in *Ashkenazi Jews*. Clinical picture: Hepatosplenomegaly and mental retardation.

Glycolipids

- They are derivatives of ceramide (discussed earlier)
- *Cerebroside*: A combination of ceramide and glucose (or galactose)
- *Sphingolipidoses*: AR diseases, *except Fabry disease*, which is *X-linked recessive* (Table 11.3)

Cholesterol

- *Synthesis*:
 1. It begins with *hepatic hydroxymethylglutaryl coenzyme A (HMG CoA)*, which is converted to *mevalonic acid* by *HMG CoA reductase enzyme* (*this is the rate-limiting step*).

TABLE 11.3 Sphingolipidoses.

Disease	Inheritance	Deficient enzyme	Clinical picture
Tay-Sachs	AR	Hexosaminidase A	Cherry red macula, blindness, <i>hyperacusis</i> , and seizures due to accumulation of GM2 gangliosides
GM1 Sandhoff	AR	Galactosidase	Hepatomegaly, mental retardation
	AR	Hexosaminidase A	Similar to Tay-Sachs
		Hexosaminidase B	
Fabry	XLR	Galactosidase	Purple rash, heart failure due to deposition of ceramide trihexoside
Krabbe	AR	Galactosidase	Globoid bodies in white matter due to accumulation of galactocerebrosides
Farber	AR	Ceraminidase	Joint deformities
Gaucher	AR	Glucocerebrosidase	Hepatosplenomegaly due to accumulation of glucocerebrosides Cells show pathognomonic <i>wrinkled paper</i> cytoplasm
Metachromatic leukodystrophy	AR	Arylsulfatase A	Wide-based gait, ataxia, and difficulty climbing stairs; nerves stain yellow with cresyl violet

AD, autosomal dominant; AR, autosomal recessive; XLR, X-linked recessive.

2. From mevalonic acid, a series of reactions follows including the formation of squalene, lanosterol, and finally cholesterol.

- **Regulators:** HMG CoA reductase is stimulated by *insulin*, and inhibited by *glucagon* and *statin drugs*.
- **Note:** The liver has two different HMG CoA synthase enzymes:
 1. Cytoplasmic: For cholesterol synthesis
 2. Mitochondrial: For ketogenesis
- **Degradation:**
 1. Cholesterol degradation yields *cholestanol* and *coprostanol*.
 2. 7α -hydroxylase can degrade cholesterol to cholic acid, a bile acid. Intestinal flora process cholic acid to deoxycholic acid, which is reabsorbed into the enterohepatic circulation.

Important Reactions

- Propionyl CoA is converted to methylmalonyl CoA by *carboxylase*. This reaction is regulated by *biotin*.
- Methylmalonyl CoA is converted to succinyl CoA by *mutase*. This reaction is regulated by *vitamin B₁₂*. That is why *B₁₂* deficiency causes high serum methylmalonic acid level.

Protein

Amino Acids (Fig. 11.7)

- A 70-kg human requires *55 or 56 g of protein/day*.
- **Types:**
 1. Acidic, e.g., aspartate, glutamate
 2. Basic, e.g., arginine, histidine, and lysine
- **Groups and parts:**
 1. Each amino acid has a *negative carboxyl group* and a *positive amino group*, except *proline*, which is an *imino acid*.
 2. Amino acids arrange in such a way that the hydrophobic parts are situated toward the center, while the *hydrophilic* ones are situated *peripherally*.
 3. Isomerism: All amino acids have isomers, except *glycine*.
 4. Glutamine is the only amino acid that has an *amide group*.
 5. Serine is the only amino acid that contains a *hydroxyl group in its side chain*.
- **Forms:**
 1. L form (*most common form*), e.g., *proteins*
 2. D form, e.g., *bacterial cell wall*

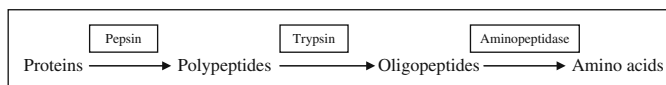


FIG. 11.7 Protein metabolism. Note that trypsin is activated by enterokinase

- *Unique amino acids:*
 1. Essential amino acids (helpful to remember “MTV’s PAT HILL”): Methionine, threonine, valine, phenylalanine, arginine, tryptophan, histidine, isoleucine, leucine, lysine.
 2. The only purely ketogenic amino acids: *Leucine* and *lysine*
 3. Cysteine: It has the ability to form *disulfide bonds*.
 4. Isoleucine: A *hydrophobic amino acid*, which is almost always situated in the *central part* of proteins
 5. *Ninhydrin*: It gives a purple color if mixed with any amino acid, except with proline, where the reaction yields a *yellow* color.
- *Zwitterion*: An *isoelectric* form of amino acids, i.e., no net charge). Amino acids that have isoelectrical forms are known as *amphoterics* or *ampholytes*. Zwitterion can survive in any medium by changing its charge, as follows:
 1. Acidic medium: It acquires positive charge.
 2. Basic medium: It acquires negative charge.
 3. Neutral medium: It acquires both charges (*isoelectric point*).
- *Notes:*
 1. Uncharged molecules, unlike charged ones, cross membranes easily. (Remember: “If you are charged with something, you will be stopped everywhere.”)
 2. *Henderson-Hasselbalch equation*: $\text{pH} = \text{pK} + \log(\text{HCO}_3/\text{CO}_2)$

Protein Structure

- *Primary*: It is a simple $C = N$ peptide bond. This bond is *double, rigid*, in *trans* form, and contains *no charges*. Note the following:
 1. Peptide bond can be hydrolyzed by acids, changing the nature of amino acids, e.g., glutamine changes to glutamate, asparagine changes to aspartate, while tryptophan is completely destroyed after acid hydrolysis.
 2. Trypsin destroys arginine or lysine into small peptides.
 3. Cyanogen bromide destroys *methionine*.
 4. Performic acid destroys *disulfide bonds*.
- *Secondary*: Examples are collagen, hemoglobin, and keratin. It can exist in any of the following three forms:
 1. Alpha helix: Each turn contains *3.6* amino acids. The helix is stabilized by *hydrogen bonds*. Note:

Proline cannot share in the formation of alpha helix.

2. Beta sheet: It is the mechanism of formation of globular, fibrous, and amyloid proteins (*responsible for Alzheimer’s dementia*).
 3. Beta bends: Each bend contains *four* amino acids. Bends *connect* beta sheets together. Beta bends are stabilized by *hydrogen* and ionic bonds. Note: *Proline* and *glycine* are almost always involved in forming these bends.
- *Tertiary*: It is a combination of many secondary structures together, e.g., hemoglobin (*alpha helices*), immunoglobulin (*beta sheets*). Tertiary structures are stabilized by *disulfide bonds*, and are folded together by polypeptide chain binding proteins referred to as *chaperones*.
 - *Quaternary*: A multiunit molecule, e.g., hemoglobin A has four polypeptides.

Hemoglobin (Hb)

- Each hemoglobin molecule can carry *four* oxygen molecules. Heme portion of Hb is formed of *ferrous iron* and *protoporphyrin IX*.
- *Structure*: Two *dimers*; each contains *two chains* attached by *hydrophobic bonds*.
- *Forms*: T: taut, deoxygenated form; R: relaxed, oxygenated form
- *Hemoglobin-oxygen dissociation curve* (Fig. 11.8): The curve is *sigmoidal*, but myoglobin O_2 dissociation curve is *hyperbolic*. The reason behind the sigmoidality is *positive cooperativity*, i.e., Hb affinity for oxygen increases until all four sites are occupied by oxygen. Note that the curve plateaus between values of 60 and 100, which enables us to sustain a good blood oxygen level even in hypoxic situations. Shifts of the curve are discussed below and in Table 11.4:

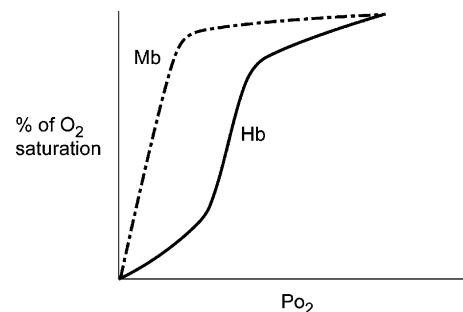


FIG. 11.8 Oxygen dissociation curves for hemoglobin (Hb) and myoglobin (Mb)

TABLE 11.4 Causes of hemoglobin O₂ dissociation curve.

Factor	Right shift	Left shift
CO ₂	High CO ₂	Low CO ₂ (causes alkalosis), also called the Bohr effect
Hydrogen content	High hydrogen content = acidosis = low pH	Low hydrogen content = alkalosis = high pH
2,3-Bisphosphoglycerate (2,3-BPG)	High 2,3-BPG (binds to beta chains of hemoglobin)	Low 2,3-BPG

1. Right shift: Indicates *decreased* affinity of hemoglobin for oxygen, so the oxygen is released to the tissues and Hb attains the *T form*.
 2. Left shift: Indicates *increased* affinity of Hb for oxygen, so the oxygen released to the tissues decreases and Hb attains the *R form*, e.g., carbon monoxide poisoning (treated by 100% oxygen).
- *P50*: It is the PO₂ at which half oxygen saturation is achieved. Hemoglobin's P50 is 25 to 26 torr of oxygen.
 - *Notes*:
 1. Storage of blood products in dextrose solutions depletes them of 2,3-bisphosphoglycerate (BPG), which helps facilitate O₂ release from Hb. This depletion could be prevented by adding *inosine* to banked blood.
 2. Hemoglobin F has higher oxygen affinity than any other form of hemoglobin, due to the *low 2,3-BPG affinity of the HbF gamma chains*.
 3. Methemoglobin converts to hemoglobin by *NADH cytochrome b5 reductase*.
 4. Carboxyhemoglobin inhibits cytochrome oxidase enzyme, while methemoglobin does not have any effect on that enzyme.
 5. Hemoglobin C results from a genetic disorder that leads to replacement of glutamate with *lysine*, while sickle cell disease occurs due to replacement of glutamate with *valine*.
 6. Genes regulating Hb chains synthesis are located on *chromosome 16 (for alpha chains)* and *chromosome 11 (for beta chains)*
 7. Myoglobin: Formed of *eight alpha helices (A to H)*. It contains two histidines and the last amino acid in the sequence is *proline*. Myoglobin carries *only one* oxygen molecule and its P50 is 1. On the curve shown in Fig. 11.8, you can see that *myoglobin has higher O₂ affinity than hemoglobin*.

Collagen

- *Structure*: It is formed of *tropocollagen* molecules. Each tropocollagen molecule is formed of *three alpha chains coiled in a helix*.
- *Composition*: *Glycine-X-Y*, where X is usually *proline*, and Y is usually either *hydroxyproline* or

hydroxylysine, formed by *posttranslational modification*. This modification includes attaching a *glucose* or *galactose* molecule.

- *Types*:

1. Collagen I: Formed of *two alpha-1 and one alpha-2 chains*. It is the most abundant, has the highest tensile strength, and is famous for its *cross-banding pattern every 64 nm*. It is the collagen of *bone*.
2. Collagen II: Formed of *three alpha-1 chains*. It is the collagen of *hyaline cartilage*.
3. Collagen III: Formed of *three alpha-1 chains, just like type II*. It is also known as *reticulin*, and serves as a *supporting tissue* in the liver, spleen, and lymph nodes.
4. Collagen IV: Formed of *two alpha-1 and one alpha-2 chains, just like type I*. It is the collagen of *basement membranes*.
5. Collagen V: It is the collagen of *epiphyseal growth plates*.

Elastin and Keratin

- *Elastin*:

1. Formed of *small amino acids*, e.g., glycine, proline, hydroxyproline, but *never hydroxylysine*. Elastin molecules have *lysine* side chains, which can bind together to form *desmosine*.
2. α_1 -Antitrypsin is an antiproteinase, e.g., anti-elastase, and is secreted by the *liver* and *alveolar macrophages*. Absence of α_1 -antitrypsin is an *autosomal recessive* disorder that results in congenital *pan-acinar emphysema* and *congenital liver cirrhosis*.

- *Keratin*: Formed of protofibrils, made of *cysteine*. Each protofibril contains *two pairs of alpha helices* that bind to form thicker fibrils.

Cystinuria

- *Mechanism*: *AR* defect in reabsorption of proximal convoluted tubules (PCT)
- *Clinical picture*: *Recurrent renal calculi*
- *Diagnosis*: Elevated *urinary Cysteine, Ornithine, Arginine, and Lysine (COAL)*

- *Treatment: Penicillamine, low methionine diet, and alkalinization of urine*

Homocystinuria

- *Mechanism: Deficiency of cystathionine synthase, which participates in converting homocysteine to cysteine.*
- *Clinical picture: Thromboembolic events, bone deformities, and lens dislocation*
- *Treatment: Increase dietary cysteine, and decrease dietary methionine*

Alkaptonuria

- *Mechanism: Deficiency of homogentisic acid oxidase, which participates in the degradation of tyrosine*
- *Clinical picture: Dark cartilaginous structures, e.g., nose, ears*
- *On exam: Urine gets dark if left standing*

Maple Syrup Urine Disease

- *Mechanism: Deficiency of alpha-ketoacid dehydrogenase, which is needed to break down branched*

amino acids. Accordingly, there is accumulation of *alpha amino acids and keto-acids*, e.g., leucine, isoleucine, and valine.

- *Clinical picture: Urine smells like maple syrup*
- *Treatment: Restrict proteins in diet; recommend increase in the intake of water and juices.*

Urea Cycle

- *Location: Liver. Urea then travels to the kidneys for excretion.*
- *Nitrogen source: Urea is formed of two nitrogen molecules from two (AA) separate sources: Ammonia and Aspartate.*

Steps (Fig. 11.9)

- *The rate-limiting step: Combination of ammonia and HCO_3^- to form carbamoyl phosphate. This reaction is mediated by *carbamoyl phosphate synthase I*, and is stimulated by *N-acetylglutamate (NAG)*.*
- *End result: Arginine converting to ornithine and urea*

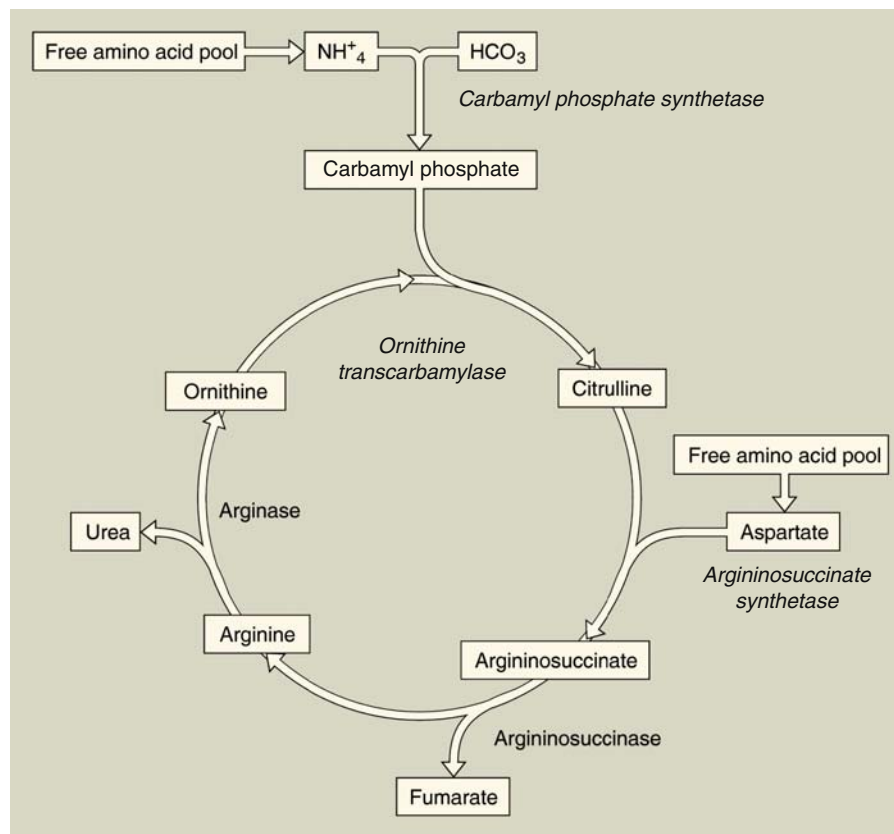


FIG. 11.9 Urea cycle

- *Note: Carbamoyl phosphate synthase II is the rate-limiting enzyme of pyrimidine synthesis and does not need the help of NAG.*

Ammonia Intoxication

- In renal or hepatic failure, urea excretion is impaired and may lead to encephalopathy.
- *Clinical picture: Reversed sleep rhythm and altered mental status are the first signs, followed by confusion, lethargy, and finally coma.*
- *Treatment:*
 1. Protein restriction in diet
 2. Emptying the intestine of protein: Using *lactulose* or *enema*
 3. Eradicate urea producing bacterial flora: Using *neomycin* or *metronidazole*

Ornithine Transcarbamoylase (OTC) Deficiency

- *Mechanism: X-linked recessive*
- *Pathology: This enzyme normally binds ornithine to carbamoyl phosphate to form citrulline inside the mitochondria during the urea cycle.*
- *Clinical picture: Vomiting, headache, lethargy, and seizures after ingestion of high-protein diet, mainly due to hyperammonemia and hypernitrogenemia.*
- *Diagnosis: High orotic acid levels in the urine*

- *Treatment: Nitrogen excretion using benzoic acid and phenylacetate*

Porphyrins

Steps (Fig. 11.10)

- Porphyrin is formed of *four pyrrole rings* linked together by *methionyl bridges*.
- *Regulators:*
 1. Hemin inhibits aminolevulinic acid (ALA) synthase.
 2. Phenobarbitone stimulates ALA synthase by activating the cytochrome P-450 system.
 3. Lead inhibits ALA dehydrase and ferrochelatase.
 4. Iron stimulates ferrochelatase.

Porphyrrias

- *Porphyria cutanea tarda (AD):* It is the most common porphyria. Mechanism: Deficiency of *uroporphyrinogen decarboxylase*, which normally converts uroporphyrin to coproporphyrin. Clinical picture: *Rash and photosensitivity.*
- *Acute intermittent porphyria (AD):* Mechanism: Deficiency of *porphobilinogen deaminase*. Clinical picture: Unexplained vague abdominal pains, neuropsychiatric manifestations, and dark urine. Note: These patients do not have photosensitivity. Diagnosis: High urinary levels of porphobilinogen (PBG).

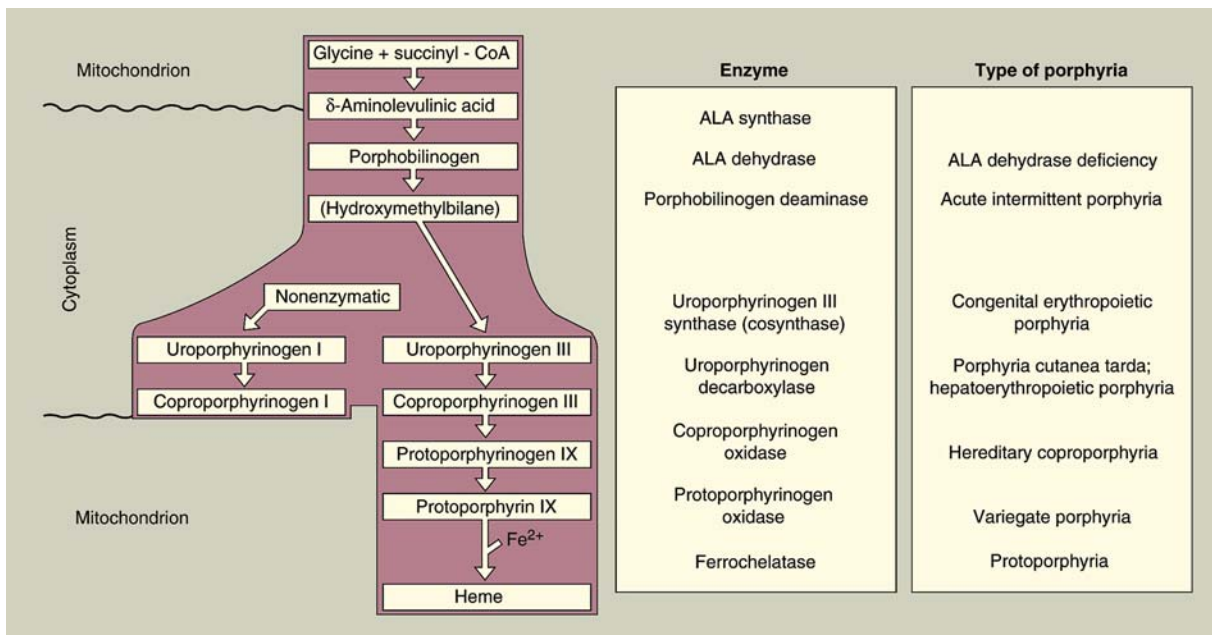


FIG. 11.10 Porphyrin synthesis

- *Congenital erythropoietic porphyria (AR)*: Mechanism: Deficiency of *uroporphyrinogen III cosynthase*. Clinical picture: *Rash and photosensitivity*.

Hormones and Vitamins

Insulin

- *Structure*: A 51-amino-acid protein arranged in two chains; the two chains are attached by a *disulfide bond*.
- *Synthesis*: Begins with the protein *pre-proinsulin*, which is converted to proinsulin. Proinsulin is cleaved to form *insulin* and *C-peptide*.
- *Regulators*:
 1. Stimulators of insulin release: Glucose, arginine, secretin
 2. Inhibitors of insulin release: Catecholamines
- *Insulin actions*:
 1. Increases cellular glucose uptake; inhibits gluconeogenesis and glycogenolysis
 2. Stimulates protein synthesis
 3. Increases triglyceride anabolism by *activating lipoprotein lipase*
 4. Decreases triglyceride catabolism by *inhibiting hormone sensitive lipase*
- *Insulin receptor*: Formed of four subunits: two alpha and two beta. The beta subunits are attached to a *tyrosine kinase* enzyme. Note that insulin and nitric oxide receptors are similar in having a rod-like transmembrane structure.
- *Notes*:
 1. Insulin-independent tissues: Brain, RBCs, intestine, cornea, kidneys, and liver (remember them with the mnemonic “BRICK-L”)
 2. Fasting hypoglycemia may be caused by multiple factors, including alcohol, which inhibits gluconeogenesis; however, the *most common form of hypoglycemia is the postprandial one*. Note: *Hypoglycemia associated with high serum insulin and low serum C-peptide levels is indicative of exogenous insulin use*.
 3. The first hormones to act in hypoglycemia are *glucagon and epinephrine*.

4. Half-life of human insulin is *6 minutes*. For therapeutic insulin types, their onset of action and half-lives, see Chapter 9, Pharmacology.

Catecholamines (Figs. 11.11 to 11.14)

Vitamins, Minerals, and Electrolytes (Tables 11.5 and 11.6)

Nucleotides

- *DNA*: Formed of purines (adenine and guanine) and pyrimidines (cytosine and thymine)
- *RNA*: Formed of purines (adenine and guanine) and pyrimidines (cytosine and *uracil*)
- *Rings*: Purines have a *nine-carbon-ring* structure, while pyrimidines have a *six-carbon-ring* (Figs. 11.15 and 11.16)
- *Bonds*: Adenine binds to thymine via a *double bond (A = T)*, while guanine is more tightly bound to cytosine by a *triple bond*.
- *Nucleoside*: Purine or pyrimidine and ribose or a deoxyribose
- *Nucleotide*: Nucleoside and phosphate

Purine Synthesis

- *Steps*: See Figs. 11.17 to 11.19
- *Lesch-Nyhan syndrome*: Autosomal recessive deficiency of hypoxanthine guanine phosphoribosyl transferase (HGPRT), which normally converts *guanine* to *guanosine monophosphate (GMP)*, and *hypoxanthine* to *inosine monophosphate (IMP)*. This leads to accumulation of phosphoribosyl-pyrophosphate (PRPP), hypoxanthine, and guanine. *Clinical picture*: Excessive serum uric acid leading to mental retardation and severe gouty arthritis, which results in self-mutilation (*due to self biting*) and deformed joints.

Purine Degradation

- *Steps*:
 1. Adenosine deaminase converts adenosine to inosine.

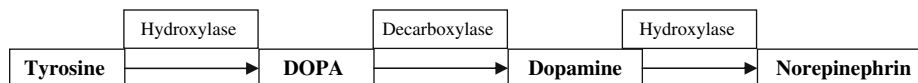


FIG. 11.11 Catecholamine synthesis

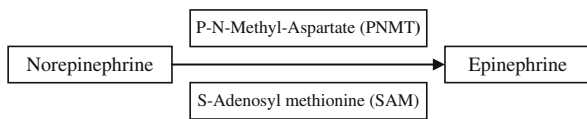


FIG. 11.12 Catecholamine synthesis

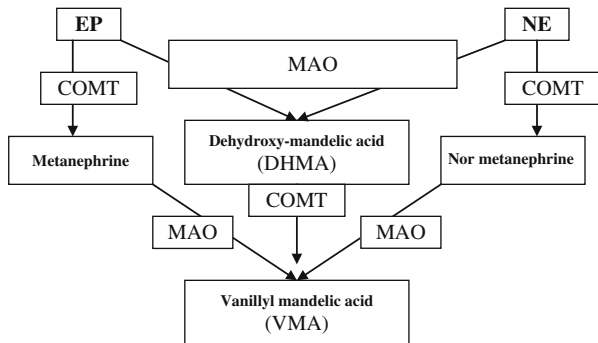


FIG. 11.13 Catecholamine metabolism. MAO, monoamine oxidase; COMT, catecholamine O-methyl transferase; EP, epinephrine; NE, norepinephrine

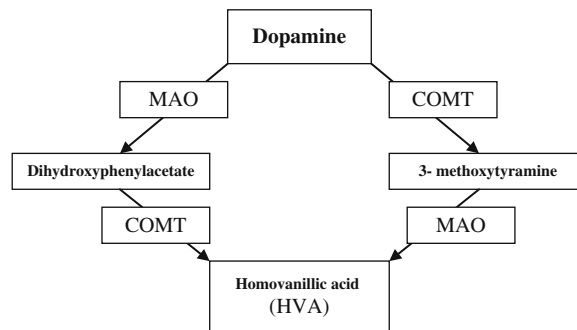


FIG. 11.14 Catecholamine metabolism

2. IMP and GMP then undergo degradation by nucleotidase and phosphorylase enzymes. The end result of the process is *hypoxanthine* and *guanine*.

• *Adenosine deaminase (ADA) deficiency*: Results in severe combined immunodeficiency (SCID). These

patients suffer from accumulation of 2'-deoxyadenosine 5'-triphosphate (*dATP*) in their RBCs, which in turn inhibits *ribonucleotide reductase*.

• *Notes*:

1. Deficiency of phosphorylase leads to T cell dysfunction.
2. Xanthine oxidase normally converts *xanthine* to *uric acid*, and is inhibited by allopurinol. Allopurinol is used in cases of chronic gout to decrease uric acid production, and hence decrease the gouty arthritis.

TABLE 11.5 Vitamins and minerals.

Vitamin	Properties	Deficiency
Vitamin A	<ul style="list-style-type: none"> • Fat soluble • Retinoic acid is used in cases of acne • Isotretinoin is a teratogenic form 	<ul style="list-style-type: none"> • Night blindness, <i>bitot spots</i>; dry skin and hair • Toxicity: increased intracranial pressure and joint pains
Vitamin D	<ul style="list-style-type: none"> • Fat soluble • D₂ is consumed in milk • D₃ is formed under the skin by UV stimulation • Active form is 1,25-dihydroxycholecalciferol • It increases calcium and phosphate absorption from intestine 	<ul style="list-style-type: none"> • Fatigue, muscle and bone weakness, and fractures • Toxicity: hypercalcemia manifested by altered mental status, polyuria and constipation; common in hyperparathyroidism and sarcoidosis
Vitamin E	<ul style="list-style-type: none"> • Fat soluble • Antioxidant function: protects RBCs from hemolysis 	<ul style="list-style-type: none"> • Fragile RBCs and higher risk of hemolysis
Vitamin K	<ul style="list-style-type: none"> • Fat soluble • Synthesized by intestinal flora • It forms gamma-carboxyglutamate, upon which some clotting factors depend for activation, namely <i>factors II, VII, IX and X, and proteins C and S</i> 	<ul style="list-style-type: none"> • Causes <ol style="list-style-type: none"> 1. Vitamin K antagonists, e.g., warfarin 2. Destruction of intestinal flora by long-term use of antibiotics • Coagulopathy with high bleeding tendency • Patients have <i>high prothrombin time (PT) and activated partial thromboplastin time (APTT)</i>
Vitamin B ₁ (thiamine)	<ul style="list-style-type: none"> • Water soluble • Thiamine pyrophosphate is a cofactor for two reactions: <ol style="list-style-type: none"> 1. Oxidative decarboxylation of keto acids 2. Transketolase of hexose monophosphate (HMP) shunt 	<ul style="list-style-type: none"> • Two important deficiency syndromes: <ol style="list-style-type: none"> 1. Beriberi: polyneuropathy and congestive heart failure 2. Wernicke-Korsakoff syndrome: triad of <i>encephalopathy, nystagmus, and ataxia</i>; Korsakoff is manifested by <i>anterograde amnesia and confabulations</i>

TABLE 11.5 (continued)

Vitamin	Properties	Deficiency
Vitamin B ₂ (riboflavin)	<ul style="list-style-type: none"> • Water soluble • It is a cofactor in oxidation and reduction reactions forming flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) 	<ul style="list-style-type: none"> • Angular stomatitis • Cheilitis • Corneal vascularization
Vitamin B ₃ (niacin)	<ul style="list-style-type: none"> • Water soluble • It is a cofactor in oxidation and reduction reactions forming nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) • It inhibits lipolysis, so used in type II hyperlipidemia to <i>increase HDL</i> and decrease LDL and VLDL. • Side effects: <i>Facial flushing and pruritus</i> 	<ul style="list-style-type: none"> • Pellagra triad: <ol style="list-style-type: none"> 1. <i>Diarrhea</i> 2. <i>Dermatitis</i> 3. <i>Dementia</i> • Dermatitis of pellagra is mainly on the face and neck arranged in a <i>necklace like</i> distribution
Vitamin B ₅ (pantothenic acid)	<ul style="list-style-type: none"> • Water soluble • It is the provider of coenzyme A (CoA) 	<ul style="list-style-type: none"> • Rash and diarrhea
Vitamin B ₆ (pyridoxine)	<ul style="list-style-type: none"> • Water soluble • Forms pyridoxal phosphate, which is essential for transamination and decarboxylation reactions 	<ul style="list-style-type: none"> • Peripheral neuropathy • Hyperexcitability and seizures • Causes: <ol style="list-style-type: none"> 1. <i>Isoniazid (INH)</i> 2. Oral contraceptive pills (OCPs)
Vitamin B ₁₂ (cobalamin)	<ul style="list-style-type: none"> • Water soluble • Stores in the liver last for at least 5 years • Absorbed in the ileum, and presence of intrinsic factor is essential for absorption • Cofactor for homocysteine and methylmalonyl CoA reactions 	<ul style="list-style-type: none"> • Macrocytic hyperchromic anemia • Subacute combined degeneration (SCD) • Causes: <ol style="list-style-type: none"> 1. Vegetarians 2. Malabsorption 3. Infestation e.g., <i>diphyllobothrium latum</i> 4. Lack of intrinsic factor = pernicious anemia 5. Lack of ileum
Vitamin C (ascorbic acid)	<ul style="list-style-type: none"> • Water soluble • It is needed for two important processes: <ol style="list-style-type: none"> 1. Intestinal iron absorption by keeping it in the ferrous state 2. Collagen synthesis by hydroxylation of proline and lysine 	<ul style="list-style-type: none"> • Caused by decreased intake, most pronounced in people not eating vegetables • <i>Vegetarians</i> → <i>vitamin B₁₂ deficiency</i> <i>Meat eaters</i> → <i>vitamin C deficiency</i> • Scurvy, manifested by: <ol style="list-style-type: none"> 1. Gingival hypertrophy 2. Easy bruising and bleeding 3. Poor healing
Folic acid	<ul style="list-style-type: none"> • Pteridine + glutamic acid + para-aminobenzoic acid (PABA) → folic acid • Dihydrofolate reductase converts folic acid to FH₄; this reaction is inhibited by methotrexate • FH₄ reacts with homocysteine to form methionine; this reaction is regulated by B₁₂ • Folic acid is essential for DNA and RNA synthesis 	<ul style="list-style-type: none"> • <i>It is the most common vitamin deficiency in the U.S.</i> • Macrocytic hyperchromic anemia • Neural tube defects if supplementation is not adequate during pregnancy
Biotin	<ul style="list-style-type: none"> • It is a cofactor for many carboxylation reaction: pyruvate → oxaloacetate • It is a cofactor for fatty acid synthesis reactions: acetyl CoA → malonyl CoA 	<ul style="list-style-type: none"> • Rash and diarrhea • Caused by ingestion of raw eggs, as the egg white contains <i>avidin</i>, which binds biotin, inhibiting its absorption
Fluorine	<ul style="list-style-type: none"> • Main source is drinking water 	<ul style="list-style-type: none"> • Deficiency: dental caries • Toxicity: chalky white patches on teeth and osteosclerosis
Zinc	<ul style="list-style-type: none"> • Normal dietary intake is 6 to 16 mg/day, only 20% of which is absorbed 	<ul style="list-style-type: none"> • Deficiency: hair loss, paronychia, rash • Toxicity: neurologic manifestations
Selenium	<ul style="list-style-type: none"> • Serves as an antioxidant 	<ul style="list-style-type: none"> • Deficiency: cardiomyopathy • Toxicity: hair loss, nail dystrophy
Copper	<ul style="list-style-type: none"> • It is a heavy metal 	<ul style="list-style-type: none"> • Deficiency: <i>Menkes' syndrome</i>; patients have <i>kinky sparse hair</i> • Toxicity: hemolysis

TABLE 11.6 Electrolyte imbalances and their effects.

Electrolyte imbalance	Effect
Hypocalcemia	<ul style="list-style-type: none"> • Neuromuscular hyperexcitability, twitching, and seizures • Peroneal sign: flexion of foot on tapping of peroneal nerve • Chvostek sign: contraction of facial muscles on tapping of facial nerve • Trousseau sign: carpal spasm on occlusion of the brachial artery with the sphygmomanometer cuff • Electrocardiogram (ECG): Q-T prolongation • Treatment: replacement and treat the cause
Hypercalcemia	<ul style="list-style-type: none"> • Causes: hyperparathyroidism or malignancy, which increases serum calcium either via osteolytic metastases or release of PTH-related peptide (treatment of malignancy-induced hypercalcemia: mithramycin or bisphosphonates) • Polyuria and constipation • Altered mental status and hyporeflexia • Tissue calcification • Osteitis fibrosa cystica • ECG: Short Q-T interval • Treatment: <i>fluid loading first</i>, then diuresis with furosemide (Lasix); treat cause
Hypokalemia	<ul style="list-style-type: none"> • Muscle cramps and weakness • Cardiac arrhythmia • ECG: depressed S-T segments and T waves + <i>prominent U waves</i> • Treatment: replacement and treat the cause
Hyperkalemia	<ul style="list-style-type: none"> • Cardiac arrhythmia • ECG: wide QRS and <i>tall peaked T waves</i> • Treatment: <ol style="list-style-type: none"> 1. Calcium chloride to protect the heart 2. Potassium exchange resins 3. Glucose and insulin: they shift K intracellularly
Hypomagnesemia	<ul style="list-style-type: none"> • Neuromuscular hyperexcitability • Common to see in <i>malnourished patients</i> and <i>alcoholics</i> • ECG: wide P-R, QRS and Q-T • Treatment: replacement
Hyponatremia	<ul style="list-style-type: none"> • Altered mental status and seizures • Common in postoperative patients, and due to diuretics • Treatment: <ol style="list-style-type: none"> 1. Fluid restriction 2. If failed, hypertonic saline and furosemide 3. Lithium and demeclocycline can also be used • Rapid correction of hyponatremia leads to <i>central pontine myelinolysis</i> • Rapid correction of hypernatremia leads to <i>brain edema</i>

Pyrimidine Synthesis

- *Steps:* It is most important to know the rate-limiting step (Fig. 11.20)

- *Orotic aciduria: Mechanism:* Deficiency of orotate phospho-ribosyl transferase (converts orotate to orotidine 5'-monophosphate (OMP)), and OMP decarboxylase (converts OMP to uridine 5'-monophosphate (UMP)). *Clinical picture:* Growth retardation, megaloblastic anemia resistant to treatment, and presence of orotic acid in the urine. *Treatment:* Uridine-rich diet.

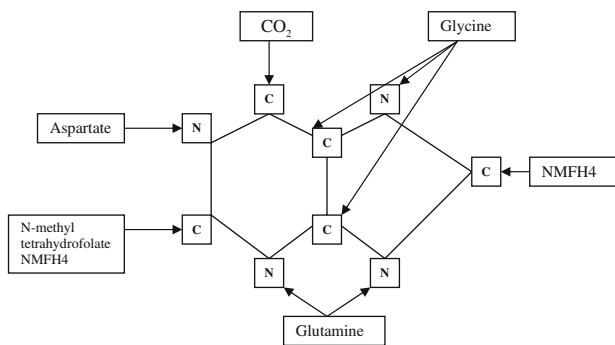


FIG. 11.15 Purine ring sources

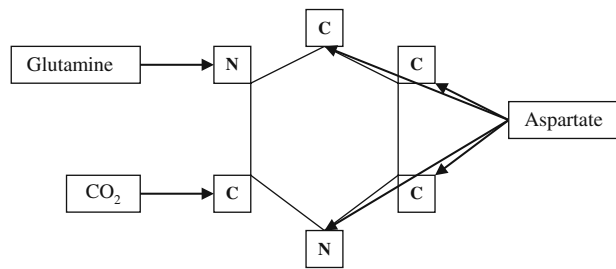


FIG. 11.16 Pyrimidine ring sources

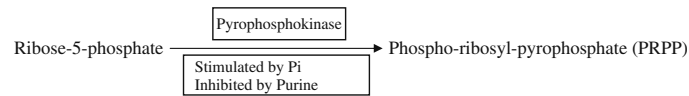


FIG. 11.17 Purine synthesis step 1

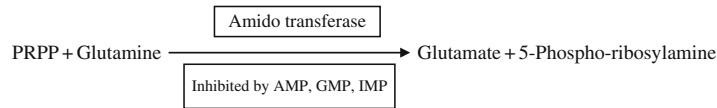


FIG. 11.18 Purine synthesis step 2; rate-limiting step of purine synthesis

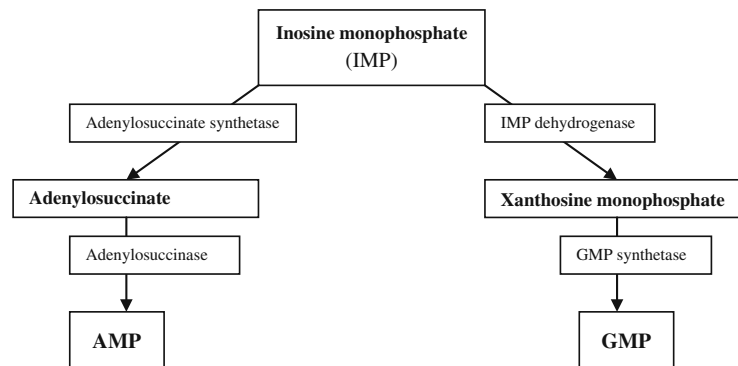


FIG. 11.19 Purine synthesis step 3. AMP, adenosine monophosphate; GMP, guanosine monophosphate

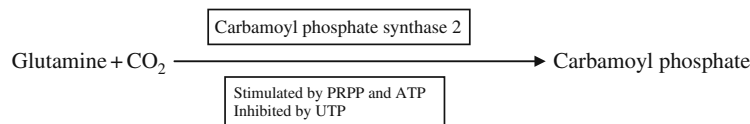


FIG. 11.20 Pyrimidine synthesis

- *Pyrimidine degradation:* Regulated by *phosphoribosyl transferase*. Note: *5-fluorouracil* inhibits the conversion of UMP to thymidine monophosphate (TMP).

DNA Synthesis (Replication)

- DNA unwinds into two separate strands via the *protein DNA helicase*.
- DNA replication begins at very specific sites known as *the consensus sequences*.
- DNA always replicates in the 5' to 3' direction, with a *replication fork* guiding the process.
- DNA untwisting and fork formation is regulated by *DNA protein A, helicase, and single-stranded DNA binding proteins (SSBP)*.
- *DNA Topoisomerase:* Supercoils in the DNA are relieved by:
 1. DNA topoisomerase I, e.g., *nuclease, ligase*. It *uncoils and relaxes* DNA supercoils. It acts *reversibly* and *does not require* ATP for activation.

2. DNA topoisomerase II, e.g., *gyrase*. It *breaks and seals* DNA strands. It uncoils positively charged coils, and *is inhibited by quinolones*.

- *Steps:*

1. DNA polymerase begins the copying process from the 3' end toward the 5' end; however, the chain still grows in the 5' to 3' direction.
2. During the copying process, small fragments are left behind by the *primase* enzyme, known as *Okazaki fragments*.
3. An essential requirement for DNA replication is an *RNA primer*. RNA primer is a short double-stranded structure with an -OH group. DNA polymerase III helps *elongate the chain* on the -OH end of the primer.
4. Once an elongated strand reaches the next RNA primer, the following steps take place:

- 3'-5' exonuclease: Proofreads the newly synthesized DNA strand removing mismatched base pairs.
 - DNA polymerase I: Removes the RNA primer from the strand and fills the gap.
 - DNA topoisomerase I: Also known as *DNA ligase*; it seals newly synthesized DNA fragments.
5. The DNA is further packed in a core of histones—H2A, H2B, H3, and H4—with the *H1* wrapped on the surface. Note that histones are rich in *arginine* and *lysine*.
- **DNA repair:** Exposure to ultraviolet rays can cause damage to DNA strands. Repair of damaged DNA is carried out in the following manner:
 1. The defect is recognized by *ultraviolet (UV) endonuclease*.
 2. A portion of the DNA including the defect is removed via *exonuclease*.
 3. *DNA polymerase I* fills the gap created by removal of the defective portion.
 4. Ends of the newly synthesized strands are sealed together by *DNA topoisomerase I*.
 - **DNA repair failure:** Failure to perform the DNA repair process, mainly due to deficiency of the *UV exonuclease* leads to accumulation of *pyrimidine dimers*, and hence *xeroderma pigmentosum* ensues. Another example of DNA repair failure is *Fanconi anemia*, which is one form of aplastic anemia in which patients *do not* have radius bones or thumbs.

RNA Synthesis (Transcription)

- **Types of RNA:**
 1. Ribosomal RNA (rRNA): Exist in ribosomes, e.g., rough endoplasmic reticulum
 2. Messenger RNA (mRNA): Has *7-methylguanosine cap* on its 5' end, and a *poly-A tail* on its 3' end. mRNA is the *largest RNA* in size and its function is to *transport codes*.
 3. Transfer RNA (tRNA): *It is the smallest RNA in size*. It looks like a *cloverleaf*, and has a *D loop*, *anticodon loop* plus a *CCA tail* on its 3' end.
- **Transcription at a glance:** It is carried out by RNA polymerases:
 1. RNA polymerase I: Synthesis of rRNA
 2. RNA polymerase II: Synthesis of mRNA and small nuclear RNA (snRNA)
 3. RNA polymerase III: Synthesis of tRNA

- **Steps:**

1. Transcription begins with the RNA polymerase at a specific site known as the *promoter region* (Pribnow box = TATAAT, or -35 sequence = TTGACA). The promoter region is recognized by *holoenzyme*, which is composed of *sigma factor* and *core enzymes*.
 2. Transcription starts at the promoter region, and proceeds in the *5' to 3' direction* until it reaches the *termination region*, where the process ends. Termination regions are recognized by *Rho factors* or *hairpins of RNA polymerase*. The hairpins base is rich in *guanine* and *cytosine*, and the rest is rich in *uracil*.
- **RNA repair:** Repair of RNA is not possible. However, damaged or unneeded groups inside the strands (introns) are removed by small nuclear ribonucleoprotein (*snRNP*). In systemic lupus erythematosus (SLE), patients have *antibodies against snRNP*.
 - **Notes:**
 1. Rifampin inhibits RNA polymerase.
 2. RNA polymerase II is inhibited by *amanitin of mushrooms*.

Protein Synthesis (Translation)

- **Steps:**
 1. Initiation: Begins at the *Shine Dalgarno sequence* (5'-AGG-AGG-3'), which is recognized by *initiation factor 2*. The most common initiation codon is *AUG*, which codes for *methionine*
 2. Termination: Codons are *UAA*, *UAG*, and *UGA*, which are recognized by *release factors*. At the end of the process, trimming of the amino acid chain is carried out by *endoprotease*.
- **Ribosomes:** They catalyze the process of protein synthesis as follows:
 1. A site: Binds *aminoacyl t-RNA*. This is where new amino acids join the chain.
 2. P site: Binds *peptidyl t-RNA*. This is where protein chain elongating occurs.
- **Protein chain elongation:** Energy-dependent process, which requires the following energy molecules:
 1. Two *ATPs*: For *t-RNA activation*
 2. Two *GTPs*: For t-RNA translocation
- **Mutations:**
 1. Silent mutation: When the DNA base sequence is changed, but the same amino acid is formed
 2. Missense mutation: The DNA base sequence codes for a different amino acid.

3. Nonsense mutation: The DNA sequence is changed to a stop codon.
 4. Frame shift mutation: If one or more nucleotides are added to or removed.
 5. Transition mutation: Substituting a purine with another purine, or a pyrimidine with a pyrimidine
 6. Transversion mutation: Substituting a purine with a pyrimidine or vice versa
- *Protein synthesis inhibitors:*
 1. Only two protein synthesis inhibitors work AT 30S subunit: Aminoglycosides and tetracycline.
 2. Streptomycin inhibits *initiation*, by binding to the *30S subunit of ribosomes*.
 3. Tetracycline inhibits *elongation* of the chain, by *inhibiting the addition of aminoacyl tRNA to rRNA*.
 4. Chloramphenicol inhibits *peptidyltransferase enzyme*, which normally transports the peptide chains from P site to A site of rRNA.
 5. Erythromycin and clindamycin inhibit *translocation*.
 6. Diphtheria toxin inhibits *elongation factor 2*.

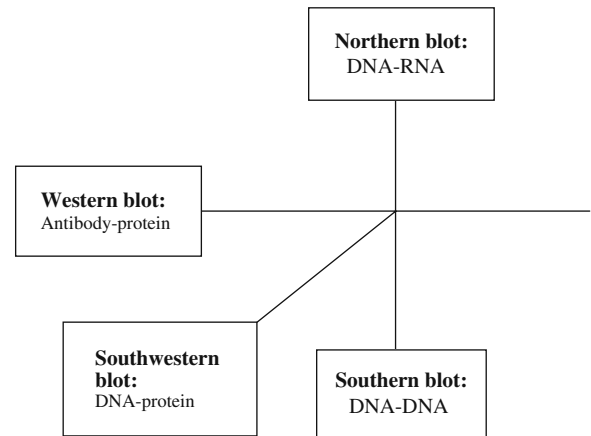


FIG. 11.21 Molecular biology plots and their respective hybridizations

Molecular Biology

- *Blot hybridizations:* See Fig. 11.21
- *Note:* Enzyme-linked immunosorbent assay (ELISA) depends on antigen antibody reactions.

Chapter 12

Behavioral Medicine

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Axes of Mental Disorders

- *I*: Clinical disorder, e.g., depression
- *II*: Personality disorder or mental retardation
- *III*: Medical disease, e.g., hypothyroidism
- *IV*: Environmental factors
- *V*: Global assessment of function (*GAF*)

Targets of Doctor–Patient Interview

- *Rapport*: Includes the following techniques:
 1. *Support*, e.g., “That must have been a horrible experience for you.”
 2. *Empathy*, e.g., “Oh, dear, you must be worried about the complications!”
 3. *Validation*, e.g., “I can understand why you felt the way you did. If I were in your place, I would have felt the same way too.”
- *Information*: Obtain information from the patient using the following techniques:
 1. *Silence*: You will get multiple cases on the USMLE about the fact that you should *never interrupt your patient* while he or she is talking. If the patient is very talkative, try to aim for *closed-ended questions, but never interrupt the patient*.
 2. *Open-ended questions*, e.g., “What brought you in today?”
 3. *Closed-ended questions*, e.g., “Do you have a cough?”
 4. *Reflection*, e.g., “Okay, so you said you fell and hit your head?”
 5. *Facilitation*, e.g., “What happened after you fell and hit your head?”
 6. *Recapitulation*, e.g., “Now that I have heard the entire story, let me summarize my understanding of what happened.”
- *Memory*: Three types of memory you need to test for:
 1. *Immediate*: Lasts for 5 minutes, and is controlled by *mammillary bodies*
 2. *Recent*: Lasts for 12 hours, and is controlled by the *hippocampus*
 3. *Remote*: Old, concrete information, e.g., name, place of birth

Important Definitions

- *Psychosis*: Loss of relation with the real world; characterized by *hallucinations*

- *Neurosis*: A mixture of anxiety, worry, and irritability
- *Mood*: The emotion that the patient feels *from within*, e.g., depressed, happy
- *Affect*: The emotion that the patient shows *from outside*, e.g., looks depressed
- *Concentration*: Tested by asking the patient to start with the number 100 and to count backward by sevens, i.e., 100, 93, 86, etc.
- *Attention*: Tested by observing the patient during the interview for how easily he/she gets distracted by surrounding stimuli
- *Cognitive ability*: Tested by asking, “How many states are in the U.S.?” or “How much is 5 multiplied by 5?”
- *Spatial ability*: Tested by asking the patient to draw a clock
- *Abstract reasoning ability*: The ability to understand metaphors, e.g., proverbs
- *Perseveration*: Patient thinks or talks about the *same* word or idea over and over again.
- *Flight of ideas*: Patient thinks or talks about *different, unrelated* words or ideas at a fast pace.
- *Delusion*: A false perception of *an idea*, e.g., “I think the FBI is watching me” or “I think that my co-workers are trying to set me up.”
- *Illusion*: A false perception of an *actual object*, e.g., a patient would look at a wire on the floor, and say, “Careful, that snake is too close to your foot.”
- *Hallucination*: Seeing, hearing, smelling, or feeling something that *does not exist*, e.g., a patient looks at the floor (*where there is nothing*) and tells you “Careful, there are spiders all over the floor” or “Jesus was talking to me yesterday and told me to try that drug. Nobody could hear him. Only I did.”
- *Idea of reference*: The belief that general ideas and concepts refer specifically to oneself, e.g., “I watched that movie on the TV last night, and it was talking about my life, it was full of details of my life, they were telling my story.”

Tests

- *Mini–Mental State Examination (MMSE)*: Used to assess *dementia*. A score of >25 (out of 30) is normal. A score of 20 to 25 indicates mild dementia, and a score of <20 indicates advanced dementia.
- *Intelligence quotient (IQ)*: $IQ = \text{Mental age} / \text{Chronological age} \times 100$. Culture plays a major role in affecting the IQ. Scoring:

1. *Normal*: 90 to 109, with standard deviation of 15
 2. *Borderline*: 70 to 89
 3. *Mental retardation*: Below 70
- *Personality tests*: Many, including the Minnesota Multiphasic Personality Inventory (MMPI) (566 true or false questions), Rorschach inkblot, sentence completion test, and Thematic Apperception Test (TAT)
 - *Neuropsychological tests*: Many, including Halsted battery (to localize brain lesions) and Nebraska test (to determine brain hemispheric dominance)
 - *Others*:
 1. Dexamethasone suppression test: Positive in cases of depression
 2. Serotonin: Low levels in cases of depression, alcoholism, and aggression
 3. Dopamine: Low level in Parkinson’s disease and high level in schizophrenia and chorea
 4. Na lactate intravenously or CO₂ inhalation: Induces panic attacks
 5. Lie detection test: Done using Na amobarbital (“truth serum”)
 6. Electroencephalogram (EEG): Normal in dementia and abnormal in delirium. Evoked EEG is used to detect cortical response to stimuli.

- *Preschooler (>2.5 to 6 years)*: Shows many important phenomena:
 1. Control over bowel function: By age 4. Encopresis (loss of control over bowels) could be due to many reasons, most common of which is voluntary retention with overflow.
 2. Control over bladder function: By age 5. Enuresis (loss of control over bladder) is best treated using a buzzer or imipramine. Functional enuresis is more frequent among boys, and occurs just before awakening in the morning.
 3. *Band-Aid phase*: During these few years, the child is overwhelmed by any minor illness or injury, so surgery is to be avoided during these years.
 4. They have no understanding of the meaning of death.
- *Schoolchild (6 to 11 years)*: By this age, the child can:
 1. Understand the meaning of death
 2. Undergo surgery and hospitalized if needed, without serious consequences
- *Adolescent*: By age 11 in girls and 13 to 14 in boys
- *Stages of development*: Also classified as shown in Table 12.1, as follows:
 1. Freud: According to the organ through which pleasure is achieved
 2. Piaget: According to learning processes (cognitive)
 3. Erikson: According to achievement of certain goals (psychosocial)

Age

Child Development

- *Infant (0 to 15 months)*:
 1. Sticks to the mother at all times. If separated from mother at this age, separation anxiety, anaclitic depression, and failure to thrive may ensue.
 2. *Stranger anxiety*: Most pronounced during the first year of life.
- *Toddler (>15 months to 2.5 years)*: Shows two important phenomena:
 1. *Rapprochement*: Separates from mother voluntarily, but returns to her intermittently for reassurance
 2. *Object permanence*: Understanding that humans and objects still exist even though they are not directly visualized

Aging

- Average life expectancy for Americans at this time is 75 years, with more predominance in Caucasians compared to African Americans, and in females compared to males (7 years difference)
- By the year 2020, about 15% of the people living in the United States will be elderly (≥65 years).
- Depression is very common among the elderly, and is commonly misdiagnosed as dementia, hence called *pseudodementia*. So when you see any elderly patient on the USMLE with what looks like dementia, make sure to look first for any symptoms indicating depression.

TABLE 12.1 Stages of human development.

Stage	Freud	Piaget	Erikson
Infant	Oral	Sensorimotor	Trust
Toddler	Anal	Sensorimotor	Shame and doubt
Preschooler	Phallic	Preoperational	Intent and guilt
Schoolchild	Latent	Concrete	Industry and inferiority
Adolescent	Genital	Abstract (formal)	Personality, intimacy, and generosity

- The elderly have low brain weight, increase in the size of ventricles and sulci, along with decreased cerebral blood flow; however, their *IQ does not change*.

Development Disorders

Attention Deficit Hyperactivity Disorder (ADHD)

- *Clinical picture:* As the name implies, the child *cannot pay any attention* and is *hyperactive*. Classic presentation is for a child who scores poorly in school, cannot follow instructions, is easily distracted, and often interrupts his teacher and classmates.
- *Treatment:* *Amphetamine* or *methylphenidate*. Side effects of these medications include insomnia, tics, night terror, and choreiform movements.
- *Notes:*
 1. Incidence of mental retardation in patients with ADHD is *10% to 20%*
 2. There is a genetic *component* in ADHD, which is strongly associated with *obsessive-compulsive disorder (OCD)* and *Tourette's syndrome*.

Conduct Disorder

- *Clinical picture:* A child who acts like a “thug.” A classic presentation is for a child who *physically assaults other kids, destroys property, lies, and steals from others*.
- *Treatment:* Psychotherapy and family therapy
- *Notes:*
 1. If this disorder persists beyond 18 years of age, it is known as *antisocial personality disorder*.
 2. Conduct disorder is frequently associated with a history of abuse by addicted parents.

Oppositional Defiant Disorder

- *Clinical picture:* A child who acts like a “thug” but only *toward authority figures*. A classic presentation is for a child who gets along with his classmates very well, but is impolite to his teachers or parents. Also carries a history of abuse.
- *Treatment:* Psychotherapy and family therapy

Autistic Disorder

- *Clinical picture:*
 1. A child who *refuses to talk or move*, and is highly nervous and anxious, *especially when anybody tries to help or touch him*

2. Characteristic features include *repetitive and destructive behavior*, e.g., *continuous spinning, repetitive head slamming against the wall*

- *Asperger disorder:* Looks just like autistic disorder, *with the exception that patients communicate and move normally*
- *Selective mutism:* A disorder that is common in *girls*, misdiagnosed as *shyness*. The child is essentially normal, but does not talk in certain situations, such as in front of strangers.

Rett Disorder

- *Clinical picture:* After a period of normal development, the child starts to *lose already acquired skills*.
- *Note:* Almost always occurs in *girls*. Another form of the disease that presents similarly in boys is called *childhood disintegrative disorder*.

Tourette's Disorder

- *Mechanism:* Dysfunction in the regulation of *dopamine* in *caudate nucleus*
- *Clinical picture:* It is more common in *boys*, where the child has *multiple motor tics* and *at least one vocal tic*. It could be transient (<1 year) or chronic (≥ 1 year).
- *Treatment:* *Haloperidol*; *treatment is lifelong*
- *Note:* There is a strong genetic link among *Tourette's, ADHD, and OCD syndromes*.

Separation Anxiety Disorder

- It is fear of loss of attachment figures.
- *Clinical picture:* A typical presentation is for a child who is refusing to leave home right after the family moved to a new house.
- *Prognosis:* These patients usually develop *agoraphobia* later in life.
- *Treatment:* Supportive by gradual acclimatization to the new situation

Abuse

Child Physical Abuse

- *Clinical picture:* *Shaken baby syndrome*, which is characterized by *retinal hemorrhage and detachment* and *spiral bone fractures*
- *Treatment:* Hospitalize the patient and *contact social services*.

Child Sexual Abuse

- Most common age involved is 9 to 12
- *Clinical picture:* Suspect sexual abuse in any child with recurrent urinary tract infections (UTIs), or with *Phthirus pubis* in eyelashes.
- *Note:* The abuser is usually a very close family relative or friend.
- *Treatment:* Contact social services.

illegal and that she has the right to seek help by contacting social services.

- *Sexual assault:* It is not a requirement that penetration or ejaculation must have been involved to call it an assault. Complication: *Posttraumatic stress disorder (PTSD)*
- *Statutory rape:* Any sexual intercourse with someone younger than 18 years of age falls under this category, regardless it was consensual or not.

Others

- *Elder abuse:* The abuser is mostly the spouse or caregiver. Treatment: Contact social services.
- *Partner abuse:* Whether physical or sexual, it starts with tension building up, followed by battery and ending up with apology. Treatment: Do not contact social services; only advise the patient that abuse is

Drug and Alcohol Abuse

- Abuse is an abnormal use of a substance that leads to some sort of impairment. *Dependence, on the other hand, is an abuse combined with tolerance and withdrawal symptoms.*
- *Types and features (Table 12.2)*

TABLE 12.2 Most commonly abused drugs and their effects.

	Transmitter	Clinical picture
Cocaine	Dopamine	<ul style="list-style-type: none"> • Mechanism: vasoconstriction • Tactile hallucinations, e.g., sensation of bugs crawling under the skin • Chest pain: due to coronary vasospasm • Perforated nasal septum • Sympathetic hyperactivity: hypertension, tachycardia, and dilated pupils • Withdrawal: crash syndrome (depression, fatigue and somnolence), followed by dysphoria and finally extinction • Cocaine metabolite: benzoylecgonine • Note: cocaine is the only anesthetic that causes vasoconstriction
Alcohol	GABA	<ul style="list-style-type: none"> • Euphoria initially, followed by depression • Wernicke's encephalopathy: encephalopathy, nystagmus, and ataxia; due to thiamine (B₁) deficiency affecting mammillary bodies • Korsakoff syndrome: amnesia (antero- and retrograde) and confabulations; due to thiamine (B₁) deficiency affecting the hippocampus • Withdrawal: delirium tremens (DTs) in 2 to 5 days, where patient has delirium, tremors, and possibly seizures; Treatment: benzodiazepine (BDZ) is the first step (best is chlordiazepoxide) plus folic acid, thiamine (B₁), and pyridoxine (B₆) • Alcohol intoxication level: 0.08% to 0.15% • If patient has blood alcohol level >0.10% and show no symptoms of intoxication, suspect tolerance • Blood alcohol level >0.4% is fatal • Chronic alcoholism causes impotence, decreased sperm count, and testosterone level
LSD (lysergic acid diethylamide)	Serotonin	<ul style="list-style-type: none"> • Mechanism: An agonist of serotonin 5-HT₁ and 5-HT₂ receptors • Dreamy-like state, e.g., patient thinks he is flying • Visual hallucinations • Bad trips: Panic attacks • Flashbacks: Patient experiences the symptoms he develops in the absence of the drug • Reversal: haloperidol
Marijuana (cannabis)	Serotonin	<ul style="list-style-type: none"> • Depersonalization • Loss of time perception • Conjunctival redness • Increased appetite ("the munchies") • Used clinically to treat chemotherapy induced emesis

TABLE 12.2 (continued)

	Transmitter	Clinical picture
PCP (angel dust)	Serotonin	<ul style="list-style-type: none"> Blocks N-methyl-D-aspartate (NMDA) receptors, which leads to inhibited uptake of norepinephrine, serotonin, and dopamine Hyperthermia, hypersalivation, aggression, and violent behavior Treatment: phentolamine, diazepam, haloperidol, and acidification of urine
Methylxanthines (caffeine)	Dopamine	<ul style="list-style-type: none"> Mechanism: Inhibit phosphodiesterase, which in turn leads to elevated cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) levels; this leads to positive inotropic and chronotropic effects Insomnia, alertness, and diuresis Side effects: increases gastric HCL production Precautions: it can cross placenta and is found in breast milk Withdrawal: headache, sleepiness, and lethargy
Amphetamine	Dopamine	<ul style="list-style-type: none"> Mechanism: it decreases the appetite and increases alertness Indications: ADHD and narcolepsy Side effects: psychosis, insomnia and GI upset Reversal: chlorpromazine
Nicotine	Dopamine	<ul style="list-style-type: none"> Mechanism: inhibits the ganglia after an initial phase of stimulation Side effects: <ol style="list-style-type: none"> Low dose: euphoria and increased alertness High dose: depression of the respiratory center Withdrawal: irritability, headache, and craving Metabolite of nicotine: cotinine

Sleep

Sleep Waves and Stages

- Patient awake, relaxed, and eyes closed: *Alpha waves*
- Patient awake, concentrating, and eyes open: *Beta waves*
- *Stage 1 of sleep: Theta waves*
- *Stage 2 of sleep: Sleep spindles and K complexes; 45% of sleeping time*
- *Stages 3 and 4 of sleep: Delta (slow) waves. Sleep walking and nocturnal enuresis occur during these two stages.*
- *Rapid eye movement (REM) sleep:*
 1. Alpha, beta, and theta waves combined, giving a *sawtooth appearance* to the sleep waves
 2. *Dreams, nightmares, sympathetic stimulation, erection, and complete skeletal muscles relaxation* occur during this stage.
 3. *REM rebound* occurs to compensate for missed REM on the previous sleep cycle.
 4. After you fall asleep, the cycle goes as *90 minutes of normal sleep* alternating with *10 minutes of REM sleep*, and the cycle keeps repeating itself.
 5. REM sleep is regulated by *acetylcholine*, and is suppressed by *monoamine oxidase inhibitors (MAOIs)*.

Regulation of Sleep

- *Serotonin and melatonin:* Induce sleep
- *Dopamine and norepinephrine:* Inhibit sleep. *That is the reason antipsychotics improve sleep.*

Sleep Disorders

- *Narcolepsy:* Uncontrollable *attacks of falling asleep*. Some key symptoms in these patients are:
 1. *Cataplexy:* Generalized loss of muscle tone; induced by any form of excitement, e.g., laughing, cough, orgasm
 2. *Hallucinations:* Either before falling asleep (*hypnagogic*), or upon waking up (*hypnopompic*)
- *Sleep terror:* This disorder occurs during *delta wave sleep (not the REM like all other dreams and nightmares)*. Patient is screaming in bed with what looks like a bad nightmare; however, it is *very hard to get him/her to wake up*. After waking up, the patient has *no recollection of the incident*. It is an indicator of possible *temporal lobe epilepsy* later in life.
- *Kleine-Levin syndrome:* Episodes of *hypersomnia and hyperphagia*, each lasting *1 to 2 weeks*
- *Sleep changes during depression:*
 1. *Normal sleep onset*
 2. Frequent awakenings during the night and in the early morning (*terminal insomnia*)

3. REM sleep: *Short latency*, and *high frequency*, which tends to decrease throughout the night

Delirium

- **Definition:** Delirium is a cyclic disorder in which the patient fluctuates in and out of *consciousness*, more commonly toward nighttime, also called *sundowning phenomenon*.
- **Population:** It is very common to see delirium in elderly patients admitted to the hospital, specifically to the intensive care unit (ICU) (*ICU psychosis*), where almost *one third* of the patients would suffer some degree of delirium.

Clinical Picture

- Altered level of consciousness
- Disorientation: *First to time*, then to place, and lastly to person
- *Visual* hallucinations
- EEG changes

Treatment

- **Treat the cause.** Delirium in the elderly is caused by *drugs, infections, or metabolic derangement (DIM)*.
- **Drug of choice:** *Haloperidol*

Schizophrenia

- It is a cycle of symptoms that lasts at least *6 months* at a time, more common in the *winter months*, and in *young adults (20 to 40 years)* of *low social class*; however, it can happen in any age and in any social class.
- **Mechanism:** Unknown, but the fact that it is more prevalent in the cold months suggest a possible link to a *viral infection*.
- **Personality:** Most patients already have *borderline personality*, characterized by *splitting, mood swings*, and suicidal attempts.
- **Risk:** 50% in monozygotic twins
- **Forms:** Paranoid, disorganized, or *catatonic (waxy flexibility)*
- **Duration:**
 1. Less than 1 month: *Brief psychotic disorder*
 2. One to 6 months: *Schizophreniform disorder*
 3. More than 6 months: *Schizophrenia*

Pathology

- **Transmitters:** Decreased gamma-aminobutyric acid (GABA) neurons in *hippocampus*
- **Hormones:** Low serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH)
- **Positron emission tomography (PET) scan:** Shows *decreased glucose uptake* by *frontal lobes*, and *hyperactive dopamine-loaded basal ganglia*
- **EEG:** *Decreased alpha* and *increased theta and delta* waves with *epileptiform activity*

Clinical Picture

- **Prodrome:** Patient is calm, and only shows some change in interests, e.g., sudden interest in politics, religion, or languages.
- **Psychosis:** Characterized by the following:
 1. **Hallucinations:** Mainly *auditory (delirious patients have visual ones)*
 2. **Thought blocking:** Patient moves his lips frequently without vocalizing
 3. **Neologism:** Patient makes up new words
 4. **Loose association:** Changing subjects quickly while talking
 5. **Tangentiality:** When you ask the patient a question, he would start the answer in a well-organized way, but then slides away from the subject into something else.
 6. **Echolalia:** Increased alertness and response to sounds, often compared to *parrots*.
- **Residual phase:** *Social withdrawal*

Types of Symptoms

- **Positive:** As above; *patients respond* to *typical antipsychotics*.
- **Negative:** Patient does not have typical presentation as discussed above. He is rather blunt and withdrawn at all times. Patients in this category *do not respond* to typical antipsychotics; however, they respond only to *atypical antipsychotics*, e.g., *clozapine* and *risperidone*.
- **Notes:**
 1. **Schizophrenia of childhood:** *More common* and *presents at an earlier age* in *males* compared to females
 2. **Schizoaffective disorder:** Schizophrenia plus a mood disorder, e.g., depression
 3. **Orbitofrontal syndrome (pseudopsychopathic):** *Disinhibited behavior, emotional lability, euphoria, and jocular affect*

Mood Disorders

Major Depressive Disorder

- **Mechanism:** Depletion of serotonin and norepinephrine
- **Best screening:** Ask the patient if he or she is depressed.
- **Clinical picture:** At least five of the following:

S: Sleeping problems

I: Loss of interest, also called *anhedonia*, and “*feeling worthless*”

G: Guilt feelings

E: Lack of energy

C: Lack of concentration

A: Change in appetite; increased or decreased

P: Psychomotor retardation and agitation

S: Suicidal ideation, which occurs in 60% to 70% of patients; however, only 15% actually do it. Women more commonly have suicidal ideas and plans than men; however, men more commonly are successful in committing suicide than women.

- **Concordance rate:** 70% in monozygotic twins, 20% in dizygotic twins
- **Treatment:** selective serotonin reuptake inhibitors (SSRIs) (*first-line treatment*) or tricyclic antidepressants (TCAs)
- **Notes:**
 1. Most antidepressants take 3 to 6 weeks to be fully effective, so do not make any changes in dosing of medication before 6 weeks from starting the medication.
 2. After initiation of therapy, it is very important to frequently follow up on the patient, as *antidepressants might give the patient enough energy to commit suicide*.
 3. *Electroconvulsive therapy (ECT)* is only indicated for severe depression that is resistant to treatment. *Side effects of ECT:* Retrograde amnesia that resolves gradually over 6 months. *Contraindication to ECT:* High intracranial pressure, e.g., tumor, bleeding, hydrocephalus.
 4. Patients with suicidal ideation must be admitted (voluntarily or involuntarily) to a psychiatric ward. Involuntary admission must be certified by *two physicians*. Risk factors for suicide: Depression, male gender, lack of spouse, alcoholism, and most importantly a *previous suicidal attempt*.
 5. Patients with homicidal ideation must be admitted (voluntarily or involuntarily) to a psychiatric ward. Also, the police and the potential victim should be contacted (based on the *Taras-off legal decision*).

6. *Dysthymia:* Patient with depressed mood for at least 2 years (“I just feel down”), but does not have any of the major depression criteria above
7. *Double depression:* Major depression episode followed by dysthymia. Treatment: *MAOI*.
8. *Atypical depression:* Depression with severe anxiety. Treatment: *MAOI*.
9. *Cyclothymia:* Patient with *hypomanic mood for at least 2 years (patient feels hypomanic)*, but does not look manic, as described below.
10. *Postpartum blues* is a *depressed mood* that occurs during the *first week* after labor; however, *postpartum depression* is a *major depressive disorder* that does not start until at least 1 month after labor (10% of women suffer from that).

Bipolar Disorder

- **Duration of symptoms:** At least 3 months
- **Types:**
 1. Type I: Depression alternating with *mania*
 2. Type II: Depression alternating with *hypomania*
- **Clinical picture:** During manic episodes, the patient feels *overjoyed*, goes out on *shopping sprees*, has *flight of ideas*, and has a strong feeling of *grandiosity*, e.g., “I won’t talk to a clerk about my application, people like me talk to CEOs directly.”
- **Risk:** 75% in monozygotic twins
- **Treatment:** *Mood stabilizers*, as follows:
 1. Lithium: Side effects include *teratogenicity (Ebstein anomaly)*, *toxicity*, *hypothyroidism*, and *nephrogenic diabetes insipidus*. Therapeutic lithium level: 0.6 to 1.2 mEq/L. Lithium toxicity: Vomiting, diarrhea, blurred vision, nystagmus, and tremors.
 2. Carbamazepine: Side effects include *syndrome of inappropriate secretion of antidiuretic hormone (SIADH)*, and *Stevens-Johnson syndrome*
- **Note:** Theories suggest a link with X chromosome

Personality and Pain Disorders

Personality Disorders

- **Paranoid:** Multiple delusions and suspicions, e.g., “I think everybody is trying to set me up at work because I am smart.”
- **Borderline:** Mood swings, stormy relationships, and *splitting*, e.g., “When I was at the hospital, all the nurses on the 7th floor were horrible, but the rest were really good.”

- *Passive aggressive: Procrastination* is the key finding. Patients show enthusiasm to whatever you suggest, but then *passively resist* doing it and they end up being aggressive when confronted; e.g., You suggest HIV testing to a patient, and he shows enthusiasm that he should have it done, but he comes back one month later without having the test done, and when you ask him, he just gets angry and flustered and says, “Well, I called the lab and they just did not answer the phone.”
- *Histrionic*: Seductive provocative personality. If you see a patient who is dressed and acting like a porn star, you know what to think!
- *Narcissistic: Grandiosity*; they believe they are better than everybody else. Do not confuse this with the grandiosity of mania, as the latter is a short-term episodic disorder, but narcissism is a lifelong *personality disorder*.
- *Avoidant*: Avoids getting involved in any activity or relationship for *fear of rejection*.
- *Dependent*: Frequently depends on someone else for decisions and actions

Pain (Somatoform) Disorders

- *Somatization (Briquet’s syndrome)*: Patient presents with at least *four pain symptoms: two gastrointestinal (GI) related, one sexual, and one neurologic*. (And yes, in the exam, you have to count.)
- *Body dysmorphic disorder*: The patient fixates on one *normal* part of her body with a complete belief that it looks wrong, e.g., a model comes to your clinic every week complaining about how big her nose is.
- *Conversion disorder*: It is a subjective, functional disturbance induced by exposure to a certain emotional event, e.g., a patient who lost her vision for one hour when she found out she failed an exam. These patients do not seem concerned about the functional disturbance; this is known as *La belle indifference*.
- *Hypochondriasis*: The patient exaggerates mild symptoms, insists there is something wrong, and demands a workup. He spends his time seeing different doctors (“*doctor shopping*”). As an example, a patient has seen 15 doctors in the last 6 months for his headaches. He is convinced he has a brain tumor when the brain imaging and clinical scenario are consistent with typical tension headaches.
- *Pain disorder*: A patient who has *unexplainable pain*, e.g., a patient who complains her arm hurts, but the workup is normal. *Similarly, if a patient complains of an unexplainable symptom (not pain),*

it is called undifferentiated somatoform disorder, e.g., a patient who complains of shortness of breath, but the workup is normal.

- *Factitious disorder (Munchausen syndrome)*: Patient fakes different symptoms, just for the sake of getting *attention*. These patients *are willing* to take medications and undergo numerous surgeries. In *Munchausen by proxy*, one person fabricates the symptoms of another person, e.g., a mother takes her child from one clinic to another, reporting numerous symptoms that the child has, but the workup is normal.
- *Malingering*: Patient fakes different symptoms, just for the sake of getting a *certain benefit*, e.g., time off, financial compensation. In contrast with Munchausen patients, these patients are *not willing* to take medications or undergo surgeries.
- *Gain*: Patients complain of pain for two types of gain:
 1. Primary: They express their emotional problems, but in the form of an illness.
 2. Secondary: Getting attention and tender loving care (TLC)
- *Treatment*: Best treatment for all the above disorders is *psychotherapy and group therapy*.

Defense Psychology

Defense Mechanisms

- *Displacement*: Displacing a certain emotion from one unacceptable situation to a more acceptable one; e.g., a lawyer who just had an argument with his domineering wife goes to his office and acts rude to his female secretary.
- *Acting out*: Irresponsible action induced by a certain emotion, usually done by teenagers, e.g., a 16-year-old who just had an argument with her mother goes to her room and destroys the TV set with a baseball bat.
- *Altruism*: Doing good things to avoid certain negative or guilt feelings, e.g., a hit man who murdered someone last week donates \$1000 to charity.
- *Identification*: Subjectively inheriting a certain behavior, e.g., a person who, as a child, was mistreated by his parents persists in mistreating his own children in the same way.
- *Fixation*: The permanence of a childish attitude, e.g., an adult watching cartoons every day.
- *Projection*: Ascribing one’s unacceptable feelings to others, e.g., a person who is angry with his

co-worker accuses his co-worker of being angry with him.

- *Rationalization*: Attempting to rethink a certain event to make it seem less serious, e.g., after failing an exam for licensure in Canada, the engineering student says, “Well, that’s okay, I never really liked Canada that much anyway.”
- *Reaction formation*: Attempting to hide certain unacceptable feelings by doing or saying something very acceptable, e.g., a worker is very angry with his boss for changing his schedule, but when he sees the boss, he says, “Hey, boss, I like your tie.”
- *Sublimation*: Expressing an unacceptable emotion in an acceptable situation, e.g., a student who is furious about failing his exam goes to the gym and practices boxing.
- *Suppression*: Deliberately not thinking about unacceptable emotions, e.g., a doctor who has a phobia about female genitalia puts his feelings aside to examine a female patient who complains of vaginal discharge.
- *Repression*: Completely forgetting an unacceptable emotion, e.g., a student who is extremely stressed about an examination experiences a period of unconcern and does not even recall when he is scheduled to take the test.
- *Regression*: Adopting a child’s attitude to escape a certain unacceptable emotion, e.g., a 55-year-old patient hospitalized for a heart attack wants his mother to stay with him in the room, and then he wets the bed during sleep.
- *Intellectualization*: An unconscious avoidance of an unacceptable emotion by using logic or focusing on the minutiae of the situation, e.g., a surgeon explains to his co-workers in detail how he was recently diagnosed with terminal lung cancer, yet he is talking casually about it without any emotion, using his case as a routine medical discussion.
- *Isolation of affect*: Failure to express emotions, e.g., the same surgeon as above explains to his co-workers about how his father died of the same cancer and the details of the days before his death, yet not showing any emotion that fits this dramatic story.

Dissociation

- *Definition*: A group of disorders that occur as a defense mechanism against fear or severe underlying anxiety
- *Dissociative amnesia*: Patient cannot recall painful events, e.g., a man who does not remember anything about a motor vehicle accident that killed his wife and children.

- *Dissociative fugue*: Patient cannot recall a change in identity and location, e.g., a woman who once lived in England and then moved to the U.S. gives her history to her physician and has no recollection of having lived in England or of having moved.
- *Dissociative identity*: A patient who has more than one personality, but none of the personalities is aware of the others, e.g., a librarian who is summoned to court for stripping in public and attempting prostitution, which she has no recollection of, states that there must be some misunderstanding, even when she is shown pictures of herself naked in the street.
- *Depersonalization*: Patient believes he lives outside of his own body and can watch himself.
- *Treatment*: For all above conditions, treatment is *hypnosis and psychotherapy*.

Eating Disorders

- Common among *females, adolescents, and persons under stress*.
- At least *30%* of the American population falls in the obese range, and *20%* in the overweight range.

Anorexia Nervosa

- *Weight loss*: Loss of at least *15%* of body weight
- *Eating behavior*: Starvation
- *Personality*: perfection seeking personality, with good scores in school and *fear of getting fat*
- *Sexual*: Amenorrhea and absence of any interest in sex
- *Metabolic*: Metabolic acidosis, hyperlipidemia, and osteoporosis
- *CBC*: Anemia and leucopenia
- *Skin*: *Lanugo* (downy hair)
- *GI*: Melanosis coli (pigmentation of colon wall), due to *overuse of laxatives*

Bulimia Nervosa

- *Weight loss*: Normal body weight or even overweight
- *Eating behavior*: Binges of eating followed by induced vomiting
- *GI*: Esophageal varices, parotid gland swelling, and eroded enamel of anterior teeth
- *Signs of induced gagging*: Scars and marks on the dorsum of hands

Treatment

- *Anorexia nervosa*: Amitriptyline, cyproheptadine, or SSRIs, plus behavioral and family psychotherapy
- *Bulimia nervosa*: SSRIs, plus behavioral and family psychotherapy

Sex

Gender Identity and Role

- *Gender identity*: The child can identify his/her gender, i.e., male vs. female, which usually occurs around 3 years of age.
- *Gender role*: How the person acts, i.e., like a male or a female

Sex Cycle

- *Excitement*: Characterized by *erection* in males, and *tenting of uterus* in females
- *Plateau*: Enlarged inner part and contraction of outer part of the vagina
- *Orgasm*: Characterized by *ejaculation* in males and *uterine contraction* in females. *Contraction of anal sphincter* also occurs during this stage.
- *Resolution*: Muscle relaxation

Sexual Disorders

- Multiple; the most common are:
 1. Males: *Secondary impotence*, i.e., secondary to stress or anxiety
 2. Females: *Failure to orgasm*
- *Medically related sexual disorders*: Multiple, the most common are:
 1. Coronary artery disease (CAD): Patients have decreased libido due to *fear* of suffering another heart attack. If the patient can climb *two flights of stairs* or accommodate a heart rate of *130 bpm* without a problem, he can have sex.
 2. Diabetes mellitus (DM): Impotence and retrograde ejaculation
 3. Spinal cord injury: Retrograde ejaculation
- *Medication or drug-related sexual disorders*:
 1. Increased sexuality: Antidepressants, antipsychotics, marijuana, cocaine, amphetamine, and small amounts of alcohol
 2. Decreased sexuality: Excessive amounts or long duration of alcohol use.

- *Premature ejaculation*: A common sexual problem. Treatment: *SSRI*.
- *Hypoactive sexual desire*: Decreased sexual desire of one partner toward another
- *Sexual arousal disorder*: Absence of sexual arousal during intercourse
- *Sexual aversion*: A normal person who is not interested in sex. The patient is not homosexual and does not have any psychological problems.
- *Transvestite fetishism*: A man wearing women's clothing or vice versa
- *Frotteurism*: A man who anonymously attempts to touch or rub against women in an elevator or on mass transit.
- *Voyeurism*: A person who enjoys watching other people having sex
- *Sadism*: A person who enjoys *giving* physical pain to his partner during sex
- *Masochism*: A person who enjoys *receiving* physical pain during sex
- *Vaginismus*: A painful contraction of the outer part of the vagina, preventing sexual intercourse

Important Disorders

Obsessive-Compulsive Disorder (OCD)

- *Definition*: A disorder in which patients have recurrent thoughts and repetitive behaviors that *interfere* with their daily activities. They have *strong insight* (they know they have a problem) and *ego dystonia* (they view their behavior as inconsistent with the way they see themselves).
- *Mechanism*: *Obsession* with a certain idea, followed by a *compulsion* to do something
- *The most common form*: Obsessions with contamination, e.g., *frequent hand washing*
- *Treatment*: *SSRI* are the drugs of choice. Clomipramine (TCA with serotonin activity) is another option.
- *Note*: Ego dystonia of OCD is absent during childhood.

Panic Attacks

- *Mechanism*: Possibly genetic disease, more common in *females*
- *Common medical association*: *Mitral valve prolapse*
- *Clinical picture*: At least *two attacks a week*:
 1. Hyperventilation and tachycardia
 2. Chest pain, diaphoresis, tremors, and sense of *impending death*

3. Anxiety and fear of having attacks (*anticipatory anxiety*), especially when present in an open place (*agoraphobia*)

- *Treatment:*

1. Acute attacks: *Benzodiazepine*, e.g., *alprazolam*
2. Maintenance: *SSRI*

Phobia

- *Definition:* Irrational fear (without a cause) of something or of a situation
- *Examples:*
 1. Agoraphobia: Fear of open places; common in *panic attacks* and *separation anxiety*
 2. Acrophobia: Fear of *heights*
 3. Claustrophobia: Fear of *small closed places*
 4. Social phobia: Fear of social gatherings. Best treatment: *SSRIs*.
- *Treatment:* Behavioral and cognitive therapy

Posttraumatic Stress Disorder (PTSD)

- *Definition:* A stress disorder that follows a *life-threatening event*, e.g., war, motor vehicle accident, rape, assault
- *Clinical picture:* Anxiety, *nightmares*, *flashbacks*, and social withdrawal
- *Duration of symptoms:*
 1. One month or longer: PTSD
 2. Shorter than 1 month: *Acute stress disorder*
- *Note:* If the same symptoms develop after a *non-life-threatening event*, e.g., a breakup, divorce, death of a pet, it is called *adjustment disorder*, not PTSD.

- *Treatment:* Behavioral and group therapy is the treatment of choice. *SSRIs* are also used.

Generalized Anxiety Disorder

- *Definition:* Excessive worry and anxiety about almost everything, which has been lasting for *more than 6 months*
- *Clinical picture:* Anxiety, nervousness, irritability, and muscle tension
- *Treatment:* Drug of choice is *buspirone*; however, *BDZ* also can be used effectively in these cases.

Medically Induced Psychological Disorders

- *Cancer of tail of the pancreas:* Depression
- *Cushing syndrome:* Depression
- *Wilson's disease:* Anger and aggression
- *Temporal lobe epilepsy:* OCD and paranoia
- *Ulcerative colitis and migraine headaches:* OCD
- *Hyperparathyroidism:* Psychosis
- *Asthma:* Dependency
- *Chronic kidney disease and dialysis:* Depression and suicidal ideation

Behavioral and Cognitive Therapy (Table 12.3)

Extinction

- *Definition:* A gradual decrease of a negative behavior after positive reinforcement is removed
- *Example:* A child was used to get attention from his family every time his brother took his toys by

TABLE 12.3 Behavioral and cognitive therapy.

Therapy	Process	Explanation scenarios
Aversive conditioning	Classical conditioning	Whenever the dog barks, he gets shocked by an electric device around his neck
Systemic desensitization	Classical conditioning	Patient who is afraid of syringes: first, you show him pictures of syringes, and few visits later you have him touch an actual syringe
Implosion	Habituation	Implosion: Patient who is afraid of needles, you have him close his eyes and imagine living through a scenario where he is getting a blood draw; Flooding: Patient who is scared of needles, you perform a blood draw on him. Note that flooding is considered an operant conditioning technique
Token economy	Operant conditioning	Patients are given tokens for desired behavior, which they can exchange for certain privilege, e.g.: Making a phone call, watching TV. Common technique in psychiatry wards
Biofeedback	Operant conditioning	Patient can control his organs and functions, e.g., blood pressure, heart rate
Cognitive therapy	Supportive therapy	Patient trains herself that whenever she gets worried about her exam, she would think about passing it with high scores

claiming that his leg hurt. They rushed him to the doctor many times, and found everything was normal. For the last week, his family stopped paying attention, and eventually he stopped claiming that his leg hurts.

Reinforcement

- *Positive reinforcement: Giving a reward to change behavior, e.g., “If you are good, I will give you a cookie.”*
- *Negative reinforcement: Giving a punishment to change behavior, e.g., “If you are bad, I will take away your cookie.”*

Ethics

Living Will

- *Definition: A legal document describing what kind of medical measures should and should not be taken*
- *Rule of thumb: Simply do what the patient wants, even if it does not make perfect sense to you. If there is a Do Not Resuscitate (DNR) order already signed by the patient, do not ask the family; just do what the order says.*
- *Example: If you see a patient on the USMLE whose will includes a DNR but the only way to save him is intubation, do not intubate.*
- *Your responsibilities are:*
 1. Make sure the patient understands the advantages and disadvantages of his decision, e.g., “If you do not get intubated, you are going to die.”
 2. Do *everything else* you can to save the patient without breaking the DNR limitations; e.g., if it indicates that he does not want to have a blood transfusion but he is losing blood, you can try to give him plasma. If it indicates that he does not want intubation, but now he cannot breathe, try to use a mask or bilevel positive airway pressure (BiPAP).

Durable Power of Attorney

- A patient can choose someone to be the decision maker on his behalf *if he becomes incompetent*. This is a legal document prepared by a lawyer.
- *Example: You see a patient on the USMLE who cannot breathe and likely needs intubation, but does not have any living will or DNR, and cannot make decisions for himself. If a family member presents papers showing that he has durable power of attorney, and asks you not to intubate*

the patient and to just let him die, *then you do what he says.*

- *Your responsibilities are:*
 1. Make sure that the decision maker actually does have durable power of attorney *documentation*.
 2. Make sure that the patient is actually incompetent to make his own decisions. *The rule of thumb here is that if the patient is competent to make his own decisions, you listen to him and not to the durable power of attorney.* Again, you listen to the latter *only if the patient is incompetent to make his own decisions.*

Surrogate Decision

- The idea is to ask the people who know the patient best what they think *he would have wanted* (not what the family wants).
- *Rule of thumb: A patient on the USMLE cannot breathe and needs intubation. He is comatose, does not have a living will or a DNR order, and has not given power of attorney to anyone. Your responsibility is to ask his close family if the patient would have agreed to intubation if he were competent to make his own decision.*
- *To sum up:*
 1. First person to ask for a decision: *The patient*
 2. If patient is incompetent: *Durable power of attorney*
 3. If no power of attorney: *Surrogates*
 4. If no surrogates: *Treat the patient fully with no limitations*

Euthanasia

- *Passive: Leave the patient to die without interfering to save him. The only thing you provide is comfort measures. It is legal.*
- *Active: Speed up the patient’s death, for example, by using medications. This is illegal and is considered a crime.*

Children

- *Rule of thumb: You must get consent before treating or even touching any patient. Any child below 18 years of age is a minor who has to be consented for by his parents or legal guardians (see exceptions below).*
- *In emergency situations: Treat the child fully without limitations even if the parents decide otherwise. Example: A man and his 12-year-old son come to the emergency room (ER) after a motor vehicle*

accident. You find that the child has an intraabdominal hemorrhage and has to be taken to surgery immediately. The father states that he does not want you to take the child for surgery even though you explained that he might die otherwise. What you should do: *Take the child to surgery.*

- *In nonemergency situations:* If the parents refuse to consent to treating their child, what you should do is *get a court order to treat the child.*
- *Exceptions:* You *do not* need parental consent in the following situations:
 1. Emergency situations: Explained above
 2. Absence of parents and legal guardian: If a child is brought to the ER by his school teacher because of abdominal pain, but you could not contact his parents and he does not have a legal guardian. Do you take consent from the teacher? *No, only parents or legal guardian consent; if none is available, you treat the patient without consent.*
 3. Treatment of sexually transmitted diseases (STDs)
 4. Contraception
 5. Care during pregnancy
 6. Treatment of alcohol or drug dependence
 7. *Emancipated minors:* Any minor (<18 years of age) who has one or more of the following factors: *self-supporting and living on his own, married, has children, or is in the military.*

Pregnancy

- A pregnant woman has the right to decide for the fetus in her uterus.
- *Example:* A pregnant woman is brought to the ER after a motor vehicle accident, and she has an intraabdominal hemorrhage, but she tells you that she does not want you to do anything. You explain to her that she will die otherwise, but she does not change her mind. Then you explain that if you take her to surgery and deliver her baby, he might have a chance of living, and she still refuses. What you should do: *Do what she says.*

Criminal Law

- *Mental insanity:* Defined as having a mental or severe psychological abnormality, plus one of the following statutory criteria:
 1. M^oNaghten rule: *Most reliable criterion.* Evaluates if the patient understands his actions—what is right and what is wrong at the time of the crime.

2. American law institute model penal code: Reliable. Evaluates whether the patient understands the wrongfulness of his actions at the time of the crime and lacks the capacity to control his actions.
3. Durham: Not reliable. Evaluates if the crime was strictly induced by the mental or psychological abnormality, i.e., no accusation if mentally ill.

- *Mens rea elements:* Evaluates whether or not the crime was based on intent.
- *Irresistible impulse rule:* Defendant unable to refrain from the crime, e.g., due to a fit of rage.

Miscellaneous Ethics Issues

- *Malpractice:* 4 D's: *Dereliction of duty* causing *direct damage* to the patient. It is not a crime; however, it is a *civil wrong* punished *financially* (no jail time).
- *Tarasoff decision:* When a patient threatens to harm another person, you have to *involuntarily admit the patient to the psychiatric ward and contact the authorities and social services*, and, *most importantly, contact the potential victim.*
- *Sexual relationships:* Never have a sexual relationship with a patient. If asked on the USMLE about a patient who sees you regularly who you want to have a relationship with, the answer is *terminate your medical services to her, and ask her to start seeing another doctor.*
- *STDs:* Must be reported to the state health department, which in turn reports them to the Centers for Disease Control and Prevention (CDC)
- *Confidentiality:* A patient's diagnosis should not be disclosed to anybody other than the patient
- If family members of a patient asks you to hide a diagnosis from him/her, what should you do?
 1. Inform them that the patient has the right to know his diagnosis.
 2. Inform them that if the patient asks you directly about the diagnosis, you are obligated by law to disclose the diagnosis.
 3. *Beneficence:* If you believe that the patient will be harmed by knowing his diagnosis at that time, you can withhold that information. However, if the patient asks you directly about his diagnosis, *you must tell him.*
 4. *Nonmaleficence (do no harm):* This should be your goal at all times.
- *HIV:*
 1. If you have a patient diagnosed with HIV, you (or the Health Department) must inform his wife or sexual partners if he does not voluntarily do it.

- 2. If you have a colleague physician who was diagnosed with HIV, it is okay for him to practice medicine; however, your responsibility is to make sure he is taking all the precautions necessary to protect his patients.
- *Alcohol*: If you smell alcohol on the breath of your colleague physician, *talk to him*. If he does not acknowledge your advice, report him to the *chief of staff* and to *state boards*.

TABLE 12.4 Grief reactions.

	Normal grief reaction	Abnormal grief reaction
Sleep	Mild disturbance	Major disturbance
Interest	Still enjoys usual habits	Loss of interest
Guilt	Mild guilt feelings	Major guilt feelings
Psychosis	Illusions	Hallucinations
Suicidal	Rare	Common
Treatment	Social support	SSRI

Health Insurance

- *Private*: Multiple companies, and they cover most of the costs depending on the tier, e.g., Blue Cross/Blue Shield pays for hospitalization (*Blue Cross*) and diagnostic tests and physician fees (*Blue Shield*).
- *Federal*:
 1. Medicare: Covers the elderly (65 years and over), and is run by the *federal government*
 2. Medicaid: Covers the poor (*aid for the poor*), and is run by each *state*
- *Note*: Patients with end-stage renal disease (ESRD) on dialysis are covered by *Medicare*.

Miscellaneous

Freud's Theories of the Mind

- *Id*: "I want." Unconscious drives that begin at birth
- *Superego*: "You cannot have it." The moral compass or conscience that develops by 6 years of age.
- *Ego*: "Let's find a way." It balances the id and superego, and it develops *at birth*.
- *Unconscious*: *Primary* thinking, which involves primitive desires with no use of logic or planning
- *Conscious*: *Secondary* thinking, which involves the use of logic and planning, e.g., ego

Kübler-Ross Stages of Dying

1. *Denial*, e.g., a patient jumps off the bed right after a myocardial infarction to do push-ups.
2. *Anger*, e.g., "It isn't fair, I didn't deserve this."
3. *Bargaining and undoing*, e.g., "If I make it through this, I'll never smoke again."
4. *Depression*: Discussed earlier
5. *Acceptance*: Patient accepts the reality and shows signs of readiness to face it

Grief Reactions

- See Table 12.4

Important Disorders

- *Kleptomania (stealing crazy)*, e.g., a rich person who walks into a restaurant and cannot resist stealing the silverware
- *Pyromania (fire crazy)*, e.g., a person who loves to set things on fire without any purpose
- *Trichotillomania (hair crazy)*, e.g., a person who cannot resist pulling on his hair

Alcoholism and CAGE Questionnaire

- *CAGE*: Used to screen for alcoholism:
 1. C: Have you ever felt you needed to Cut down on drinking?
 2. A: Have you ever felt Annoyed by anyone criticizing your drinking?
 3. G: Have you ever felt Guilty about your drinking?
 4. E: Have you ever felt you needed an Eye-opener after a night of drinking?
- *Treatment of alcoholism*:
 1. Disulfiram (Antabuse)
 2. Psychotherapy, e.g., Alcoholics Anonymous (AA)
 3. DTs: See abuse, above. *Neuroleptics are absolutely contraindicated*.

Doctor-Patient Relationship

- *Transference*: The feelings and reactions of the *patient* toward the doctor
- *Countertransference*: The feelings and reactions of the *doctor* toward the patient

Important Theorists

- *Abraham Maslow*: Personality is equal to a group of motivations.
- *Margaret Mahler*: Separation and individualization
- *John Bowlby*: Described ethological and psycho-analytical thinking
- *Rene Spitz*: Isolated kids are at risk of infections and personality disorders
- *Harry Stack Sullivan*: Interpersonal relations

Others

- *Koro*: Delusions of retraction of one's penis into the body
- *Dhat*: Pathologic concern about ejaculation, found in Asian Indian cultures
- *Nervios*: Attacks of tearfulness, abdominal pain, and headache. A term most commonly used by Hispanics.

- *Dormido*: Pathologic concern about heart attacks and strokes
- *Ghost sickness*: Pathologic concern about death and the deceased, found in the Navajo culture
- *Brain fog*: Attacks of neck pain, confusion, and headache; common among students
- *Nihilism*: The belief that existence is senseless
- *Animus*: The masculine part of a female personality
- *Anima*: The feminine part of a male personality
- *Universality*: Feeling that everybody else is just like you
- *Cohesion*: Individuals teaming up to achieve a certain goal
- *Consensual validation*: Understanding yourself through comparison to others
- *Idealization*: The perception of yourself as being "perfect"
- *Asceticism*: The pleasure obtained by refraining from basic pleasures.

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