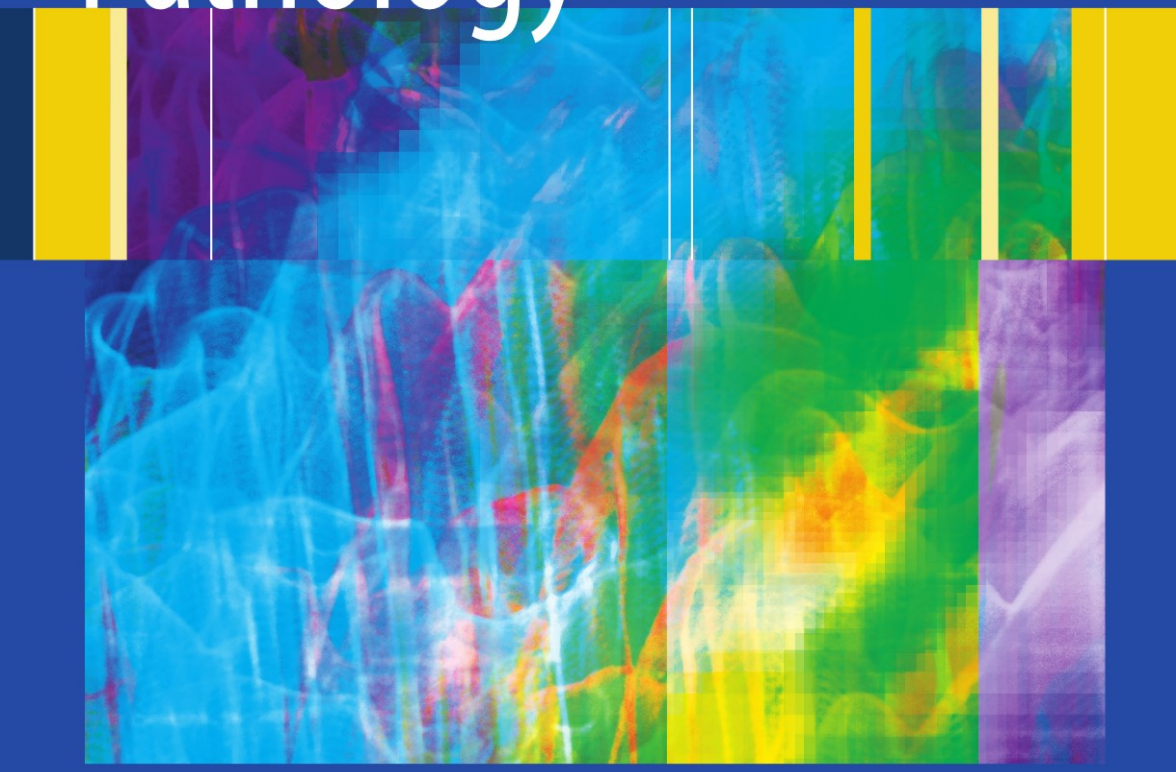
Alexander J. Howie

# Handbook of Renal Biopsy Pathology



Second Edition

Springer

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# Preface

My aim was to write a short, clear, useful, and interesting guide to the findings in renal biopsy specimens. Particular parts of this aim were to show how a diagnosis can be reached, and what information taken from a specimen is clinically significant and helpful. This guide was designed for pathologists and trainee pathologists who look at the specimens, nephrologists and transplant surgeons and their trainees who take the specimens, medical students who will be the next generation to take and look at the specimens, and anyone else who may have contact with people with renal disorders, such as dialysis and transplant nurses and pharmacists.

There is a major difference from most other texts on renal biopsy pathology, which approach the subject by a consideration of each disease separately. In real life, the disease is not known before the biopsy. This text shows how the diagnosis can be made starting from simple information, the clinical indication for the biopsy, followed by interpretation of changes seen in the specimen.

Other features not found in many texts are practical tips on the differentiation between possible diagnoses, information about eponyms and the origins of words, a guide to pronunciation of names, and a mention of famous people who have had renal disorders.

I am grateful to the nephrologists and renal transplant surgeons who have provided most of the material for this book, and have given me help and advice over the years. I also thank colleagues in pathology and related disciplines. From my time in the University of Birmingham, United Kingdom, I thank Dr D Adu, Mr A D Barnes, Ms L J Buist, Dr P Cockwell, Dr M T Drayson, Dr M A S Ferreira Baptista, Mr J Gregory, Dr S A Hulton, Dr G W Lipkin, Prof. C J Lote, Sir Jonathan Michael, Dr D V Milford, Dr F Raafat, Dr P Ramani, Mr A R Ready, Dr N T Richards, Prof. C O S Savage, Mrs J Sparke, Dr S J W Spencer, Dr C M Taylor, Prof. R H R White, and Mrs M C Williams.

In University College London and the Royal Free Hospital, London, United Kingdom, I thank Mr M Al-Akraa, Dr A Burns, Dr J O Connolly, Dr J M Cross, Prof. J Cunningham, Dr A Davenport, Dr P J Dupont, Mr B S Fernando, Mr O N Fernando, Dr J D Gillmore, Dr M A Harber, Dr K A Hillman, Dr S D Jayasena, Dr G L Jones, Prof. R F Kleta, Dr H J Lachmann, Ms J F Lewin, Ms R H H Lord, Dr M A Mansell, Prof. G H Neild, Dr J K Onwubalili,

Prof. S H Powis, Ms R F Sim, Dr H A F Stephens, Dr P Sweny, Prof. R J Unwin, Mr P S Veitch, Dr D C Wheeler, and Dr R G Woolfson.

Above all, I thank Prof. D B Brewer, who inspired me to become a renal pathologist, and whose book *Renal Biopsy* (London: Edward Arnold, 1964 and 1973) is a superb guide to renal disease based on his experience.

The chance to prepare a second edition has allowed me to include material that has appeared since the first edition, especially on segmental sclerosing glomerular disorders, lupus nephritis, human immunodeficiency virus, hypertension, and renal transplantation. For this, I am grateful to Springer, and in particular to Melissa Ramondetta, Executive Editor, Clinical Medicine, and Dianne Wuori, Editorial Assistant.

London, July 2007 A J Howie

# Contents

# Chapter 1
# Introduction

## Aims of the Book

This book is meant to be a practical guide to interpretation of renal biopsy specimens. Two things follow.

First, the book has much less text than most others on renal pathology. Only the most essential points about pathogenesis are included. There is little on other matters not directly relevant to interpretation. Diseases are not mentioned that are not investigated by biopsy, such as many developmental and urologic disorders of the kidney. Rare conditions are generally mentioned briefly, if at all. Large and comprehensive texts can be consulted where necessary.

The second thing is that this book has a different approach from standard texts in pathology. These consider each disease separately as identified, known, defined entities. This is excellent if a pathologist knows what to call the disease in a particular specimen, and wishes to confirm the diagnosis or find out more about it, but is little use if the pathologist has no idea about the diagnosis. Most pathologists have experience of the search through many descriptions of diseases, to try to find the name that seems the most appropriate for the abnormalities in a specimen. This book should be seen as a guide into the standard texts, which may be used as references for further information, once a diagnosis has been made.

This book tries to help the pathologist by the use of two rules, common things are common, and people with diseases present in characteristic clinical ways. The book is arranged by **clinical presentation** rather than by diseases, and concentrates on **common conditions**. Although there are hundreds of disorders that may affect the kidney, few are common, and these usually have typical clinical features. There is deliberate repetition, so that a pathologist should be able to give a diagnosis even if the clinical presentation is unusual or, as is more common, the clinical information is misleading.

The importance is stressed of how much the pathologist relies on the information supplied on request forms, and how much the interpretation depends upon the clinical circumstances. An apparently normal kidney in a biopsy specimen should be given a different diagnosis if there is microscopic hematuria than if there is the nephrotic syndrome. The pathologist can give most help to nephrologists and renal transplant surgeons when the clinical information provided is full and accurate.

A. J. Howie, *Handbook of Renal Biopsy Pathology.*

## Introduction to Renal Disease from a Pathologist's Point of View

The kidney is mysterious and frightening to many medical students and junior physicians. The organ cannot normally be felt or seen, the anatomy and physiology seem difficult and complicated, clinical features of renal disorders are indirect and not easily investigated, and there seems a secret language used by renal pathologists. Evidence that renal diagnoses are thought unnecessarily elaborate is that one core curriculum for medical students recommended that the pathologic classification of glomerular disorders should not be included. This book ignores classification as far as possible, and concentrates on correlation between clinical features and pathologic findings.

The kidney is essential for life, although not so immediately essential as the heart, lungs, or brain. Some types of interference with the structure or function of those organs can cause death within seconds or minutes, such as a dysrhythmia, strangulation, or an intracerebral hemorrhage. Removal of two normal kidneys would lead to death, not immediately but in a few days, from effects of accumulation of sodium and water, causing pulmonary edema and interference with gas exchange in the lungs, and effects of abnormal concentrations of solutes in body fluids, particularly potassium and hydrogen ions, causing dysrhythmias.

This shows that the main function of the kidney is to control the amount and electrolyte composition of body fluids.

Blood is filtered by glomeruli. The filtrate is altered in tubules by appropriate reabsorption and secretion of substances. Various chemical tests can be made to see how effective the kidney is at this function, which is called **renal excretory function**, or simply **renal function**. These tests are direct or indirect measures of the **glomerular filtration rate**, which is the volume of fluid filtered through glomeruli in a unit of time. If the rate is reduced, there is said to be **renal impairment** or **renal failure**.

If the kidney fails, this function can be partly replaced by either an artificial semipermeable membrane in hemodialysis, or the peritoneal membrane in peritoneal dialysis, with enough function to support life. Transplantation of a kidney is the best way that this function and other functions of the kidney can be restored.

Part of the normal function of the kidney is to filter the blood, but to prevent leakage into the filtrate of plasma proteins, especially albumin, the plasma protein in the highest concentration, and of blood cells, especially red cells, the most numerous blood cell. Disorders of the kidney, particularly of glomeruli, can cause appearance of proteins or red cells in the urine. These are called **proteinuria** and **hematuria**. These can occur together or independently, may be caused by disorders outside the kidney, such as elsewhere in the urinary tract, and even if caused by a kidney disorder, may not be associated with renal failure.

At the simplest level, pathologists will see renal biopsy specimens taken as part of the investigation of at least one of these abnormalities, **renal failure**, **proteinuria**, and **hematuria**. Biopsy of a **renal allograft** is usually because it is not working properly, which in equivalent to renal failure.

Among other functions of the kidney are the control of blood pressure, and production of hormones such as erythropoietin, but renal biopsy is hardly ever done to investigate disorders of these functions in the absence of renal failure or proteinuria or hematuria.

## The Value of a Renal Biopsy

A renal biopsy is sometimes seen as a dangerous and unnecessary investigation that gives no help in clinical management. An aim of this book is to emphasise the usefulness of information that a pathologist can give on a specimen. There are two particularly important pieces of information.

1. **The diagnosis**. The disease in a kidney, more than anything else, determines the likely clinical course. The diagnosis, which means the name put on the disease, is the most important guide to further investigations, treatment, and management. For some diseases, the diagnosis includes an assessment of how severe and active are the changes in the kidney.
2. **The amount of chronic damage in the kidney**. This gives a strong indication of the length of time that a kidney is likely to survive.

## Summary: Introduction

This book is meant to help pathologists to give a clinically useful interpretation of renal biopsy specimens, and to help others to understand pathologists' reports on these specimens.

Clinically, the term renal function refers to the excretory function of the kidney. Abnormalities of the kidney may give impairment of renal function, or leak of blood or proteins into the urine.

The two main factors that determine the clinical outcome are the disease in a kidney, and the amount of chronic damage at diagnosis.

## Further Reading: Introduction

Adu D, Tse WY, Howie AJ. Clinical investigation. In: Shena FP, editor-in-chief. Clinical Medicine Series: Nephrology. London: McGraw-Hill, 2001: 17–32.

Lote CJ. Principles of renal physiology. Fourth edition. Dordrecht: Kluwer Academic, 2000.

# Chapter 2
# General Points About Renal Biopsy Specimens

## Introduction to General Points

A renal biopsy specimen is the best example of a specimen that a pathologist cannot interpret without clinical information.

From information about age and sex of the person biopsied, reason for biopsy, and other clinical features, the pathologist should have an idea of likely appearances in the specimen, before any sections are seen on a microscope.

This is because there are two general rules.

1. Common things are common.
2. Diseases present in characteristic ways.

Strictly speaking, the second rule should state that people with diseases present in characteristic ways, because diseases do not exist on their own, but in medicine, conventionally, diseases are considered to be independent entities. For simplicity, this convention will be followed.

## Common Things Are Common and Diseases Present in Characteristic Ways

This work approaches interpretation of renal biopsy specimens with these rules. They are more helpful in real life than the standard textbook approach, which is to describe diseases, rather than to suggest how a pathologist can give a name to something that is unknown before the specimen is examined. Lists of diseases often give each one equal prominence whether they are rare or common, which is little use in practice.

## Things to Remember About the General Rules

Diseases come and go. The findings given here will become out of date. New diseases will appear.

A. J. Howie, *Handbook of Renal Biopsy Pathology.*

Diseases have different prevalences between the sexes, at different ages, and in different parts of the world.

There may be more than one disease in a kidney. In children there is usually only one, but in adults there is often more than one, if only because many have ischemic damage associated with age or hypertension, as well as something else.

There are rare conditions, but if a specimen appears out of the ordinary, the pathologist should think of an unusual form of a common disorder, or a combination of common disorders, before something rare.

A renal biopsy specimen is a tiny proportion of a kidney, and may not be representative of it. A needle biopsy specimen weighs under 100 mg, a kidney in an average adult weighs about 150 g, and so a biopsy specimen is much less than one thousandth part of a kidney by weight. A specimen may contain about twenty glomeruli, out of the several hundreds of thousands in a typical kidney. Even so, renal biopsy is helpful in most conditions, and indeed there are several in which only one glomerulus is needed to make the diagnosis.

## Importance of the Request Form to the Pathologist

The pathologist relies on information written on the request form, which may be wrong, or incomplete, or give a misleading emphasis, especially if written by an inexperienced physician. Ideally, the pathologist should be able to discuss clinical features of every person biopsied with a physician who understands what is going on, but this is not always possible.

## Indications for Renal Biopsy

There are only a few indications for renal biopsy, meaning the reasons why a biopsy is taken.

One indication is presence of protein in the urine, called **proteinuria**, which may be asymptomatic, and detected by chance or a deliberate search, or may be associated with edema and other features that are collectively called **the nephrotic syndrome**. Another is presence of blood in the urine, called **hematuria**. Others are states of reduced renal excretory function, called **acute renal failure** or **acute renal impairment**, and **chronic renal failure** or **chronic renal impairment**. Most biopsies of **renal allografts** are to investigate acute or chronic impairment of graft excretory function.

There are often combinations of these features. The terms **nephritic syndrome** and **acute nephritis** are sometimes applied to an acute illness with edema, hematuria, proteinuria, hypertension, and acute renal failure. Because the features of the nephritic syndrome may be incomplete or atypical and one feature may dominate, and the term is sometimes used in a loose and ambiguous way, there is not a separate

section on it, and the disorders that can present in this way are covered in the sections on the nephrotic syndrome, acute renal failure, and hematuria.

In someone who has had a renal biopsy, the procedure may be repeated to check on the progress of the disease, or to look for effects of treatment, or to see if another condition has developed. **Repeat specimens** can be considered in the same ways as initial specimens, with the advantage that there is previous material for comparison.

To simplify the approach to interpretation of renal biopsy specimens, the indications are considered in a way that allows for all possible combinations. If there is the nephrotic syndrome, irrespective of other features, that is regarded as the main indication. If there is acute renal failure, irrespective of features apart from the nephrotic syndrome, acute renal failure is regarded as the main indication. If there is chronic renal failure, without the nephrotic syndrome or acute renal failure, and irrespective of proteinuria or hematuria, chronic renal failure is regarded as the main indication. If there is hematuria with or without proteinuria, but with normal renal function, hematuria is regarded as the main indication. The last indication is asymptomatic proteinuria on its own.

To summarise, the indications for biopsy are considered in this order, and the first one that applies to a specimen is regarded as the main one:

first, nephrotic syndrome
second, acute renal failure
third, chronic renal failure
fourth, hematuria
fifth, asymptomatic proteinuria

**The scheme followed in this work is not rigid**, and should allow a diagnosis to be made on specimens with misleading indications written on the request form, such as one with hematuria and proteinuria in which there is chronic renal failure, although it is not noted on the request form, or one with renal failure that is considered acute clinically but actually is chronic, or a specimen on which the pathologist is not clear which is the dominant indication.

These indications may be called medical reasons for a renal biopsy. Biopsy of **a mass** in or near the kidney is uncommon, and may be called a surgical or urologic reason for a renal biopsy.

There are other clinical features that are not by themselves indications for a renal biopsy, although they may be present with features that are indications. These include hypertension, loin pain or other abdominal pain, and anemia. Suspected or definite urinary tract infection is usually considered a contraindication to biopsy.

A pathologist may see renal biopsy specimens taken for **unusual** or **accidental** reasons. Kidney may be seen in attempted biopsy of other structures, particularly of liver and masses in the region of the kidney. The specimen should be examined as if it were an intentional biopsy of the kidney, because abnormalities may be found (Fig. 2.1). Occasionally, there are none of the common indications, but a biopsy is taken to investigate the possibility of subclinical disease in the kidney, such as vasculitis, or there is a familial renal problem, or a kidney is assessed as a possible

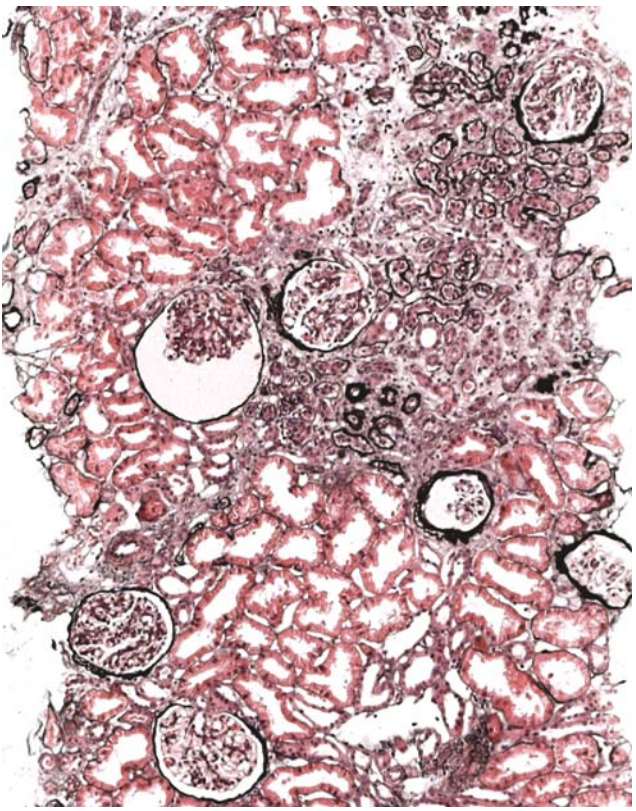

**Fig. 2.1** Attempted biopsy of a liver allograft in a woman of 45, at annual review. This is a specimen not of liver, but of renal cortex. There is chronic damage, particularly seen as tubular atrophy. One potential explanation is effects of a calcineurin inhibitor, used as an immunosuppressant. IgA nephropathy is another common finding when attempted liver biopsy specimens include kidney. Renal comes from the Latin for kidney, nephro- comes from Greek for kidney, and the word kidney is of obscure origin. Biopsy comes from Greek words meaning life and vision. In Latin, cortex meant bark of a tree. Tubule is derived from the Latin for a little pipe or tube

graft, or there is a known or suspected metabolic or tubular disorder, especially in children. During surgical exploration of a graft for a vascular or ureteric problem, a biopsy may be done simply because the surgeon is there.

Different nephrologists and renal transplant surgeons have different indications for biopsy. Some may not biopsy people with hematuria alone, or asymptomatic proteinuria, or chronic renal failure. Not all children with the nephrotic syndrome have a renal biopsy, and in some places this is also true of adults. In some transplant units, allografts are biopsied at set times irrespective of function. Different renal biopsy practices will give different frequencies of findings, but the findings given in this work are likely to be comparable with those in many centres. Findings in some parts of the world, such as in developing or low income countries, may be markedly different.

When allografts are excluded, the **frequencies of indications for biopsy** are different at different ages, and in different parts of the world. In some countries in adults, chronic renal failure, acute renal failure, and nephrotic syndrome each account for nearly a third of specimens, in descending order of commonness, with fewer taken for hematuria, and even fewer for asymptomatic proteinuria. In some countries in children, nearly half are taken for hematuria, and the order of indications for the rest is nephrotic syndrome, acute renal failure, asymptomatic proteinuria, and chronic renal failure. In some parts of the world, almost the only indication for renal biopsy is the nephrotic syndrome.

A satisfactory specimen for a pathologist is one with definite features, on which a clear cut diagnosis can be made. When allografts are excluded, the most satisfying indications from the pathologist's point of view are nephrotic syndrome and acute renal failure, because an adequate diagnosis should almost always be possible. The next are hematuria and chronic renal failure. Proteinuria is the indication most likely to frustrate the pathologist's intention to give an unequivocal diagnosis.

## Complications of a Renal Biopsy

The commonest serious complication of a biopsy is **macroscopic hematuria**, reported to follow 5–10% of procedures in most series. Hemorrhage into retroperitoneal tissues around the kidney is common, but is clinically evident after about 1% of biopsies. Either form of hemorrhage may require blood transfusion, or less commonly radiologic embolisation of material into renal arteries to block them, or even less commonly nephrectomy if there is otherwise uncontrollable bleeding. A puzzling observation is that the pathologist is hardly ever able to predict when there will be clinically significant bleeding after a renal biopsy. Large blood vessels may be seen in specimens without clinically obvious bleeding afterwards, while there may be no large vessels in specimens complicated by hemorrhage. Other complications include development of arteriovenous fistulas and consequences of puncture of intra-abdominal organs.

## Summary: General Points About Renal Biopsy Specimens

The two general rules are that common things are common, and diseases present in characteristic ways.

The main indications for a renal biopsy are the nephrotic syndrome, acute renal failure, chronic renal failure, hematuria, and asymptomatic proteinuria. Combinations of these occur.

Biopsy of a renal allograft is usually to investigate acute or chronic graft failure.

Renal biopsy may also be done to investigate a mass in the kidney.

# Chapter 3
# Technical Handling of Renal Biopsy Specimens

## Types of Renal Biopsy Specimen

There are two types. One is a needle biopsy specimen, usually taken through the skin, and called a percutaneous specimen. Transjugular specimens are similar specimens, but are taken by an internal approach to the kidney, through a cannula passed from the jugular vein into the renal vein. The other type of specimen is taken directly from a kidney by incision at operation, and often called a wedge biopsy specimen.

## Fixation and Processing of Specimens

Different laboratories have different methods of fixation. The simplest is formal saline, which is a solution of one part of 40% formaldehyde in nine parts of 0.9% sodium chloride in water. This is sometimes called 10% formalin, because that is the dilution of the original formaldehyde solution, and sometimes called 4% formalin, because that is the true final dilution of formaldehyde.

Formal saline has several advantages over other fixation methods.

1. All routine histologic staining methods work well after this fixation.
2. Many immunohistologic methods also work well.
3. If necessary before further processing, a part of the specimen can be transferred to another fixative for electron microscopy, with little effect on the quality of the electron microscopic images. This may mean that there is no need for technical staff to attend each time a biopsy is done.

In some centres, immediately after removal, the renal biopsy specimen is examined with a low magnification binocular microscope or other magnifying lens to allow identification of glomeruli, which can be seen as red dots (Fig. 3.1). A small piece, about 1 mm long, containing glomeruli is cut off and put into a solution of glutaraldehyde in buffer suitable for electron microscopy. Another piece is frozen for immunohistologic studies on unfixed sections. The rest of the specimen is then put in a fixative for orthodox light microscopic studies. The term **orthodox light**

A. J. Howie, *Handbook of Renal Biopsy Pathology.*

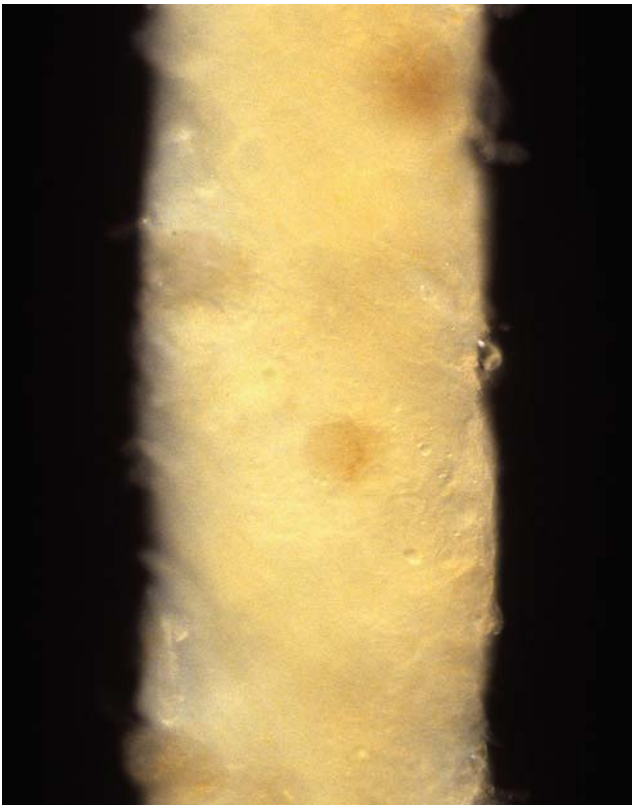

**Fig. 3.1** Needle biopsy specimen of kidney inspected in reflected light under low magnification on a microscope. Glomeruli are the dark round structures. Small pieces containing a couple of glomeruli can be cut off, and either frozen for immunofluorescence study or put in fixative suitable for electron microscopy. In Latin, glomerulus meant a little ball of thread, and the name was first used in microscopy as a description of what is now called the glomerular tuft. The tuft and the structure that surrounded it, Bowman's capsule, were originally called a Malpighian corpuscle, in which corpuscle came from the Latin word for a little body. Glomerulus is used now instead of Malpighian corpuscle. Sir William Bowman (1816–1892), whose surname is pronounced with the first syllable as in *go*, studied medicine in Birmingham, United Kingdom, and became an ophthalmic surgeon in London. His paper on the microscopic structure of the kidney was published in 1842. Marcello Malpighi (1628–1694), pronounced *mal-pee-gee* with a hard *g*, was an Italian physician and anatomist, who described the corpuscle in 1666

**microscopy** in this text means the use of routine pathologic staining methods, without immunohistologic methods.

This collection procedure means that experienced laboratory staff have to be present whenever there is a biopsy, with the risk of delays and inefficiency, or there is a risk that inexperienced medical staff will try to divide the specimen and make mistakes. The advantage is that experienced staff can usually say whether the specimen contains glomeruli, and should be adequate for study by a pathologist. An alternative procedure is that each specimen is put into formal saline by the person

who takes the biopsy, and then the specimen is taken to the laboratory as soon as possible, with a request form on which there is enough information to allow the pathologist to judge how the specimen should be handled.

There are emergencies whose immediate management can be affected by findings in renal biopsy specimens. Although sections of frozen material can be prepared quickly, they are not usually of satisfactory quality for detailed study of the kidney, and so laboratories should be able to prepare sections of material embedded in paraffin wax within a few hours of reception of specimens. Some departments of pathology offer an emergency service at any time.

The most common emergencies are **suspected rejection of a renal allograft**, and **acute renal failure**. **Suspected puncture of an organ other than kidney** is also an emergency. **Nephrotic syndrome**, because of its possible complications and implications for urgent management, can be considered an emergency. Specimens taken for these reasons should be processed as rapidly as possible. Most other specimens do not require urgent handling, but if this is available without difficulty, the pathologist should make use of it.

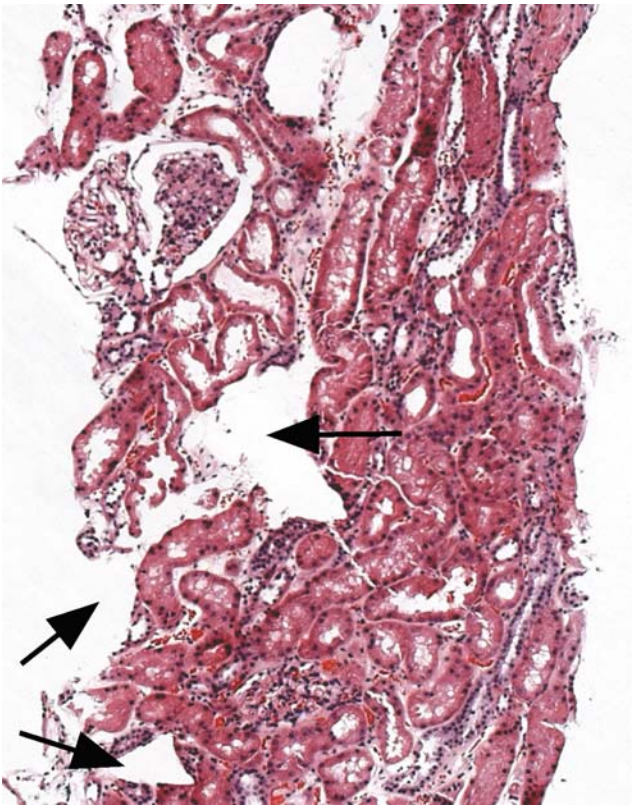

**Fig. 3.2** Renal biopsy specimen processed in a cassette packed with a plastic sponge. Artefactual distortion can be seen as indentations at the edge of the section and holes within the section, examples of both of which are arrowed

The sample to be prepared for orthodox light microscopic sections should be processed by the laboratory in its usual way and embedded in paraffin wax. An important technical point is that sponge packing should not be used in cassettes during processing of specimens, because this distorts the tissue, and leaves distinctive holes in sections (Fig. 3.2).

## Arrangements for Electron Microscopy of Specimens

If a piece of the specimen has not been fixed specially for electron microscopy at the time of removal, a piece can be removed from the sample fixed in formal saline. This is best done by inspection with a low magnification binocular microscope and transfer of a small piece of cortex into a solution of glutaraldehyde. Electron microscopy may be considered necessary for a diagnosis although all the material has been embedded in paraffin wax, in which case a piece can be removed from the wax, and reprocessed in the appropriate way. Images are not ideal after this, but may still allow the diagnosis to be made.

Some laboratories have a sample of every specimen for electron microscopy and examine them all, some are selective, and some do not have the opportunity to do electron microscopy.

Many diagnoses can be made on renal biopsy specimens without electron microscopy, by orthodox light microscopy, either on its own or with immunohistologic investigation. **The most important investigative technique on most renal biopsy specimens is the preparation and study of suitable light microscopic sections**, including immunohistology, if necessary.

Electron microscopy is most likely to help in the diagnosis in the following circumstances:

1. When there is **hematuria**, especially microscopic, with or without proteinuria, when renal excretory function is normal.
2. When there is a **family history of renal disease**.
3. When there is **asymptomatic proteinuria**, with normal renal excretory function.

Conditions in which electron microscopic investigation may be helpful, but is not usually essential for the diagnosis, are these:

1. **Nephrotic syndrome**
2. **Acute renal failure**
3. **Chronic renal failure**
4. Renal disease in **diabetes mellitus**
5. Renal disease in **systemic lupus erythematosus**
6. **Suspected rejection of a renal allograft**
7. **Repeat specimen** when the diagnosis has been made

In children, the safest procedure is to keep a sample of every specimen for possible electron microscopic examination, if this is feasible. In adults, many conditions

can be investigated adequately without electron microscopy, and this is not usually essential. Features in the clinical history of adults may suggest that there is something unusual, and that electron microscopy may be useful, for instance if the person has diabetes mellitus and hematuria, but normal renal function. If there is any doubt, and if the pathologist has access to an electron microscope, the best course is to keep a sample for possible electron microscopy.

## Sectioning of Specimens

Three suggestions about sections of renal biopsy specimens are these.

1. **Needle biopsy specimens should be embedded as straight as possible, and aligned so that the pieces run across the glass slide, not along its length**. This means that the axis of the pieces is at right angle to the long axis of the slide (Fig. 3.3). The reasons for this are that more sections can be mounted on a

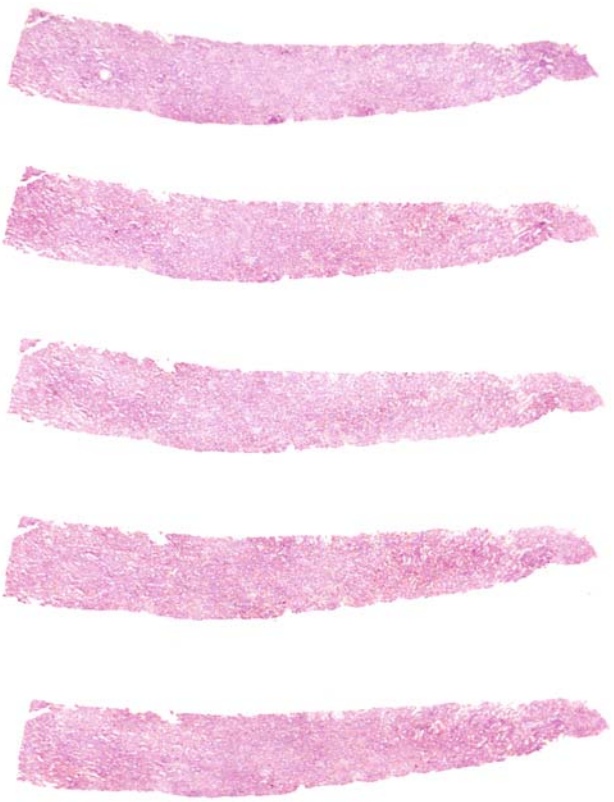

**Fig. 3.3** Serial sections of a renal biopsy specimen, mounted to run across the slide rather than along its length

slide, and this arrangement of sections makes it easy for a pathologist to follow a structure such as a glomerulus from section to section.

2. **Serial sections should be cut, and runs of these should be mounted on consecutively numbered slides**. Generally about four to eight sections can be mounted on one slide (Fig. 3.3). If these first two suggestions are followed, glomeruli and other structures can be studied efficiently by the pathologist. Serial sections allow study of glomeruli and other structures in three dimensions, rather than in the two dimensions seen on a single section.
3. **Sections should be kept and mounted right from the beginning of appearance of tissue in them**. No tissue from a renal biopsy specimen should be discarded. If necessary, extra sections can be cut with little problem, but discarded material is lost for ever.

## Staining of Specimens

Most staining methods should be in regular use in pathology laboratories. Stains required on a renal biopsy specimen are hematoxylin and eosin or periodic acid Schiff to give the general appearance, a stain such as periodic acid-methenamine silver to show basement membranes, and a connective tissue stain, such as hematoxylin van Gieson or a trichrome. Because amyloid is sometimes found unexpectedly in renal biopsy specimens, can be shown by specific methods, and may be missed if these methods are not used, a stain such as Congo red may be applied to every specimen. Congo red is also useful because it stains eosinophils, and its counterstain shows calcification. Some pathologists find other stains useful on routine sections, such as Martius scarlet blue. When appropriate, several other stains can be used, such as Gram stain for bacteria, Perls' Prussian blue for iron deposits, and von Kossa's method for calcium, or rather, for insoluble phosphate and carbonate, which are usually calcium salts.

Which stains are used and how many sections are cut are usually determined by personal preference of the pathologist. These matters are probably of little importance, compared with the ability of the pathologist to give a diagnosis that corresponds most closely with the disease in the specimen, and to provide other information of clinical significance.

One possible set of slides and staining methods is this. On each of 10 consecutively numbered slides, six to eight serial sections are mounted, most cut at about 3 μm thickness, and those on slides numbered 7 and 8 at 2 μm thickness. Slides numbered 2 and 10 are stained immediately by hematoxylin and eosin. Number 4 is stained by hematoxylin van Gieson, number 6 by Congo red, and the slides with thin sections, numbers 7 and 8, by periodic acid-methenamine silver. Slides numbered 1, 3, 5 and 9 can be stained if necessary in other ways, or further studies can be made with stains already used. All spare slides should be stored with the stained slides, in case they are ever needed. Further sections can be cut from the paraffin block, if necessary.

## Immunohistologic Study of Specimens

Many renal biopsy specimens can only be analysed properly when studies are made of the distribution of various molecules, particularly immunoglobulins and complement components. **This is because many renal diseases are complications of disorders of the immune system.** The term immunohistology refers to the method of detection, which is by use of immunoglobulins as antibodies rather than to the substances detected, which are not all immunoproteins.

Laboratories have different practices. Many use **immunofluorescence** techniques on frozen sections, and routinely stain for antigens such as immunoglobulins G, A, and M, fibrinogen/fibrin, and complement components, particularly C1q and C3. Usually the antibodies to these antigens are directly conjugated to fluorescein isothiocyanate.

Other laboratories use **immunoenzyme** techniques on paraffin sections, with a variety of ways of detection of antigens, but mostly with a final step including reagents labelled with either peroxidase or alkaline phosphatase. An extra set of sections can be cut routinely from specimens, including those from allografts, if necessary. These sections should be mounted on slides suitable for immunohistologic procedures, meaning that they are coated with reagents such as albumin or poly L lysine, to help adhesion of the sections. The number depends upon the antibodies usually used by the laboratory. One practice is to have four extra slides, each with at least one section. These are stained by an immunoperoxidase method for immunoglobulins G, A, and M, and a complement component C9. Other sections can be cut and stained using antibodies to other substances such as kappa and lambda light chains and amyloid A.

Immunofluorescence methods on frozen sections are technically easier and have been used longer. Immunoperoxidase methods on paraffin sections have the disadvantage that sections have to be treated with proteolytic enzymes before immunostaining, to remove the plasma fixed in blood vessels. Plasma contains immunoproteins which obscure staining of immune deposits, although proteolysis can be controlled, so that the quality of immunostaining can be equivalent to that of immunofluorescence methods on frozen sections. Immunofluorescence methods can also be applied to fixed material after treatment with proteolytic enzymes.

Immunoperoxidase methods on paraffin sections have advantages over immunofluorescence methods on frozen sections. Most of the advantages are also over immunofluorescence methods on paraffin sections of fixed material.

**The advantages of immunoperoxidase methods** are these. Stained sections are permanent, although fluorescence fades and has to be recorded by photography. Immunoperoxidase sections are examined with an ordinary light microscope rather than a fluorescence microscope, are the same size as the sections stained with routine methods, and can be counterstained so that sites of immunostaining can be identified precisely, unlike on immunofluorescence sections, where the background is dark. Immunoperoxidase methods are generally more economic than immunofluorescence methods, because directly labelled antibodies have to be used at higher concentration than antibodies detected by indirect techniques. Because of technical

arrangements, sometimes immunofluorescence material is examined and reported by people other than the pathologist who examines the orthodox light microscopic sections. Material for immunoperoxidase sections does not need special arrangements for collection and storage. The technique can be applied retrospectively to renal biopsy specimens stored in paraffin wax for many years.

Nearly all illustrations of immunohistologic investigations in this book are of sections stained by immunoperoxidase methods, but findings of immunofluorescence methods are comparable.

## Summary: Technical Handling of Renal Biopsy Specimens

Fixation, processing, sectioning, and staining should be designed to give the pathologist the best possible opportunity to study renal biopsy specimens by light microscopy.

Immunohistologic study can be done either by immunofluorescence techniques, usually on frozen sections, or by immunoenzyme techniques on paraffin sections.

Electron microscopy is useful in investigation of some renal biopsy specimens.

## Further Reading: Technical Handling of Renal Biopsy Specimens

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Gregory J, Howie AJ. Protease digestion of renal biopsy specimens for immunohistological study. *Journal of Cellular Pathology* 1996; **1:** 166–169. This and the next reference give practical details of immunoperoxidase methods.

Howie AJ, Gregory J, Thompson RA, Adkins MA, Niblett AJ. Technical improvements in the immunoperoxidase study of renal biopsy specimens. *Journal of Clinical Pathology* 1990; **43:** 257–259.

Jennette JC, Olson JL, Schwartz MM, Silva FG. Heptinstall's Pathology of the Kidney. Sixth ed. Philadelphia: Lippincott Williams and Wilkins, 2007. Chapter 3.

# Chapter 4
# How to Look at a Renal Biopsy Specimen: Preliminary Study

## Immediate Study of Initial Sections

When sections stained by hematoxylin and eosin are available, the pathologist should look at them immediately, before sections stained in other ways are ready. **This should be done whatever was the indication for biopsy**. The reasons are these.

1. **There may be no kidney in the specimen.** A percutaneous renal biopsy is a more difficult procedure than biopsy of skin, or liver, or organs that can be seen by endoscopy. Blood and connective tissues including fat, fibrous tissue, nerves, skeletal muscle, and blood vessels are often found, with or without kidney. Hemosiderin deposits are common if there was a previous renal biopsy on the same side. Perls' Prussian blue stain will confirm that these deposits contain iron, but this is not usually important.

   **All tissues should be examined, whether or not there is kidney**. Occasionally a significant abnormality can be detected outside the kidney, such as myositis (Fig. 4.1), or lymphoma (Fig. 4.2), or pus, which may be seen particularly around renal allografts (Fig. 4.3).
2. **There may be other abdominal organs in the specimen, with or without kidney.** The commonest is bowel, sometimes just muscle layers rather than full thickness with mucosa, and more often small intestine than large intestine (Fig. 4.4). Spleen and liver are seen less often. Adrenal gland, pancreas, and lymph node are uncommon. Skin is hardly ever seen, because the skin is cut to make an opening for the biopsy needle. **All tissues should still be examined** (Fig. 4.5).
3. **The only parts of the kidney in the specimen may be medulla or renal pelvis.** Occasionally, these may allow the pathologist to make a diagnosis, for instance if there is papillary necrosis, or amyloid, or vasculitis (Fig. 4.6). **Usually cortex is needed to make a diagnosis**, even if the medulla shows abnormalities such as deposits of pus or urate crystals (Fig. 4.7), because these can occur together with disorders that are not evident in the medulla.
4. **There may be cortex in the specimen, but not much.** Cortex is recognised by the presence of glomeruli and convoluted parts of tubules. The pathologist has

A. J. Howie, *Handbook of Renal Biopsy Pathology.*

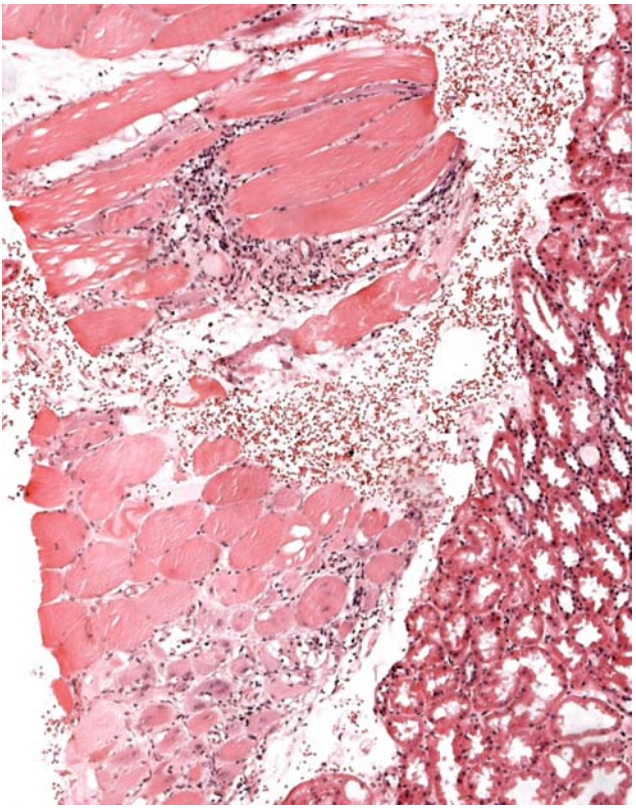

**Fig. 4.1** Skeletal muscle included in a renal biopsy specimen from a woman of 34 with the nephrotic syndrome and a multisystem illness. There is active myositis. This and **Figs** 4.2–4.5 show that tissues as well as kidney in a specimen should always be examined

to judge the chances that a diagnosis will be made. No rule can say how much cortex is necessary for a diagnosis. One glomerulus, even without any other renal tissue, may be enough to allow a diagnosis of IgA nephropathy, or vasculitic glomerulonephritis, or membranous nephropathy, or diabetic glomerulopathy, or amyloid, among others (Fig. 4.8). A small sample of cortex may not be adequate for proper assessment of conditions such as suspected rejection of an allograft or suspected vasculitis.

Occasionally, there are recommendations about the minimum number of glomeruli or amount of cortex necessary to consider a renal biopsy specimen **adequate**. The answer to the question of what is an adequate specimen is "It depends". It depends upon the clinical circumstances, and the pathologic findings. On some specimens, a satisfactory diagnosis may be given with hardly any glomeruli (Fig. 4.8), or without cortex (Fig. 4.6), or even without kidney (Fig. 4.5), while on others with many glomeruli and a large amount of cortex, the pathologist may not be able to give a satisfactory diagnosis. Some pathologists

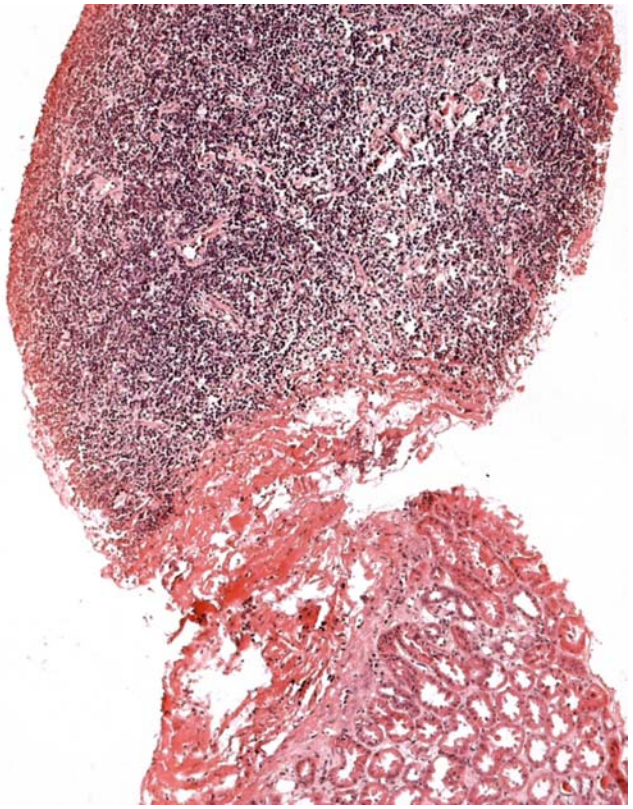

**Fig. 4.2** Renal biopsy specimen from a man of 56 with the nephrotic syndrome, and an IgM paraprotein in serum. There is a lymphoplasmacytoid lymphoma outside the capsule of the kidney. The man had Waldenström's macroglobulinemia, named after Jan Gosta Waldenström (1906–1996), a Swedish physician. In English, the name is often pronounced as it looks, *wall-den-strome*, which is not the Swedish pronunciation

are more ready than others to call a specimen inadequate, but as much useful information as possible should always be given on a specimen, which may be the only one ever available.

5. **There may be findings in the specimen that could have an influence on immediate clinical management.** These could be expected or unexpected. Often in acute renal failure, a renal biopsy is taken to investigate the possibility of renal vasculitis, which is a nephrologic emergency. Vasculitis is usually easy to diagnose on sections stained by hematoxylin and eosin. Similarly, biopsy of an allograft is usually taken to see whether there is active rejection, which may be treated immediately. These are among the few occasions when a pathologist can have an important role in urgent clinical problems. Occasionally, unexpected findings of immediate significance are seen. For example, neoplasms are sometimes found by surprise (Fig. 4.9).

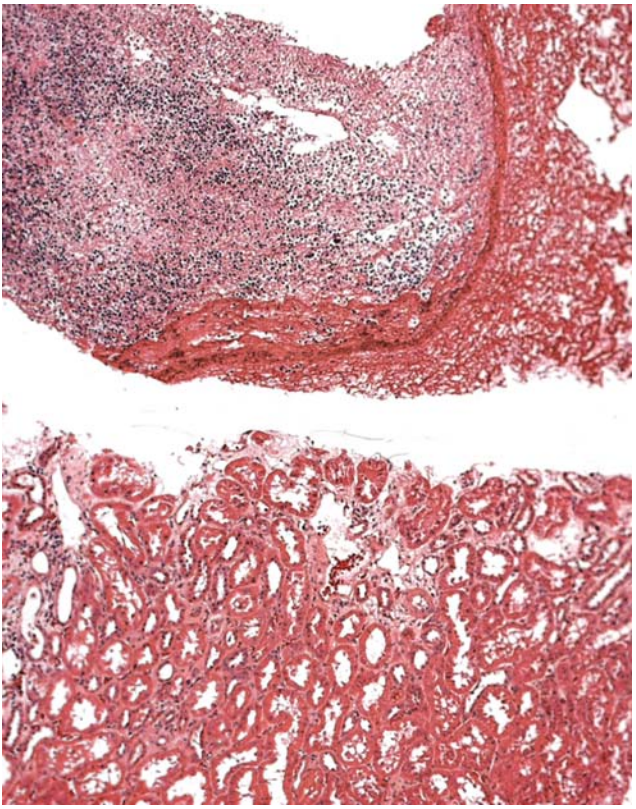

**Fig. 4.3** Needle biopsy specimen of a renal allograft in a woman of 25, three months after transplantation. The specimen includes hemorrhagic pus from around the kidney, which has no evidence of significant rejection

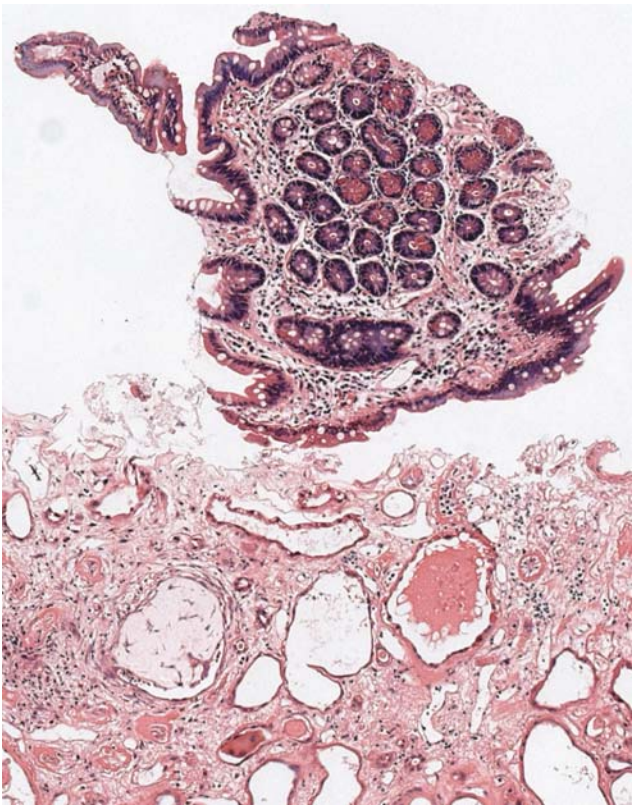

**Fig. 4.4** Small intestine included in a renal biopsy specimen from a man of 69 with renal failure, which clinically seemed acute. The kidney has late damage from tubular effects of myeloma

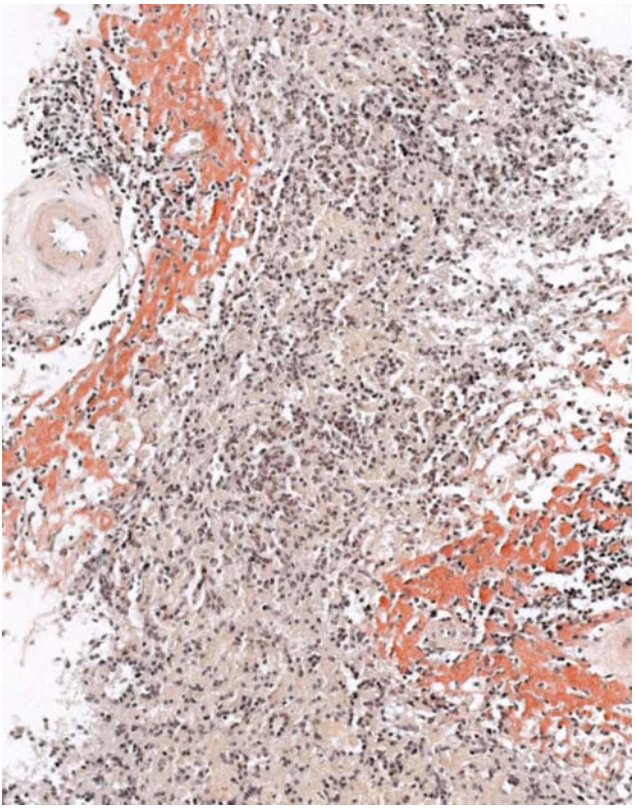

**Fig. 4.5** Attempted renal biopsy in a man of 54 with the nephrotic syndrome and psoriatic arthropathy. There is no kidney in the specimen, but there is spleen, and this contains amyloid stained by Congo red, shown to be AA amyloid. The nephrotic syndrome was assumed to be due to AA amyloidosis. Amyloid, from Greek words meaning starch and resembling or like, is sometimes mistakenly considered one of the many words invented by Rudolf Ludwig Karl Virchow (1821–1902), called the greatest figure in the history of pathology by E R Long in *A History of Pathology*, 1928. Virchow apparently pronounced his surname *feer-cho*, with the *ch* as the Scottish pronounce it in *loch*, but several other pronunciations are used in English. The word amyloid was first used by two Germans J Vogel and M J Schleiden in 1839, because of the similar staining properties of cellulose and starch. Virchow showed that waxy or lardaceous change of the spleen was due to amyloid, which he thought was a cellulose like meterial

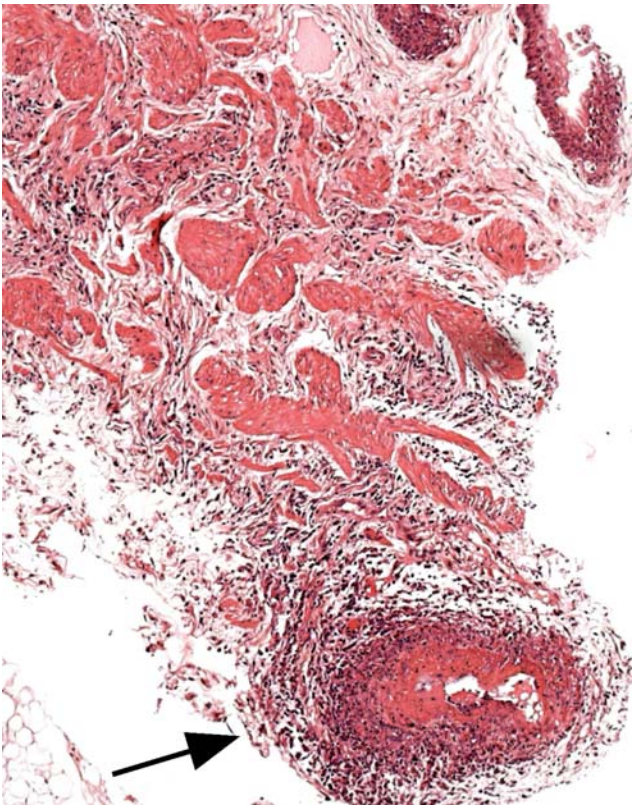

**Fig. 4.6** Renal biopsy specimen from a man of 53 with hematuria, proteinuria, upper respiratory tract abnormalities, and a high titer of antineutrophil cytoplasmic antibodies. There is only renal pelvis in the specimen, but this shows acute arteritis, arrowed

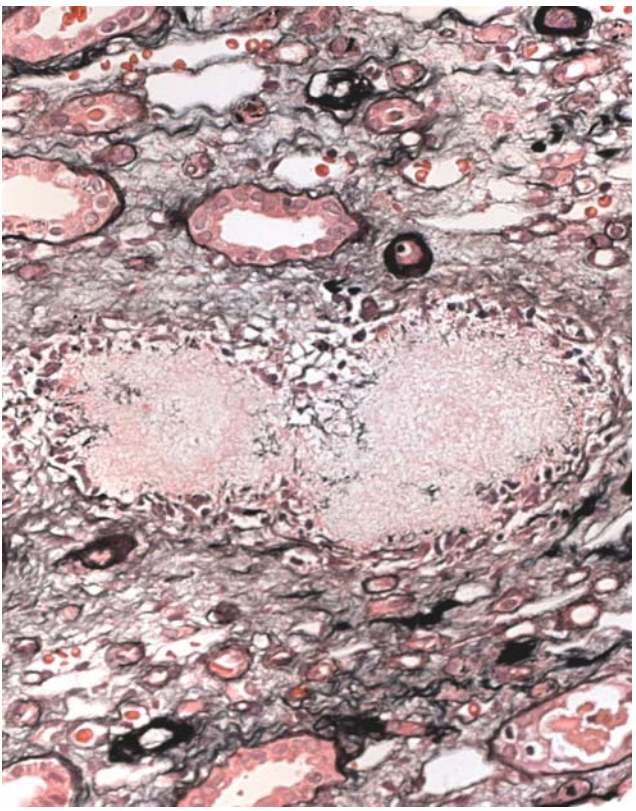

**Fig. 4.7** Medulla in a renal biopsy specimen from a man of 50. The cortex shows late changes of IgA nephropathy. There is an amorphous mass surrounded by inflammatory cells, with the appearances of urate deposits. The crystals do not remain after fixation and processing. Medulla meant marrow in Latin

**Fig. 4.8** Renal biopsy specimen from a man of 67 with chronic renal failure and proteinuria. There is only one glomerulus in the specimen, arrowed, but immunoperoxidase staining shows that this contains IgA, and gives the diagnosis of IgA nephropathy

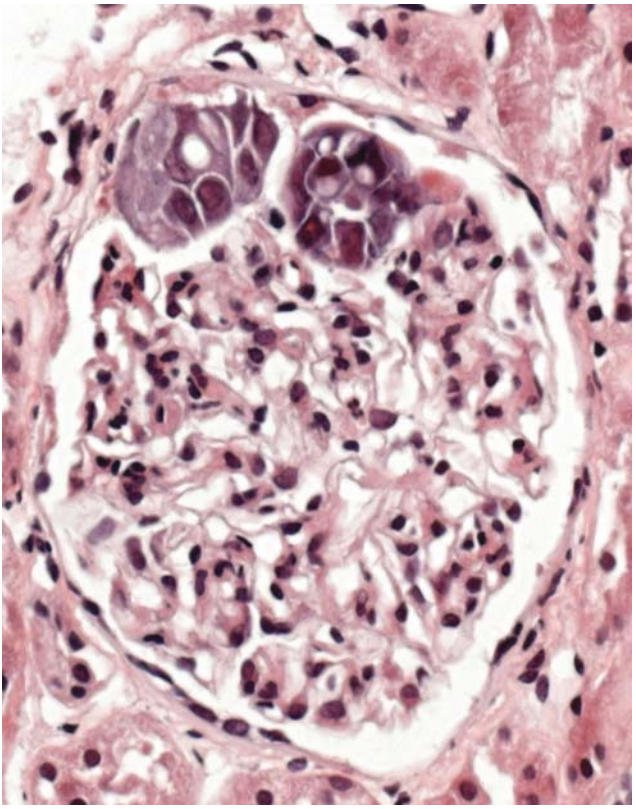

**Fig. 4.9** Wedge biopsy specimen taken at the time of transplantation of a cadaveric kidney from a man of 45 into a man of 61. A glomerulus contains metastatic carcinoma. This finding had an immediate effect on clinical management. The story is given in Barnes AD, Fox M. Transplantation of tumour with a kidney graft. *British Medical Journal* 1976; **1:** 1442–1444

## Actions After Immediate Study of Initial Sections

Actions to take are these.

1. If there is a possibility that **further sections** may help to show more cortex, these should be requested from the laboratory. If there is no kidney in the specimen, immediate inspection should prevent the laboratory from wasting time and resources on unnecessary staining.
2. If a diagnosis is unlikely to be made, usually because there is no cortex in the specimen, or if an organ other than kidney is seen, **the nephrologists or surgeons should be told immediately**. They may wish to repeat the biopsy if there

is no cortex, and will be prepared if there is a clinical problem from damage to the bowel, or spleen, or other organ.

3. Nephrologists or surgeons should be told about findings in a biopsy specimen taken for **an urgent indication**, even if only a provisional diagnosis is possible. They should also be told about unexpected findings likely to be of clinical importance.

## Summary: How to Look at a Renal Biopsy Specimen: Preliminary Study

The pathologist should look immediately at sections of a renal biopsy specimen stained by hematoxylin and eosin, because the findings may be of clinical or technical importance.

All tissues in a specimen should be examined, even if there is no cortex.

Judgment should be used by the pathologist to decide whether the specimen is adequate to allow a diagnosis to be made, given the clinical circumstances and the pathologic findings.

# Chapter 5
# How to Look at a Renal Biopsy Specimen: Initial Study of the Kidney

## Introduction to Initial Study of the Kidney

Renal biopsy specimens should only be examined when the pathologist knows the **sex** and **age** of the person biopsied, and the **clinical indication** for biopsy.

The most important factor in a kidney is the **disease** in it, which should correspond with the name that is given to the changes seen by the pathologist, and called the diagnosis. More than anything else, the disease determines the likely clinical course, including the response to treatment.

The next most important factor is the **state of the tubules**, particularly the amount of chronic damage to tubules. **Renal excretory function has more correlation with structural changes in tubules, than with any other structural change in the kidney**.

Tubules and interstitial tissues are often considered as a unit, as in the term tubulo-interstitial disorders. There must be doubt whether clinical renal problems ever arise from interstitial abnormalities alone, rather than from associated tubular changes. Analogies are in the heart and brain, in which clinical disorders are due to abnormalities of myocytes and neurones, rather than due to changes in connective tissues. In the kidney, tubules and interstitial tissues are best analysed separately.

## Initial Study of Tubules

The pathologist should look at all pieces of kidney at low power on the microscope. This is to judge **how much cortex there is** and **the state of the tubules**. The pathologist should decide whether the kidney looks normal. To say whether something is normal is sometimes difficult for pathologists, shown by the phrases and words many use to avoid the word normal, such as within normal limits or unremarkable. Unremarkable, meaning not worthy of note, seems an inappropriate word for anything to do with the kidney, a remarkable organ whose range of functions has not been approached by any machine.

What can be accepted as normal in the kidney is different at different ages. This is one reason why the pathologist should know the age of the person biopsied before the specimen is examined.

A. J. Howie, *Handbook of Renal Biopsy Pathology.*

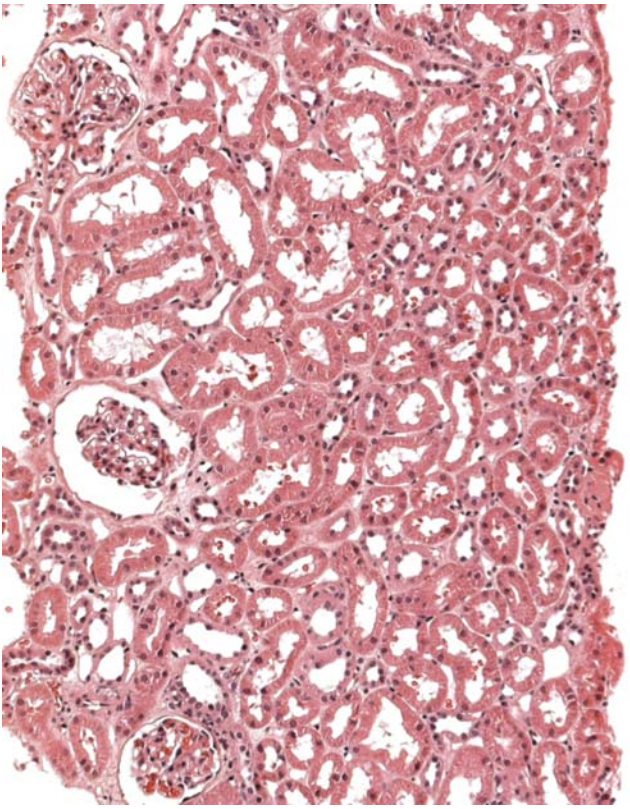

**Fig. 5.1** Normal cortex in a renal biopsy specimen from a girl of 15 with microscopic hematuria and thin glomerular basement membrane disease. Most of the cortex consists of proximal tubules. There is only a little interstitial tissue

Most of the normal cortex consists of proximal tubules (Fig. 5.1). Normal children and young adults have no sign of tubules that are **atrophic**, which means they are irreversibly damaged. Atrophy of tubules is significant, because affected tubules will never recover. Tubules may be abnormal, but provided they are not atrophic, they may recover.

## Assessment of Atrophy

Areas with atrophic tubules are often seen as irregularly shaped parts of the cortex that contain small tubules with thick basement membranes, more widely separated than normal tubules, with fibrous tissue and lymphocytes between tubules (Figs 2.1 and 5.2). In early atrophy, tubules have thick basement membranes, but may be only slightly smaller than normal. Another form of atrophy has dilated tubules with thin epithelium, solid material in the lumen of tubules, and hardly any interstitial

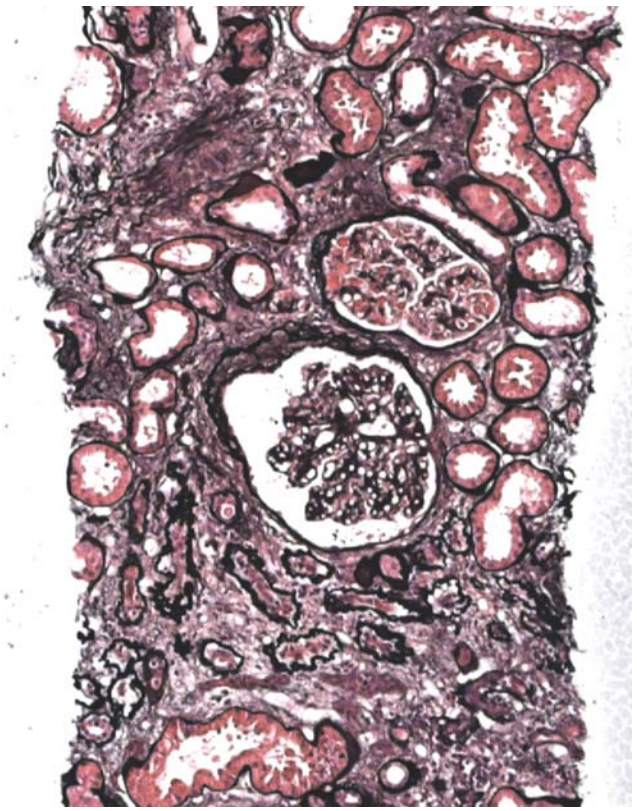

**Fig. 5.2** Cortex in a renal biopsy specimen from a man of 44 with chronic renal failure, and clinical evidence of hydronephrosis caused by retroperitoneal fibrosis. There are patches of atrophic tubules, and in these areas interstitial tissues are expanded. Surviving tubules are larger than normal. Glomeruli have extra layers of thickening on the inside of Bowman's capsule

tissue between tubules. This is called thyroidisation, because it has a resemblance to thyroid follicles (Fig. 5.3). Any solid material in the lumen of tubules can be called a **cast**, and this may contain cells. When atrophy has been present for a long time, atrophic tubules disappear, and surviving tubules are enlarged (Fig. 5.2).

With age, tubules become atrophic from effects of chronic ischemia, especially at the outer edge of the kidney next to the renal capsule (Fig. 5.4). **Ischemia** is the state of reduced blood supply to an organ, and may be acute or chronic. Acute ischemia may not have a permanent effect on the kidney, but chronic ischemia always has a permanent effect.

In a child or young adult, tubular atrophy suggests a disease that has been present a long time and is likely to progress, such as IgA nephropathy or hereditary nephropathy of Alport type. In older adults, tubular atrophy may not be a sign of a glomerular disorder, and the pathologist has to judge whether there is more atrophy than is appropriate for the age of the person biopsied. There may be a surprising

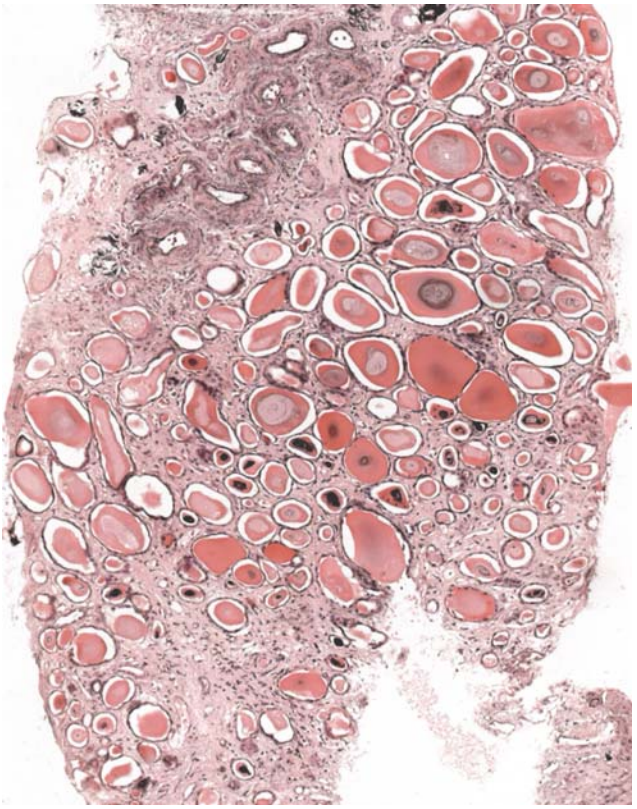

**Fig. 5.3** Renal biopsy specimen from a woman of 70 with chronic renal failure and ureteric tuberculosis. Many tubules appear thyroidised

amount of atrophy in specimens from people reported to have normal renal excretory function, because clinical measures of renal function are often crude and insensitive (Fig. 5.5).

The pathologist occasionally has also to assess whether one feature in a specimen, such as the amount of tubular atrophy, is out of proportion to another feature, such as the amount of glomerular damage. This may give a hint that there is more than one condition in the kidney.

Often, the extent of atrophy and other changes are reported in a crude way, such as by the use of words such as mild, moderate, and severe, or with a grading system. Although these assessments are subjective, depend on guesswork, and show poor reproducibility, they are better than nothing, and can give useful guidance to nephrologists. Several methods of more objective measurement of changes, using various techniques of **morphometry**, have been described. Some are not feasible in routine practice, but a few can be applied in everyday use. An example is a method of image analysis in which areas of chronic damage are outlined on a computer

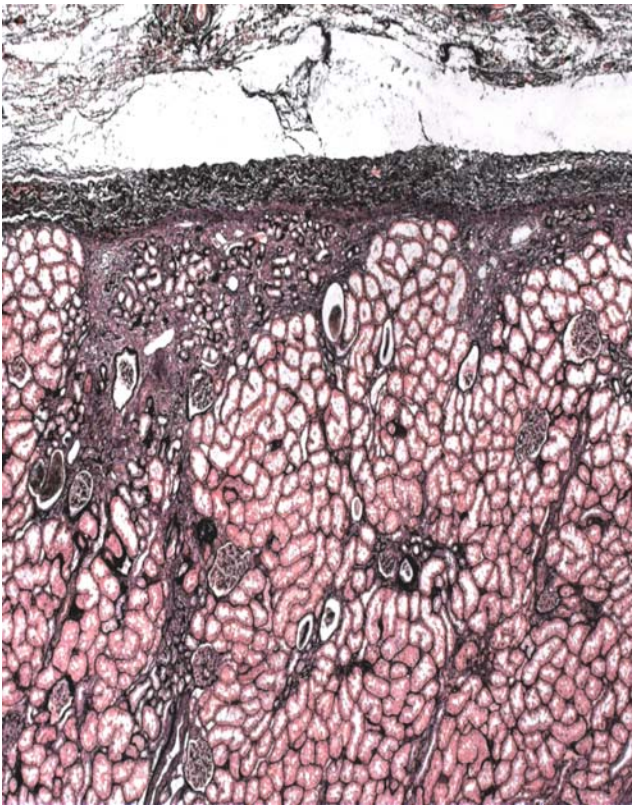

**Fig. 5.4** Capsular surface of a nephrectomy specimen from a woman of 39 showing nearly triangular areas of atrophy, apparently caused by compressive effects of a nearby oncocytoma

image of a biopsy specimen, and their total is expressed as a proportion of cortical area, to give a measurement called the index of chronic damage (Fig. 5.6).

## A Note on Hypertension and the Kidney

**Hypertension** worsens the renal ischemia and tubular atrophy associated with ageing, and can be regarded as causing the kidney to age more quickly. Similarly, hypertension adds ischemic damage to damage caused by any other process (Fig. 5.5).

Hypertension is a complication of most renal disorders, including chronic ischemic damage, but most hypertensive people have no identifiable cause of hypertension, although they must have had a cause at some stage in their life. Chronic renal failure is frequently attributed to hypertension, and sometimes the term **hypertensive nephrosclerosis** is used when there is chronic renal damage that seems due to effects of hypertension alone, without an identifiable underlying renal abnormality. **Sclerosis** comes from a Greek word and means hardness or hardening,

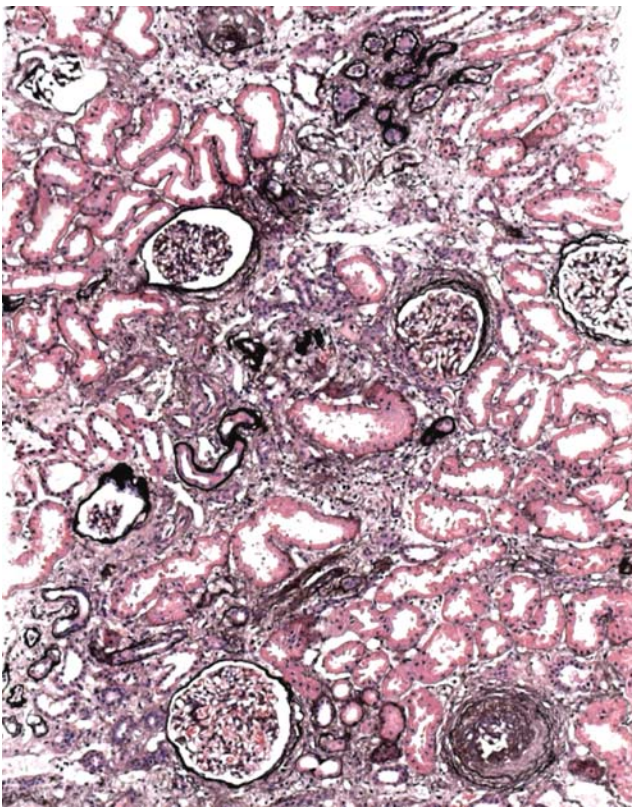

**Fig. 5.5** Renal biopsy specimen from a man of 40 with proteinuria and hypertension, reported to have normal renal function. The cortex is not normal and shows patches of tubular atrophy, with globally sclerosed glomeruli. Hypertension damages the kidney, and the damage may result in renal failure. The singer Barry White (1944–2003), originally named Barrence Eugene Carter, developed renal failure, ascribed to hypertensive effects, in 2002, and was on dialysis until his death at the age of 58

and is applied to the whole kidney in the term nephrosclerosis, and to a glomerulus when part or all appears more solid than normal.

Because hypertensive nephrosclerosis is diagnosed when there is established damage, a problem is to know whether the kidney was normal or abnormal before the development of hypertension. If the kidney was normal, hypertension by definition was not caused by a renal disorder, but then caused renal damage, corresponding to genuinely hypertensive nephrosclerosis. If the kidney was abnormal, hypertension was caused by the renal abnormality, and contributed to progressive damage. In this case, hypertension could not be considered the true, underlying cause of the renal damage, and the term hypertensive nephrosclerosis would be inappropriate.

There is evidence that hypertension in adult life, in at least some people, is related to intrauterine growth retardation when the person was a fetus. Growth retardation

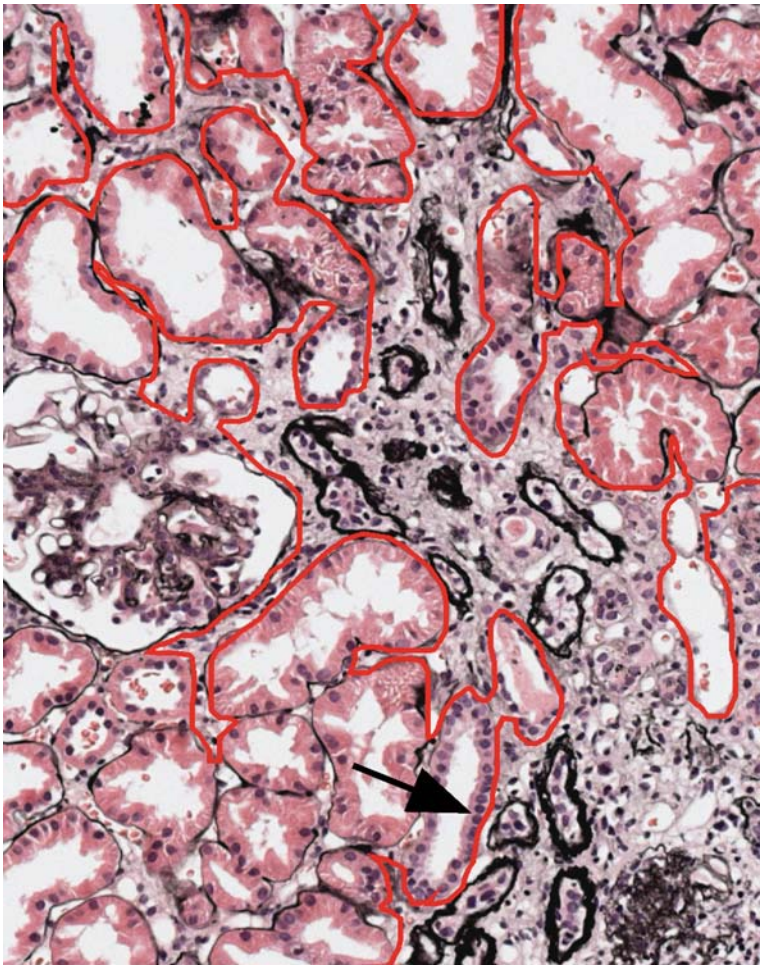

**Fig. 5.6** A method of measurement of the amount of chronic damage in a renal biopsy specimen. On computer images of cortex, freehand drawing can be used on most image analysis systems to outline parts with globally sclerosed glomeruli, atrophic tubules, and interstitial fibrosis, as shown by the arrowed line. The area of these parts is measured in any units, such as pixels, and expressed as a percentage of the total area of cortex in the specimen. This percentage is the index of chronic damage. Details of the method are given in Howie AJ, Ferreira MAS, Adu D. Prognostic value of simple measurement of chronic damage in renal biopsy specimens. *Nephrology Dialysis Transplantation* 2001; **16:** 1163–1169

is associated with failure of normal development of the kidney, particularly causing a reduced number of **nephrons**, meaning glomeruli and their associated tubules. The reduction may be slight, and not apparent by any clinical test currently available. These observations suggest that hypertension may develop as a consequence of underdevelopment of the kidney. Although hypertension undoubtedly damages the kidney, the implication of the terms hypertensive renal failure and hypertensive nephrosclerosis, that hypertension was the primary event, may be incorrect.

## Initial Study of Glomeruli: Glomerular Size

The pathologist should then examine **glomeruli**. These are roughly spherical structures, which can be cut in any plane. A glomerulus has a tuft consisting of capillaries, with basement membranes lined by endothelial cells and covered by visceral epithelial cells, also called podocytes. These capillaries are perfused at arteriolar pressure, which is a higher pressure than in capillaries elsewhere, and they are held together by specialised muscle cells, called mesangial cells. An afferent arteriole brings blood to the tuft, and an efferent arteriole takes the blood to capillaries in tissues outside the glomerulus. The tuft is enclosed within a fibrous capsule called Bowman's capsule, lined by parietal epithelial cells (Fig. 5.7).

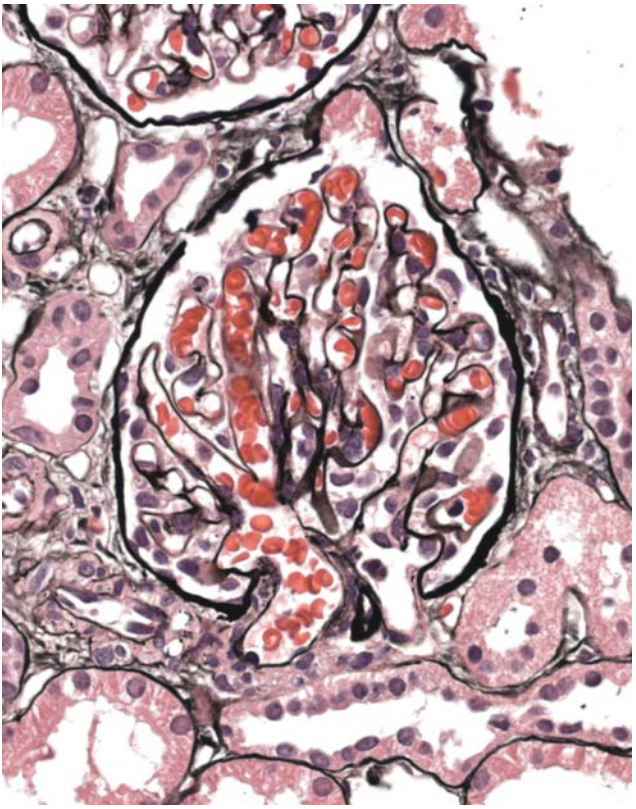

**Fig. 5.7** Glomerulus in the renal biopsy specimen from the girl of 15 with thin glomerular basement membrane disease, which is illustrated in **Fig. 5.1**. This appears normal on orthodox light microscopy, and shows the two landmarks that allow the position of a segmental lesion to be determined. These are the vascular pole, or hilum, where the arterioles cross Bowman's capsule, and the tubular origin, or opening of the proximal tubule from Bowman's space. In Latin, hilum meant a trifle, or that which adheres to a bean. The word is used in botany to mean the scar on a seed where it was attached to its stalk, and in anatomy to mean the site where structures enter or leave an organ

One glomerulus can appear of any size on sections, from the minimum recognisable as a glomerulus to the maximum diameter of that glomerulus. Glomeruli do not all have the same absolute diameter, but a range of diameters. A random section of cortex contains glomeruli not only of different apparent sizes, because they are cut in different planes, but also of different absolute sizes. The human eye is able to determine the relative size of objects, but determination of absolute size is difficult. If there are enough glomeruli, the pathologist can get an impression of the general size. Serial sections of renal biopsy specimens are valuable in assessment of this. Serial sections are also necessary to determine the proportion of glomeruli affected by any condition, and the position of abnormalities within glomeruli (Fig. 5.7).

Normal glomeruli are different at different ages. Glomeruli enlarge in children from birth in proportion to their age, until adult size is reached in the early teenage years. In adults, glomerular size is proportional to body size. There is no normal glomerular size, just as there is no normal height or body weight, but there is a range of normality. Because of this, assessment of the significance of glomerular size is not straightforward. Measurement is possible, but is not done in everyday practice. Even if it were, a measure of glomerular size in one specimen would be difficult to interpret. Measurement in groups of specimens is easier to interpret, because this allows in a crude way for effects of variation of body size on glomerular size. A change in glomerular size is significant in repeat biopsies.

Glomerular tufts that look **small** to the pathologist, when allowance is made for age, are usually either underdeveloped or ischemic, although another explanation may be the condition of collapsing glomerulopathy, which is covered in Chapter 6. **Underdeveloped glomeruli** have the fetal appearance in the tuft, with a spray of epithelial cells around empty basement membranes. Bowman's capsule also appears small (Fig. 5.8). **Ischemic glomeruli** have a shrunken tuft with wrinkled basement membranes. The tuft seems too small for Bowman's capsule, which is comparable in size to most others in the specimen. Bowman's space appears larger than normal (Fig. 5.9).

When the glomerulus has been ischemic for a long time, Bowman's capsule often appears thicker than normal and is wrinkled with new layers of material on its inner side (Fig. 5.2). This is sometimes called periglomerular fibrosis. On sections stained by hematoxylin and eosin, ischemic glomeruli appear solid and hypercellular, with thickened basement membranes. Periodic acid-methenamine silver staining shows that the apparent hypercellularity is explained by shrinkage of the tuft, and basement membrane thickening is explained by wrinkling of membranes that are no longer distended by the pressure of blood within them (Fig. 5.9).

If glomeruli appear **large** to the pathologist, either all or only some may show enlargement. **Any glomerular abnormality that affects all glomeruli is called diffuse**. **Any abnormality that affects only some is called focal**. Diffuse enlargement may be because the person biopsied is large, or has only one kidney, or was born with too few glomeruli, but glomeruli appear otherwise normal (Figs 5.10 and 5.11). Another explanation is that there is a glomerular disorder, such as some types of glomerulonephritis. Focal enlargement is because there has been a condition that has made some glomeruli shrink or disappear, and surviving glomeruli enlarge in

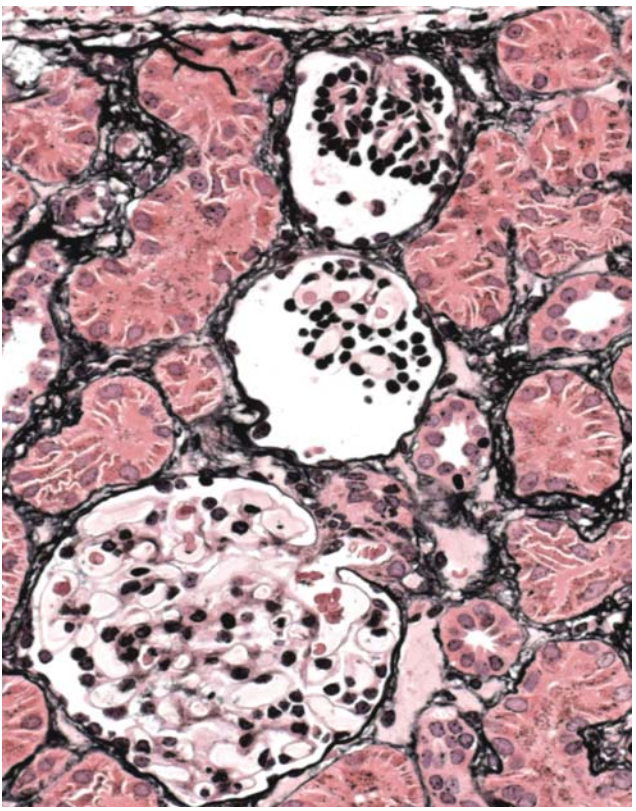

**Fig. 5.8** Two underdeveloped or fetal glomeruli, and one apparently normal glomerulus, near the renal capsule, in a renal biopsy specimen from a boy of 3 with minimal change nephropathy

compensation. Compensatory enlargement is rarely uniform between glomeruli, and there is almost always a range of glomerular sizes.

## Initial Study of Glomeruli: Distribution of Glomerular Abnormalities

Glomeruli should be inspected to see if they all look the same, and if so, whether they look normal. An abnormality of a glomerulus can affect either the whole of it, when it is called a **global** disorder, or only part of it, called a **segmental** disorder. The term segmental is often confused with focal, but has a different meaning in renal pathology. Often, focal and segmental are automatically linked in descriptions or diagnoses, but the pathologist should remember that a focal disorder may be global, and a segmental disorder may be diffuse.

For a report, but not necessarily on initial inspection, the pathologist should count glomeruli on a section that seems representative of the specimen, preferably a section stained by periodic acid-methenamine silver, which helps the pathologist

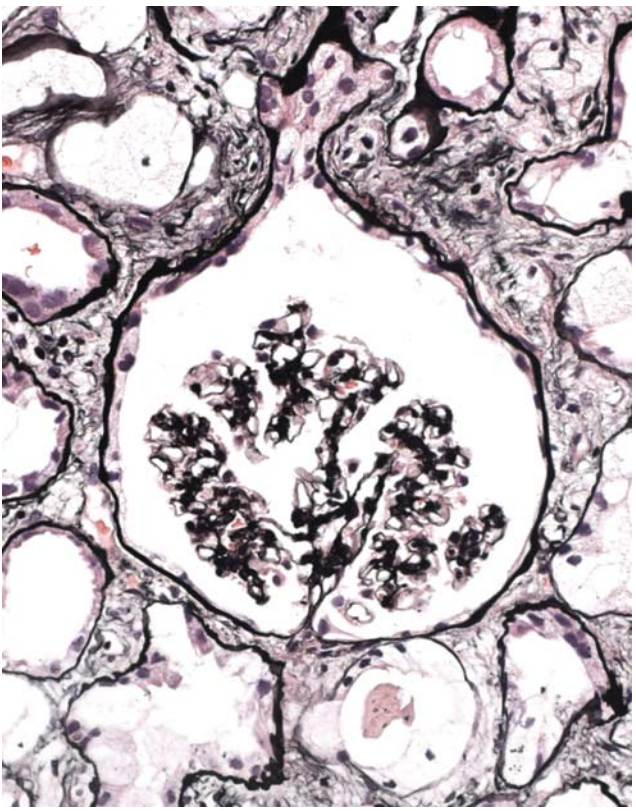

**Fig. 5.9** Severely ischemic glomerulus in a renal biopsy specimen from a woman of 55 with prolonged acute renal failure after staphylococcal pneumonia. The tuft is shrunken, appears more solid than normal, has wrinkled basement membranes, and seems too small for Bowman's capsule. Tubules have irregularly flattened epithelium, with fine vacuolation

to identify all glomeruli. A count is easily done, especially with the aid of manual counting devices, such as those used in hematology laboratories to calculate the proportions of different types of cells in aspirated marrow samples.

At the simplest level, the count of glomeruli should divide them into those with global sclerosis and the rest. **Global sclerosis** means that there is solid tissue, acellular or nearly so, that replaces the original glomerulus (Fig. 5.5). Usually, remains of Bowman's capsule, and of the glomerular tuft and abnormalities in it, can still be recognised with the periodic acid-methenamine silver stain (Fig. 5.12). Glomeruli with global sclerosis shrink and eventually disappear. The significance of these glomeruli is that they will never function again, and they indicate irreversible renal damage. The proportion of glomeruli that are globally sclerosed is a crude measure of the extent of chronic damage.

Because there are different implications of global sclerosis and segmental sclerosis, the pathologist should always specify the distribution of sclerosis. Glomerular sclerosis or scarring or similar terms are not helpful without qualification.

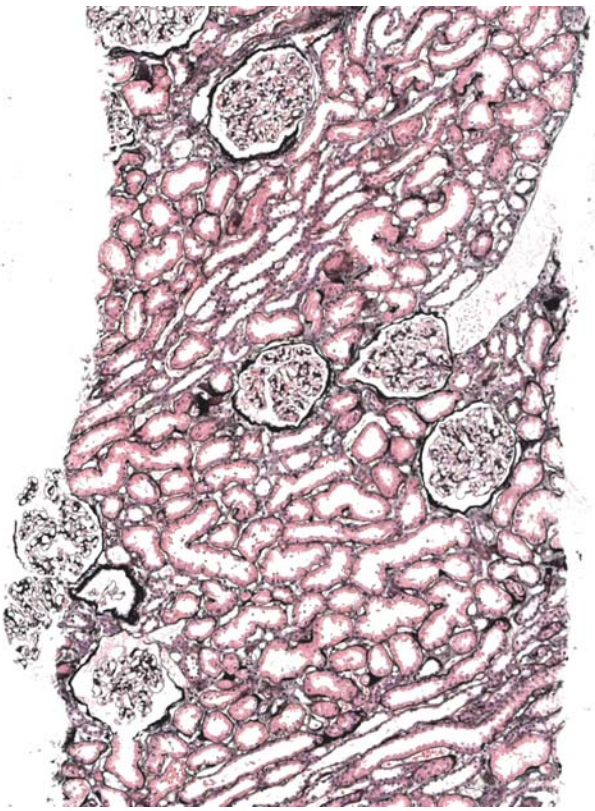

**Fig. 5.10** Glomeruli of normal size in a renal biopsy specimen from a man of 51 with microscopic hematuria and thin glomerular basement membrane disease, taken at the same magnification as **Fig. 5.11**

Sometimes, the terms glomerular obsolescence or obsolescent glomeruli are used. These have a functional implication, because obsolete means worn out, or no longer working, or imperceptible. Global sclerosis is an accurate description of what is seen and is a preferable term, if only because some glomeruli that are no longer working do not have global sclerosis, for instance glomeruli with ischemic shrinkage.

The pathologist should decide whether glomeruli that are not globally sclerosed look normal or not, after subjective assessment of size. A large glomerulus may still look otherwise normal. Normality of glomeruli is not easy to define, mainly because the appearance of glomeruli depends on how a specimen is fixed and processed for microscopy, how thick the sections are, and how the sections are stained. This variation makes assessment of specimens from other laboratories difficult for a pathologist, who should have an impression from specimens routinely handled in the pathologist's own laboratory of the normal appearance. Even for experienced pathologists, there may be specimens in which glomeruli cannot be said to be either

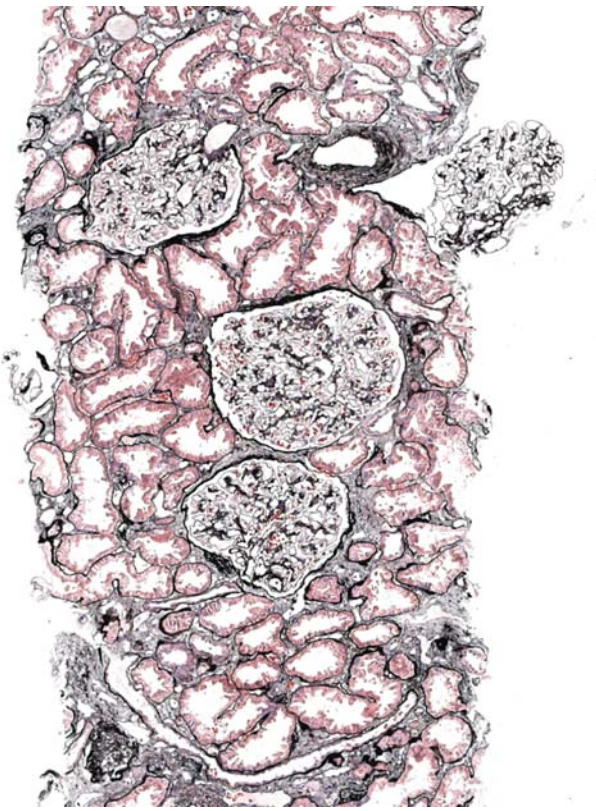

**Fig. 5.11** Cortex in a renal biopsy specimen from a man of 69 with mild renal impairment and one kidney, taken at the same magnification as **Fig. 5.10**. Glomeruli are large

definitely normal or definitely abnormal. This particularly applies to determination of whether there is an increase in the amount of mesangium. Definitions of normal mesangium are usually based on the number of cells per mesangial area, often said to be no more than three in sections 2–3-μm thick, and the amount of mesangial matrix, assessed subjectively.

Assessment of **segmental disorders** is helped by serial sections. Although the position of segmental changes in glomeruli does not seem important in some conditions, such as vasculitis, in other conditions it is of major importance, such as in conditions with the nephrotic syndrome. The position of segmental changes can only be determined if a landmark is seen, which means either the hilum where the arterioles cross Bowman's capsule, or the opening of the tubule (Figs 5.7 and 5.13). The hilum is larger and is more often seen than the tubular opening.

Segmental sclerosis is used when part of the glomerular tuft appears solid, usually stains with periodic acid-methenamine silver, and sometimes adheres to Bowman's capsule. Another type of segmental change is **hyalinosis**, derived from a

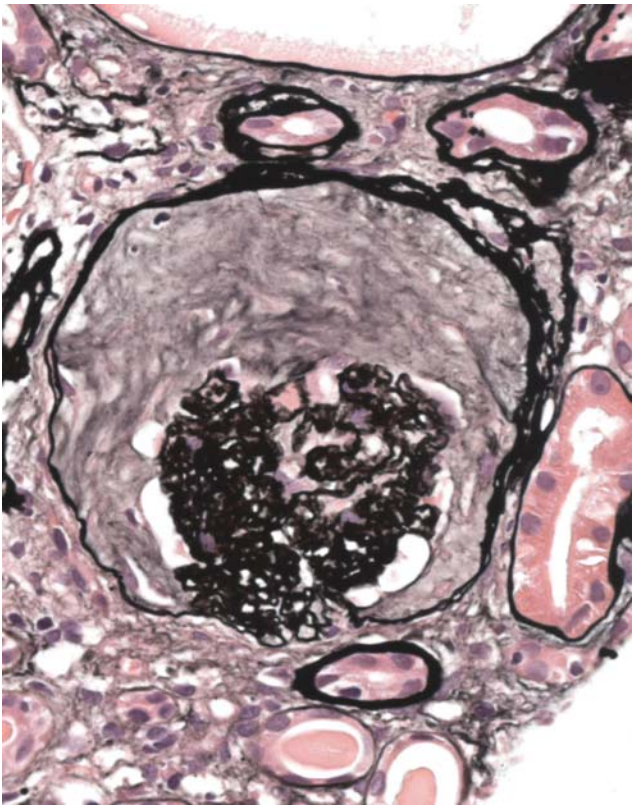

**Fig. 5.12** Globally sclerosed glomerulus in a renal biopsy specimen from a man of 53 with chronic ischemic damage. On a section stained by periodic acid-methenamine silver, the shrunken tuft and Bowman's capsule are still recognisable

Greek word meaning glass or crystal, when acellular material is seen, stained pink by hematoxylin and eosin, but not stained by periodic acid-methenamine silver (Fig. 5.13).

## Initial Study of Interstitial Tissues

In the normal cortex, there is hardly any tissue between tubules, glomeruli, and blood vessels (Fig. 5.1). Expansion of interstitial tissues may be because there has been atrophy of tubules, or because there is edema, an inflammatory infiltrate, or fibrosis (Fig. 5.2). In general, tubular changes are more important than changes in interstitial tissues.

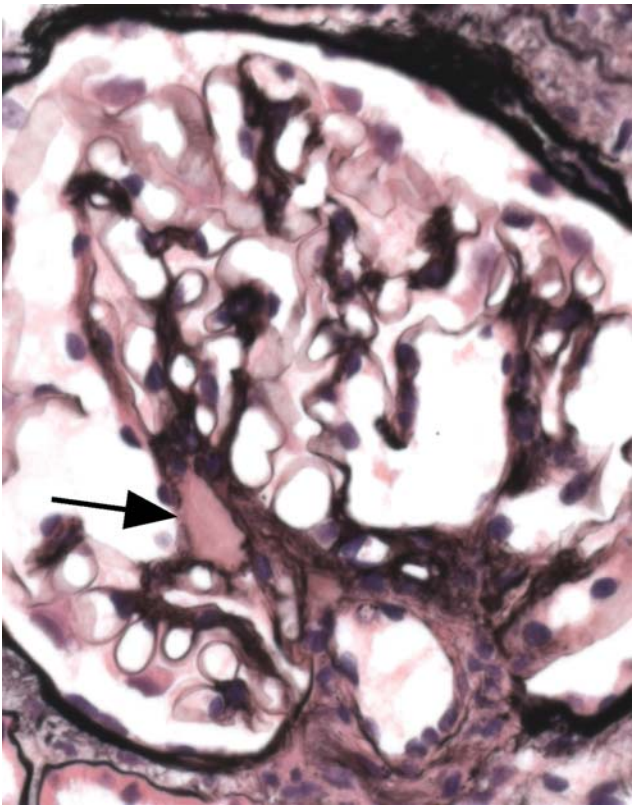

**Fig. 5.13** Glomerulus in a renal biopsy specimen from a man of 51 with proteinuria, chronic renal failure, and one kidney. There is a segmental abnormality (arrowed), which is a nodule of hyaline material, not stained by periodic acid-methenamine silver, next to the vascular pole of the glomerulus

## Initial Study of Blood Vessels

With age, there are changes in blood vessels in the kidney. Arteries develop intimal thickening, which can be shown to be due to accumulation of collagen and elastic tissue if stains are used such as elastin hematoxylin van Gieson, although these are not usually necessary (Fig. 5.14). The walls of arterioles develop nodules of acellular, hyaline material, which contains plasma proteins such as IgM (Fig. 5.15). Both the intimal thickening of arteries and the nodular hyalinosis of arterioles appear earlier and are more severe in hypertensive people, and are not seen in normal children. Veins in the cortex have little more than endothelium in their walls, and usually appear empty.

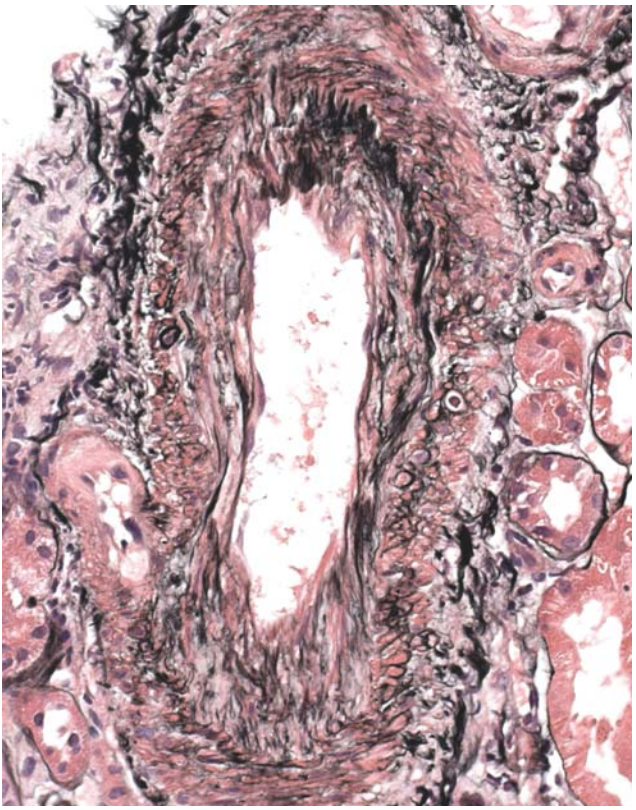

**Fig. 5.14** Arcuate artery in a renal biopsy specimen from a man of 73 with chronic renal failure. The artery has chronic concentric intimal thickening which is found with ageing, but is made worse by hypertension. A smaller artery has hyalinosis

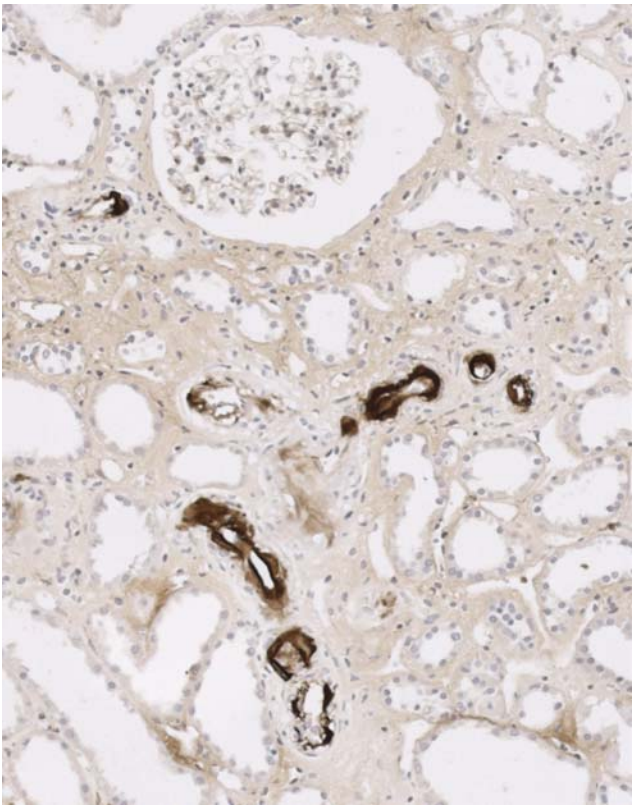

**Fig. 5.15** Cortex in a wedge biopsy specimen taken at the time of transplantation of a cadaveric kidney from a man of 49, who died of a subarachnoid hemorrhage, stained by an immunoperoxidase method to detect IgM. Arterioles have extensive deposition of IgM in their walls, which indicates severe hyalinosis, and suggests that the donor had been hypertensive

## Summary: How to Look at a Renal Biopsy Specimen: Initial Study of the Kidney

In all specimens, the most important part of initial study is to determine the extent of tubular atrophy.

The pathologist should assess glomerular size, whether glomeruli look normal, whether abnormalities are in every glomerulus, called diffuse, or only in some glomeruli, called focal, and whether abnormalities are throughout a glomerulus, called global, or only in part of a glomerulus, called segmental.

## Further Reading: How to Look at a Renal Biopsy Specimen: Initial Study of the Kidney

D'Agati VD, Jennette JC, Silva FG. Non-Neoplastic Kidney Diseases. Atlas of Nontumor Pathology, first series, fascicle 4. Washington, DC: American Registry of Pathology and Armed Forces Institute of Pathology, 2005. Chapter 16.

Jennette JC, Olson JL, Schwartz MM, Silva FG. Heptinstall's Pathology of the Kidney. Sixth ed. Philadelphia: Lippincott Williams and Wilkins, 2007. Chapter 3.

# Chapter 6
# Indication for Biopsy: Nephrotic Syndrome

## Introduction to the Nephrotic Syndrome

This means heavy proteinuria accompanied by hypoalbuminemia and edema, often seen as swelling of the ankles and higher up the lower limbs, which is usually the clinical feature that makes people seek the help of a physician. Occasionally, proteinuria is in the nephrotic range without the other features of the syndrome. Renal excretory function may be normal or abnormal. There may be hematuria or hypertension. There is hyperlipidemia as part of the syndrome.

Edema and hypertension are due to increased retention of sodium and water by renal tubules. Hyperlipidemia is due to increased synthesis of low density lipoproteins, and decreased catabolism of cholesterol.

The nephrotic syndrome is commoner in boys than in girls, and in men than in women.

The nephrotic syndrome is dangerous because it is associated with a risk of thrombosis, susceptibility to infection, and wasting of muscles. Thrombosis is due to increased concentration of coagulation factors in the blood, with reduced concentration of thrombolytic and antithrombotic factors. Susceptibility to infection is partly due to loss of immunoglobulins in the urine, and to increased catabolism of immunoglobulins. Muscle wasting is due to increased protein catabolism.

Syndrome, in this context, means a set of clinical features produced by different diseases. The conditions that produce the nephrotic syndrome have something in common, because they all increase glomerular permeability to protein. The nephrotic syndrome **always indicates a glomerular disorder**. Protein can be found in the urine for reasons other than increased glomerular permeability, but nothing else can produce heavy enough loss of protein to give the nephrotic syndrome. In **glomerular proteinuria**, the main protein in the urine is albumin. The selectivity of the proteinuria, or relative concentrations of albumin or similarly sized proteins, and larger proteins, was considered clinically useful in the past, but is now rarely measured.

A. J. Howie, *Handbook of Renal Biopsy Pathology.*

## Detection and Measurement of Proteinuria

Understanding the detection and measurement of proteinuria may help the pathologist in interpretation of renal biopsy specimens. In particular, knowledge of potential difficulties and inaccuracies in measurement may be useful.

Proteinuria is detected by the use of reagent strips, called dipsticks, that are dipped in urine, and change colour if protein is present. These strips detect other substances as well, such as blood, and are the way in which microscopic hematuria is discovered. This is called **urinalysis**. Proteinuria can only be assessed crudely by this method.

Usually, if proteinuria is detected, this is measured. Often, this is expressed as output per 24 h, which is sometimes loosely called output per day, although that expression is ambiguous, because there is an implication that the night is ignored. Output per 24 h is measured, because the protein content of the urine varies over 24 h. Total protein output is often assessed. In normal adults, the total is under 150 mg per 24 h, and this includes Tamm–Horsfall protein and others derived from the urinary tract, as well as tiny amounts of protein from the blood. There are various chemical methods in use, some sensitive to interference by materials other than proteins. A specific protein, albumin, is sometimes measured by immunologic methods. Urinary albumin excretion is a more sensitive test of significant proteinuria than total protein output, and in normal adults is under 30 mg per 24 h.

Heavy proteinuria in adults is defined arbitrarily as at least 3 g total protein output in the urine per 24 h, although some definitions say 3.5 g.

All measurements that rely on a timed urine collection are suspect, because this has the risk of inaccuracy arising from incomplete collection. For this reason, proteinuria is often assessed in other ways. Measurement of the concentration of either total protein or albumin in a urine sample is relatively straightforward, but is not usually used on its own. The state of dilution or concentration of the urine affects this measurement, but this can be standardised by simultaneous measurement of the concentration of creatinine in the sample. These days, proteinuria is often expressed as the ratio of concentrations of either total protein or albumin to creatinine in a single sample of urine, in various units. Clinical chemical laboratories usually have their own reference range for these ratios.

In children, timed urine collections are hardly ever done and if they are, body size has to be considered when proteinuria is measured as total output. Use of protein/creatinine or albumin/creatinine concentration ratios removes the need to calculate body surface area or other indicators of body size.

## Value of a Renal Biopsy in the Nephrotic Syndrome

Most or all adults with the nephrotic syndrome have a renal biopsy, but most children with the nephrotic syndrome do not. This is because they are assumed to have minimal change nephropathy, and are managed accordingly. A biopsy is done in a child if there are unusual clinical features, such as presentation in late childhood or

with an insidious onset. Minimal change nephropathy typically gives an abrupt onset of edema, and is particularly common in children under the age of five, especially boys. A biopsy is also done if the response to treatment is not typical of minimal change nephropathy.

The diagnosis in the nephrotic syndrome is a great help to nephrologists, to make clinical decisions about management. For instance, minimal change nephropathy should respond to appropriate treatment and should not progress to chronic renal failure, although membranous nephropathy may not respond to any treatment and may progress.

The biopsy specimen may give clues that there are complications of the nephrotic syndrome, particularly renal vein thrombosis.

The amount of chronic damage in the specimen is a guide to the long-term outlook for the kidney.

## Approach to the Diagnosis in the Nephrotic Syndrome

Renal biopsy specimens in the nephrotic syndrome are usually straightforward and satisfying for the pathologist, because a definite diagnosis can almost always be given.

The pathologist should examine the renal biopsy specimen with the rule in mind that common things are common. The prevalence of various conditions in specimens depends upon the age of people biopsied, the part of the world, and whether nephrologists biopsy everyone with the nephrotic syndrome, or are selective in their biopsy practice. The syndrome is commoner in developing countries than elsewhere.

In **adults** with the nephrotic syndrome, three conditions are found in the majority of specimens. These are membranous nephropathy, various segmental sclerosing disorders often called focal segmental glomerulosclerosis, and minimal change nephropathy.

The pathologist has a high expectation of finding one of these three conditions before the specimen is examined. The proportion of specimens that have these conditions varies depending upon factors such as the willingness of nephrologists to biopsy people with the nephrotic syndrome associated with other disorders, particularly diabetes mellitus and systemic lupus erythematosus. Where nearly all adults with the nephrotic syndrome are biopsied, membranous nephropathy, segmental sclerosing disorders, and minimal change nephropathy together account for about two-thirds of specimens in descending order of frequency, and these conditions with diabetic glomerulopathy, lupus nephritis, and amyloid account for nearly nine-tenths of specimens. Various glomerular conditions are found in the relatively few other adults with the nephrotic syndrome.

In the relatively few **children** with the nephrotic syndrome who have a renal biopsy, most have minimal change nephropathy, and about three-quarters have this condition or a segmental sclerosing disorder.

Various other findings occur in the rest of the children, with different frequencies from adults. Membranous nephropathy is rare in children in higher income

countries, and diabetic glomerulopathy and amyloid are hardly ever seen in children. There is a group of disorders causing congenital or infantile nephrotic syndrome, some of which are only found in young children.

## Initial Inspection of a Renal Biopsy Specimen in the Nephrotic Syndrome

Although glomeruli have to be examined in detail in the nephrotic syndrome, renal biopsy specimens should first be inspected at low power on the microscope, to see whether **tubules** look normal or not. If they are not normal, the next question is whether there is acute damage, or chronic damage, or a mixture. In **acute tubular damage**, there is an apparently normal number of tubules in the renal cortex, when the age of the person biopsied is taken into consideration. Acutely damaged tubules

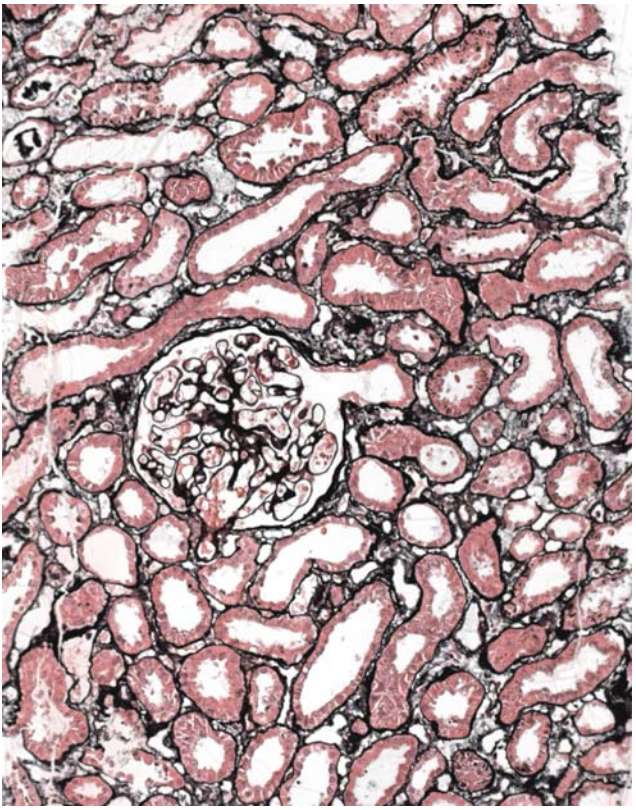

**Fig. 6.1** Cortex in a renal biopsy specimen from a woman of 49 with the nephrotic syndrome and mild acute renal impairment. The nephrotic syndrome is explained by minimal change nephropathy. There is extensive acute damage to tubules, which are dilated, with irregular epithelium. This appearance in the nephrotic syndrome suggests the possibility of renal vein thrombosis, which the woman was shown to have on radiologic investigation

have any of a variety of changes including irregular flattening of the epithelium, vacuolation, loss of the brush border, and accumulation of material in the lumen. If acute tubular damage is easily seen, there is likely to be acute renal failure as well as the nephrotic syndrome.

Acute tubular damage, especially if widespread and uniform, may indicate **renal vein thrombosis**, a complication of the nephrotic syndrome arising from the hypercoagulable state. Renal vein thrombosis is difficult to diagnose with certainty on a renal biopsy specimen. Thrombus is unlikely to be seen in veins included in a biopsy specimen, but if the pathologist sees extensive tubular damage, renal vein thrombosis should be reported as a possibility (Fig. 6.1). This damages tubules by impairing blood flow through the kidney, and causing ischemia. The danger is that if there is renal vein thrombosis that is not treated, there may be irreversible damage to tubules (Fig. 6.2). This is not the only cause of acute tubular damage in

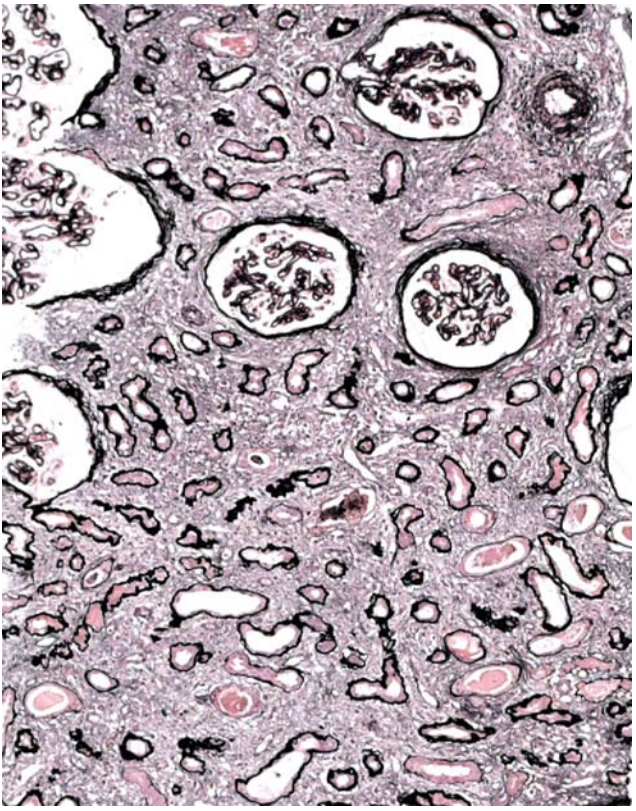

**Fig. 6.2** Cortex in a renal biopsy specimen from a man of 38 known to have membranous nephropathy, shown by a biopsy nearly 2 years before this one. The nephrotic syndrome had persisted since the first biopsy, and acute renal failure had developed 1 month before this biopsy. There is now widespread uniform tubular atrophy, which suggests longstanding renal vein thrombosis. This was confirmed by radiologic investigation. Renal function did not recover

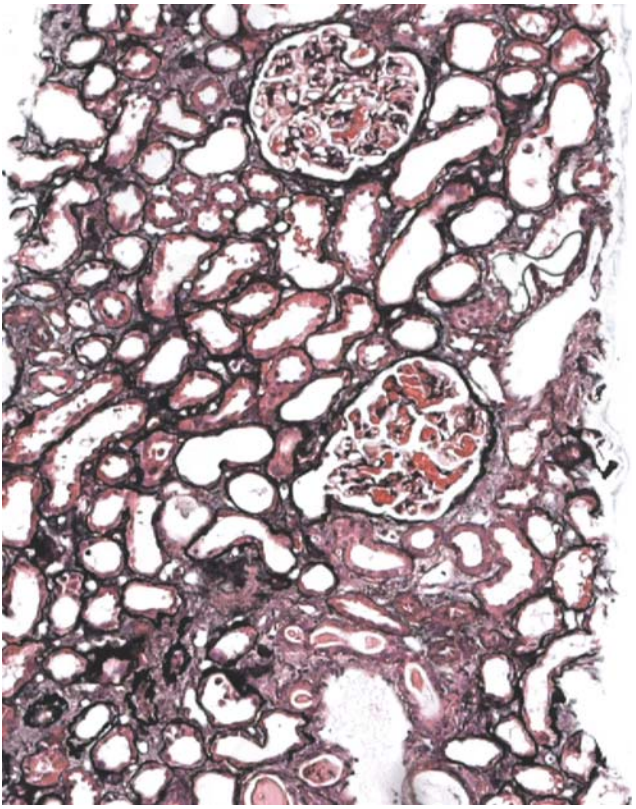

**Fig. 6.3** Cortex in a renal biopsy specimen from a man of 56 with the nephrotic syndrome and acute renal failure. The nephrotic syndrome is explained by an early form of classic segmental sclerosing glomerulonephritis. There is acute tubular damage, resembling the appearances in **Fig. 6.1**. Renal vein thrombosis was suggested as a possible explanation, but was excluded by appropriate investigations. Later, the renal failure recovered almost to normal, but the cause was not identified

the nephrotic syndrome. Other explanations include toxic effects of luminal protein on tubules, and intravascular fluid depletion, for instance from effects of powerful diuretics, or movement of fluid out of vessels as a consequence of the nephrotic state, particularly from osmotic consequences of the low plasma albumin concentration (Fig. 6.3).

**Chronic damage** means changes such as global sclerosis of glomeruli, atrophy of tubules, and interstitial fibrosis. An amount of chronic damage that seems disproportionately large for age has prognostic significance, indicates that there is a longstanding disorder, and means that renal function is never likely to recover to be completely normal.

### *Do Glomeruli Look Normal? Is the Diagnosis Minimal Change Nephropathy?*

**Minimal change nephropathy** is a diagnosis that has immense prognostic significance, since the person with it should respond to appropriate treatment and never progress to renal failure, even though there may be relapses of the nephrotic syndrome. The condition can occur at any age. Children respond more quickly than adults, but even without treatment, the condition should eventually resolve, provided there are no complications of the nephrotic state.

In most people, the explanation of minimal change nephropathy is not yet known, but a likely cause is that lymphocytes produce a circulating factor that increases the permeability of glomerular basement membranes to protein. Rare causes of the condition are nonsteroidal anti-inflammatory drugs and lymphomas, but the pathologist is usually not able to detect these on a renal biopsy specimen.

**The diagnosis of minimal change nephropathy should only be used when there is the nephrotic syndrome**, but is sometimes misused when applied by pathologists to specimens taken for hematuria or other indications, and which seem to show no abnormality.

Minimal change nephropathy is a difficult diagnosis to make. The pathologist should use the term with care. Because it is largely a diagnosis of exclusion of other things, the fewer the glomeruli in a specimen, the less certain a pathologist can be about the diagnosis.

## Diagnosis of Minimal Change Nephropathy

In minimal change nephropathy, glomeruli look normal on light microscopy. There is no increase in cellularity, nor are there segmental abnormalities, nor enlargement, although a pathologist may find difficult in certainty about these features (Figs 6.4 and 6.5). **Only one definite segmental abnormality has to be seen to exclude this diagnosis**.

Immunohistology shows no deposition of immunoproteins on glomerular basement membranes, and either no deposition of immunoproteins or only IgM in mesangium. Mesangial deposition of IgM does not exclude minimal change nephropathy, if all other features support this diagnosis.

Electron microscopy can be done, but is not necessary for the diagnosis of minimal change nephropathy. This will show loss of epithelial foot processes on the outside of glomerular basement membranes, and replacement by sheets of epithelial cell cytoplasm, which is due to swelling of foot processes, rather than their fusion, as it is sometimes called (Figs 6.6 and 6.7). Effacement is also used to describe this change, which seems a response to proteinuria, found in all specimens in the nephrotic syndrome. Electron microscopy will exclude immune deposits, for instance on glomerular capillary loops, but satisfactory immunohistologic staining excludes these anyway.

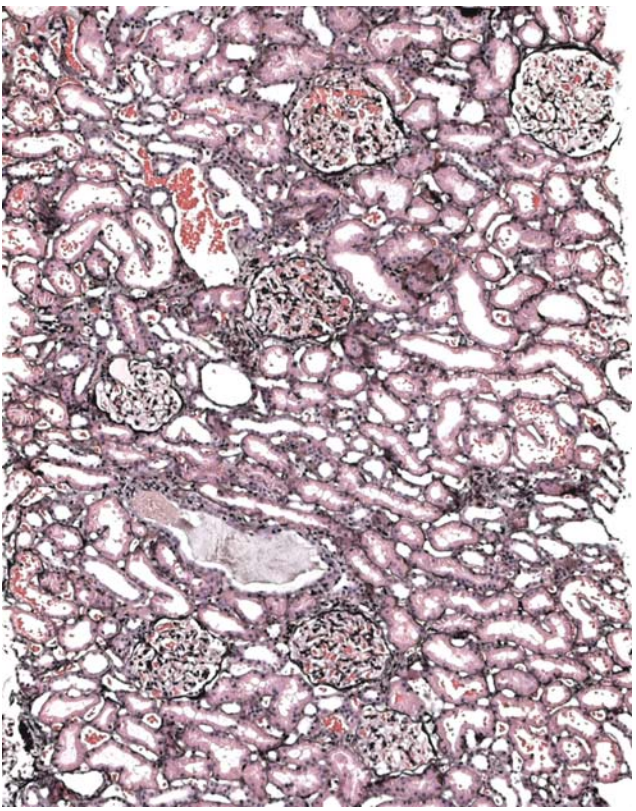

**Fig. 6.4** Cortex in a renal biopsy specimen from a man of 62 who was spontaneously beginning to recover from the nephrotic syndrome. Glomeruli appear of normal size and cellularity, have no segmental lesions on any of the full set of sections, and show no significant deposition of immunoproteins on immunohistologic study. The diagnosis is minimal change nephropathy

## Differential Diagnosis of Minimal Change Nephropathy

On initial sections, without a full set of stains and without immunohistology, the pathologist may see no glomerular abnormality. If pressed for a diagnosis by nephrologists, the pathologist should be cautious, and offer a provisional diagnosis that minimal change nephropathy is a possibility. Early membranous nephropathy may show little or no abnormality on orthodox staining, and can be easily mistaken for minimal change nephropathy, but will be immediately apparent on immunohistology. The full set of sections may show a segmental abnormality, which excludes minimal change nephropathy. The more glomeruli that are examined, the more confident the pathologist can be that there is no segmental disorder. Small amounts of amyloid in glomeruli may be missed, if a Congo red stain is not done or is technically unsatisfactory, or if the mesangium is not inspected thoroughly.

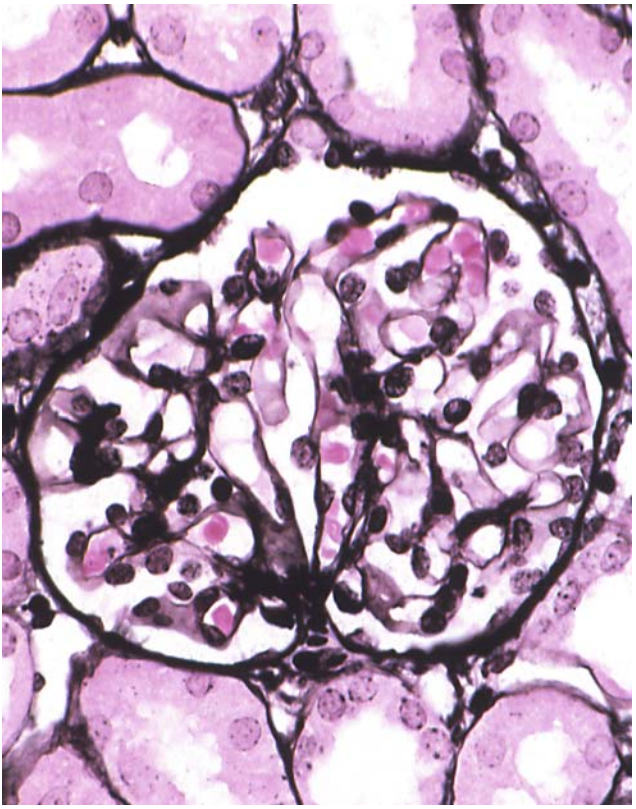

**Fig. 6.5** Glomerulus in a renal biopsy specimen from a girl aged 21 months with the nephrotic syndrome for 2 weeks. This glomerulus and all others appear normal, and there is no significant deposition of immunoproteins on immunohistologic study. The diagnosis is minimal change nephropathy

## *Are Glomeruli Abnormal? Is There Membranous Nephropathy?*

**Membranous nephropathy** is almost always an easy diagnosis to make. Because the condition affects the whole of every glomerulus, only one glomerulus is needed to make the diagnosis.

Membranous nephropathy is the commonest finding in the nephrotic syndrome in adults in several parts of the world, but is generally rare in children. This disorder is also common in cats and dogs with the nephrotic syndrome.

In most people, the cause is not yet apparent. Sometimes, in the absence of known causes or associations, the word "idiopathic" is used. This appears a respectable term, but simply means that the cause is not known. The pathogenesis of membranous nephropathy may be related to the fact that the main immunoglobulin subclass found in glomeruli in this condition is IgG4. This is associated with antibodies of low affinity for antigen, which do not activate the classic pathway of the complement

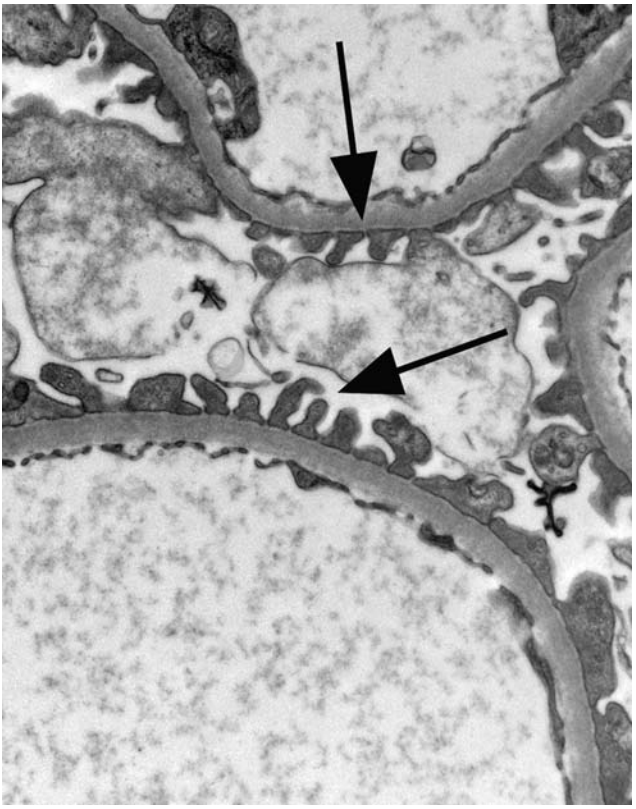

**Fig. 6.6** Electron micrograph of a renal biopsy specimen from a man of 47 with mild acute tubular damage, but no glomerular abnormality. Glomerular basement membranes have the normal adult appearance and thickness, from 270 to 340 nm. On the outside of the membranes, there are foot processes of epithelial cells (arrowed), separated by slit pores

system. Immune complexes containing IgG4 may not be cleared from the circulation, but settle in glomeruli, where they dissociate on the inside of basement membranes and reform on the outside.

A few people have an underlying explanation of membranous nephropathy. Recognised factors include drugs such as gold and penicillamine, infections such as with hepatitis B and hepatitis C viruses, neoplasms such as carcinoma of the bronchus, and use of skin creams containing mercury. The pathologist is unlikely to be able to identify an underlying explanation of membranous nephropathy from appearances in a biopsy specimen, although there may be clues, such as inclusions in lysosomes of proximal tubular cells after treatment with gold. Systemic lupus erythematosus can produce nearly every glomerular disorder including membranous nephropathy, but the diagnosis should be given as lupus nephritis, suitably qualified, rather than membranous nephropathy, if this is an abnormality found in a person with lupus.

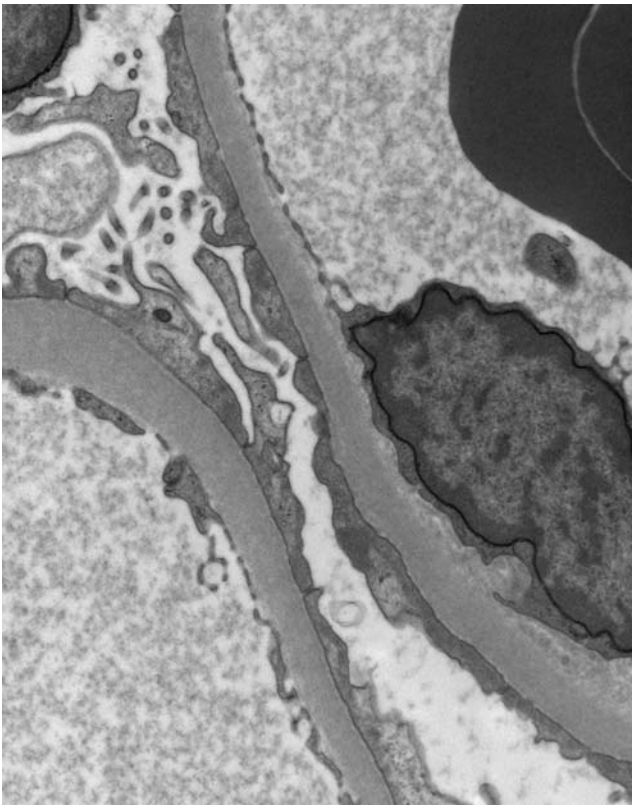

**Fig. 6.7** Electron micrograph of a renal biopsy specimen from a man of 38 with the nephrotic syndrome and minimal change nephropathy. Glomerular basement membranes are covered on the outside by a sheet of epithelial cell cytoplasm

## Diagnosis of Membranous Nephropathy

Orthodox light microscopy often suggests the diagnosis, because even on sections stained by hematoxylin and eosin, glomerular basement membranes appear uniformly thickened and more rigid than normal. The earliest stages may not show this, and may be mistaken for minimal change nephropathy if immunohistology is not done (Figs 6.8 and 6.9). Later stages are easy to identify on sections stained by periodic acid-methenamine silver, on which there are uniform spikes on the outside of glomerular basement membranes, which progress to give the appearance of chain links as the tips of the spikes join together (Fig. 6.10). These days, spikes are usually not well developed at first presentation of membranous nephropathy, and because they are not essential for the diagnosis, there is no need for the pathologist to search hard for them, either on especially thin sections or with an oil immersion objective lens on the microscope. Generally, the cellularity of glomeruli in membranous nephropathy appears normal, or close to normal.

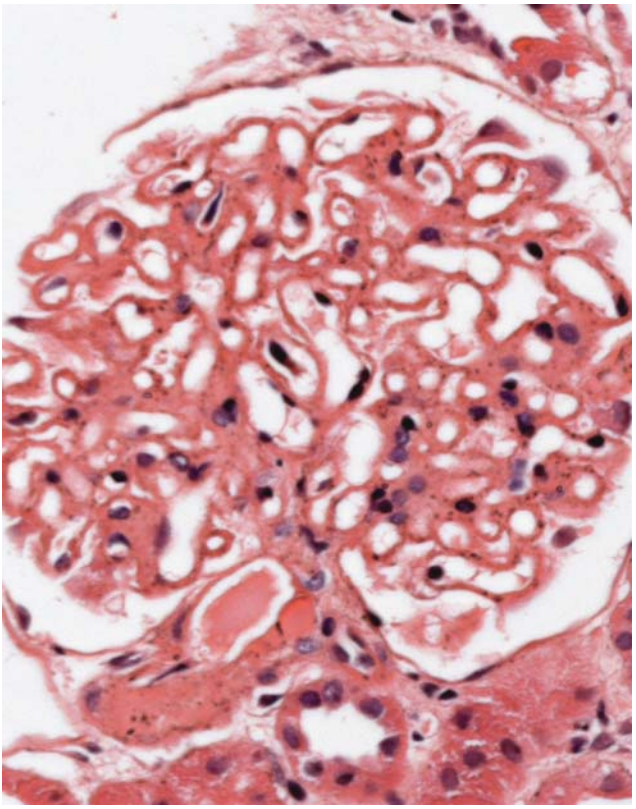

**Fig. 6.8** Glomerulus in a renal biopsy specimen from a man of 73 with the nephrotic syndrome. On hematoxylin and eosin staining, there is uniform thickening of basement membranes, which makes them appear rigid. These features suggest membranous nephropathy, but further investigations, particularly immunohistologic study, are necessary to allow the diagnosis to be made

**Immunohistology gives the diagnosis**, because there is strikingly uniform, granular deposition of IgG and complement on the outer surface of basement membranes, in every loop of every glomerulus (Figs 6.11 and 6.12). These granules may be so close that they give the impression of linear deposition on basement membranes, but inspection of thin parts of sections or tangential cuts of basement membranes will show the granularity. IgM is often seen in mesangium, but not other immunoproteins. Additional findings of mesangial deposition of IgG, and IgA on basement membranes, indicate that the membranous nephropathy is a sign of lupus nephritis.

If immunohistology is done properly, electron microscopy is not necessary for the diagnosis of membranous nephropathy, but will confirm regular deposits on the outer aspect of glomerular basement membranes (Fig. 6.13).

There may be segmental changes of various types in membranous nephropathy, which do not usually change the diagnosis, unless there are clinical or pathologic

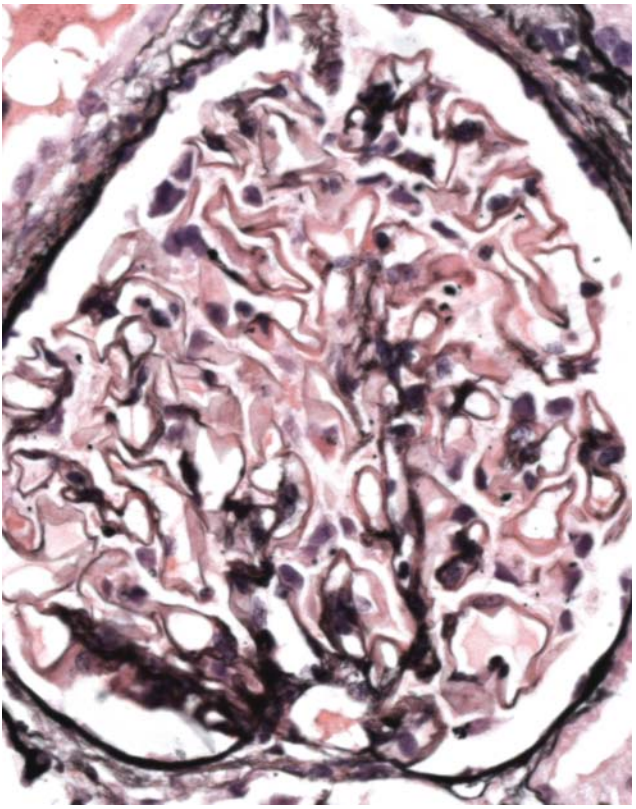

**Fig. 6.9** Glomerulus stained by periodic acid-methenamine silver in a renal biopsy specimen from a man of 80 with the nephrotic syndrome. There is a hint of thickening of basement membranes, but there are no spikes. Immunohistology illustrated in **Figs 6.11** and **6.12** shows that this is membranous nephropathy. The lack of spikes indicates an early stage

indications of **lupus nephritis**, when that should be given as the diagnosis. Almost always, the pathologist is given the information on the request form that the person biopsied has systemic lupus erythematosus, but if not, this should always be kept in mind as a possible diagnosis in any young woman with the nephrotic syndrome. Clues to lupus nephritis are the presence of other immunoglobulins as well as IgG on basement membranes, and the finding of other glomerular changes such as mesangial hypercellularity, mesangial deposition of immunoproteins especially IgG and IgA, and segmental abnormalities of vasculitic type.

A segmental disorder that is common in membranous nephropathy, and should not change the diagnosis, is adhesion of the glomerular tuft to Bowman's capsule next to the opening of the proximal tubule. This may be seen at all stages of membranous nephropathy (Figs 6.10 and 6.14). In late stages, there may be areas of segmental sclerosis at various sites in glomeruli, but the diagnosis should still be membranous nephropathy.

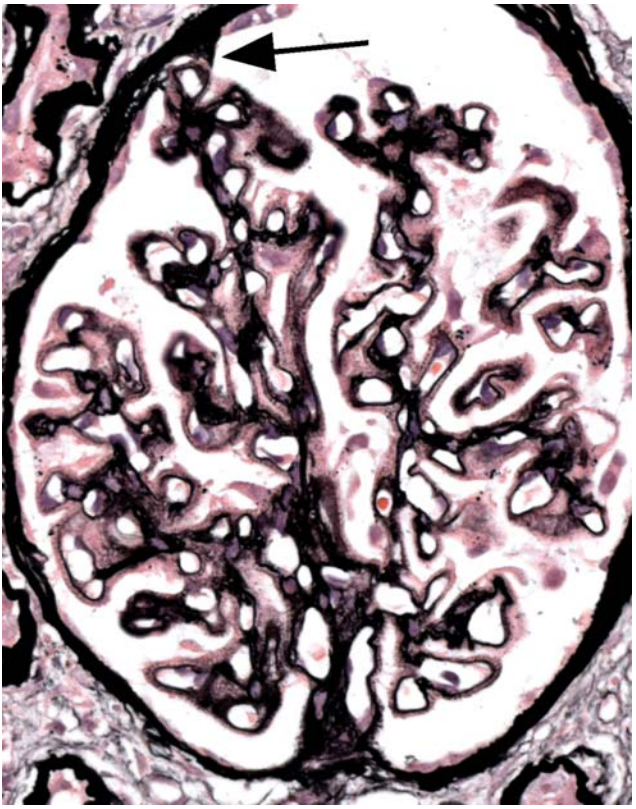

**Fig. 6.10** Glomerulus stained by periodic acid-methenamine silver in the renal biopsy specimen, which is illustrated in **Fig. 6.2**, from the man of 38 known to have membranous nephropathy for 2 years. There are uniform spikes on the outside of capillary loops. These indicate a later stage of membranous nephropathy than in **Fig. 6.9**. The arrow indicates adhesion of the glomerular tuft to Bowman's capsule, next to the tubular opening, opposite the hilum

Rarely, in people who have no evidence of systemic lupus erythematosus, membranous nephropathy is seen with vasculitic glomerular lesions, and this combination should be given as the diagnosis (Fig. 6.15). When these two conditions occur together, there is generally a more aggressive clinical course than is usual in membranous nephropathy. Goodpasture's disease, in which there are antibodies to glomerular basement membranes, and glomeruli show global and diffuse vasculitic lesions, has occasionally been seen in combination with membranous nephropathy.

There is a system of staging membranous nephropathy based on changes in glomerular basement membranes, but this is less useful than assessment of the extent of chronic damage to tubules in prognosis.

Proteinuria is lost in many children with membranous nephropathy as a complication of hepatitis B viral infection. At 10 years after diagnosis of membranous

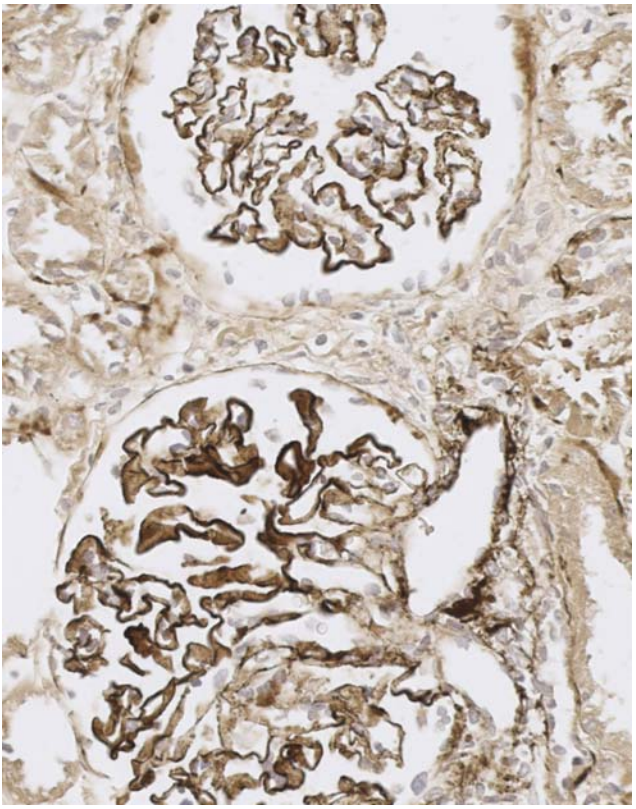

**Fig. 6.11** Cortex in the renal biopsy specimen from the man of 80 that is illustrated in **Fig. 6.9**, stained by an immunoperoxidase method to detect complement component C9. On microscopy at low magnification, there seems linear staining of every glomerular capillary loop, but the staining is finely granular. This indicates membranous nephropathy

nephropathy, about one-third of adults have progressed to renal failure or have died, about one-third have recovered, and about one-third have persistent proteinuria.

## Differential Diagnosis of Membranous Nephropathy

A disorder that may be confused with membranous nephropathy is **dense deposit disease**, also called membranoproliferative or mesangiocapillary glomerulonephritis type two, although these names are misleading because there is little resemblance to membranoproliferative or mesangiocapillary glomerulonephritis type one, also called subendothelial membranoproliferative glomerulonephritis. This use of the same name for different conditions perpetuates a historical mistake.

Dense deposit disease is much less common than membranous nephropathy, but may present with the nephrotic syndrome, and can give the appearance of thickened glomerular basement membranes.

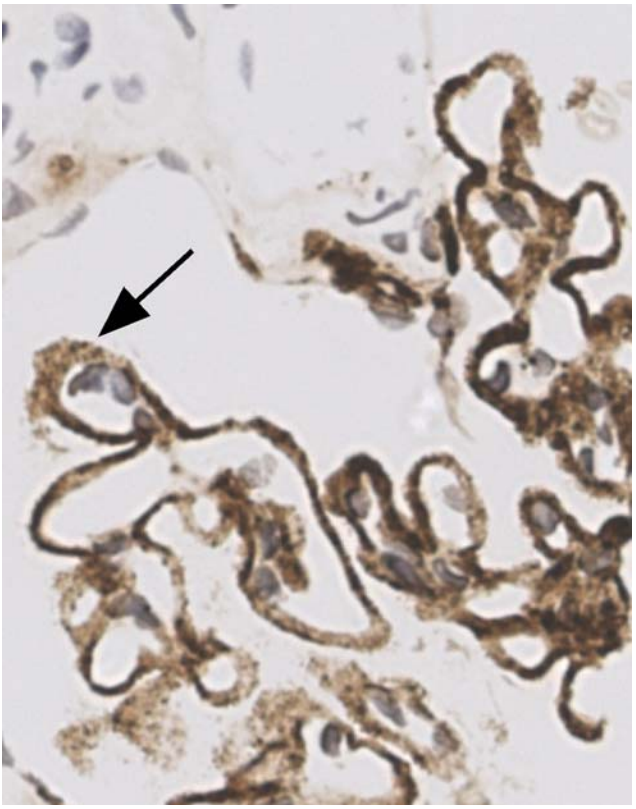

**Fig. 6.12** Glomerulus in the renal biopsy specimen from the man of 80, which is illustrated in **Figs** 6.9 and **6.11**, stained by an immunoperoxidase method to detect C9. Especially where basement membranes are seen tangentially, there are uniform fine granules, arrowed. This finding indicates membranous nephropathy

Dense deposit disease is usually diagnosed in children or young adults, who often have the nephrotic syndrome, but may have various clinical features as well, such as hematuria, renal failure, and partial lipodystrophy, which means a lack of subcutaneous fat. Complement component C3 has a persistently low concentration in serum. Often, there is an antibody in serum to one of the components of the alternate pathway of complement activation, C3 convertase. The antibody, called C3 nephritic factor, prevents inactivation of this component by its inhibitor, factor H, and allows persistent generation of active C3. Generally, the disorder is unremitting, and progresses to renal failure.

In dense deposit disease, glomeruli can appear nearly normal, or have various amounts of mesangial hypercellularity. Clues to the diagnosis are that there are no spikes, basement membranes are not uniformly thickened, and often the membranes have a brown colour, rather than black, on sections stained by periodic acid-methenamine silver (Fig. 6.16). On immunohistology, there are coarse

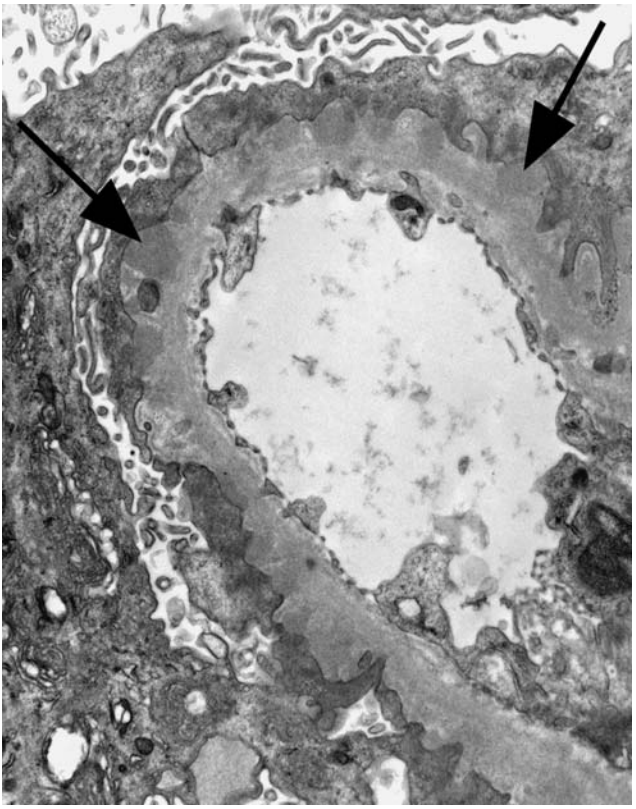

**Fig. 6.13** Electron micrograph of a renal biopsy specimen from a man of 80 with the nephrotic syndrome. There are immune deposits (arrowed) on the outer aspect of the glomerular basement membrane. These indicate early membranous nephropathy

granules of complement in mesangium and glomerular basement membranes, generally without immunoglobulins (Fig. 6.17). If this diagnosis is suspected, electron microscopy should be done. This shows large, irregular dense deposits within glomerular basement membranes and mesangium, rather than regular deposits on the outside of membranes that would indicate membranous nephropathy (Fig. 6.18). Similar immunohistologic and electron microscopic findings to those in glomeruli may be seen in Bowman's capsule and tubular basement membranes.

## *Are Glomeruli Abnormal? Is There a Segmental Sclerosing Disorder?*

**Segmental sclerosing glomerular disorders** are difficult. The term focal segmental glomerulosclerosis is widespread, but those who use it accept that it is applied to many different conditions, and that it has no specific meaning. This problem has

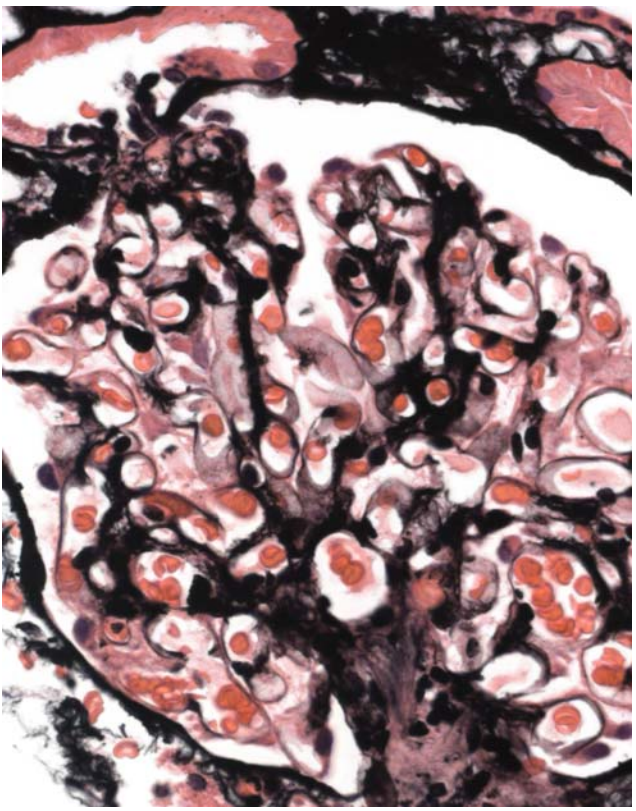

**Fig. 6.14** Glomerulus stained by periodic acid-methenamine silver in a renal biopsy specimen from a man of 52 with the nephrotic syndrome. Immunohistology shows that this is membranous nephropathy, early because there are no spikes. There is adhesion of the tuft to Bowman's capsule at the opening of the tubule, with hyaline material in capillary loops at this site

arisen through uncritical use of the term during the development of renal pathology as a specialty, when the same label was given to different entities, and the label is now difficult to remove. A pathologist can often refine the diagnosis to give more useful information to nephrologists. Whenever possible, the pathologist should try to avoid use of the unqualified term focal segmental glomerulosclerosis as a diagnosis.

Although the adjectives focal and segmental almost always appear together, the important one is segmental, meaning affecting only part of the glomerulus. Segmental lesions may be diffuse, meaning present in every glomerulus, rather than focal, but this will not be apparent on a single section or on a few random sections.

In the nephrotic syndrome, if glomeruli have segmental areas of foamy cells, or sclerosed material, or hyaline material, or a mixture of these, such as in Fig. 6.19, there is a temptation to use the diagnosis focal segmental glomerulosclerosis. The pathologist should first consider two questions.

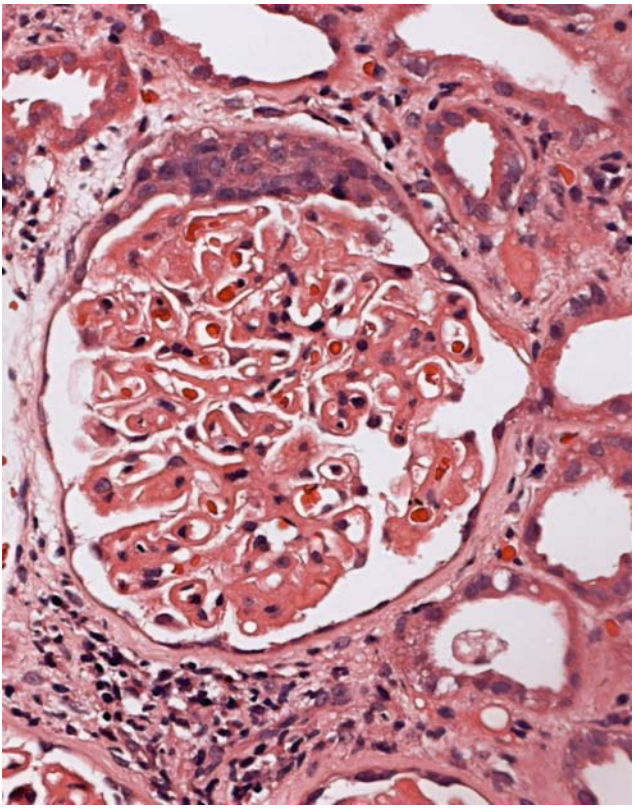

**Fig. 6.15** Glomerulus in a renal biopsy specimen from a man of 36 with the nephrotic syndrome and acute renal failure, taken 5 months after a biopsy that had shown early membranous nephropathy. There is now a segmental glomerular lesion of vasculitic type, in addition to membranous nephropathy

1. Is there evidence of **an underlying condition**, such as membranous nephropathy? If so, the underlying condition should be given as the diagnosis.
2. What is the **site** of the segmental abnormalities in glomeruli?

## Segmental Abnormalities at the Tubular Opening

In the nephrotic syndrome, the first site in a glomerulus at which segmental abnormalities appear is **next to the opening of the tubule**, which can also be called the tubular origin (Fig. 6.14). This part of the glomerulus should always be examined closely in a biopsy specimen. Serial sections give the pathologist the best chance to see tubular origins. Only if there are no structural changes at this site, in a specimen that at first glance has no segmental abnormalities, can a segmental sclerosing condition be said to be unlikely. The fewer the glomeruli seen in a biopsy specimen,

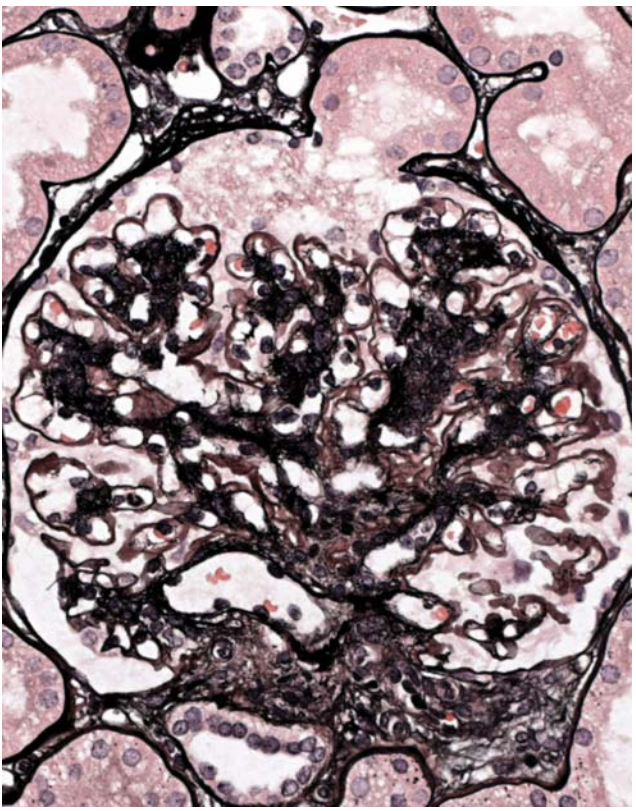

**Fig. 6.16** Glomerulus stained by periodic acid-methenamine silver in a renal biopsy specimen from a woman of 24 with persistent proteinuria postpartum. There is mesangial increase and basement membranes appear thickened, but not so uniformly as in membranous nephropathy. This is dense deposit disease, confirmed by further investigations that include immunohistology, illustrated in **Fig. 6.17**

the less confident the pathologist can be about exclusion of a segmental sclerosing condition.

If structural changes are seen next to the opening of the tubule, interpretation depends on the condition of the rest of the glomerular tuft. This is because these changes, that can be called **tip changes**, are **not a disease in themselves**, but are always **a complication of a glomerular disorder**.

Tip changes develop as a consequence of temporary prolapse of the glomerular tuft into the opening of the tubule, because the tuft swells acutely in various disorders (Fig. 6.20). The earliest recognisable changes are adhesion of the basement membrane of the tuft to the basement membrane of Bowman's capsule in the vicinity of the tubular opening. There are various abnormalities in the affected part of the tuft, including accumulation of foamy macrophages in capillary loops, and sometimes vacuolation and granularity of the cytoplasm of epithelial cells, with flattening

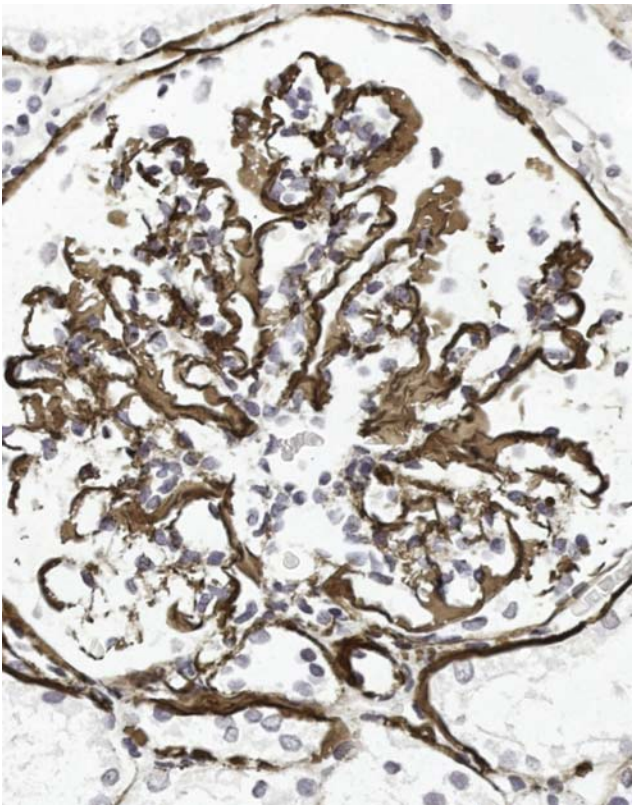

**Fig. 6.17** Glomerulus in the renal biopsy specimen from the woman of 24 with dense deposit disease that is illustrated in **Fig. 6.16**. Immunoperoxidase staining to detect C9 shows heavy deposition in glomerular basement membranes, but not so regularly or completely as in membranous nephropathy, illustrated in **Figs 6.11** and **6.12**

of the first proximal tubular cells (Figs 6.20 and 6.21). Later the foamy cells disappear, and are replaced by sclerosed material stained by periodic acid-methenamine silver, or hyaline material stained by eosin (Figs 6.14 and 6.19), or the only evidence of tip changes may be persistence of a thin adhesion or strand of basement membrane material, linking the tuft and Bowman's capsule (Figs 6.10 and 6.22). Immunohistologic study shows IgM and complement in tip changes (Fig. 6.23).

The rest of the tuft in a specimen with tip changes can appear normal or abnormal.

If the rest of the tuft appears normal in a person with the nephrotic syndrome, the diagnosis would have been minimal change nephropathy, if tip changes had not been present (Figs 6.21, 6.22, and 6.24). This corresponds to the **glomerular tip lesion**, as it was originally defined. The clinical course should be that of minimal change nephropathy, without progression to renal failure, which supports the idea that this is indeed minimal change nephropathy, complicated by tip changes. Although only

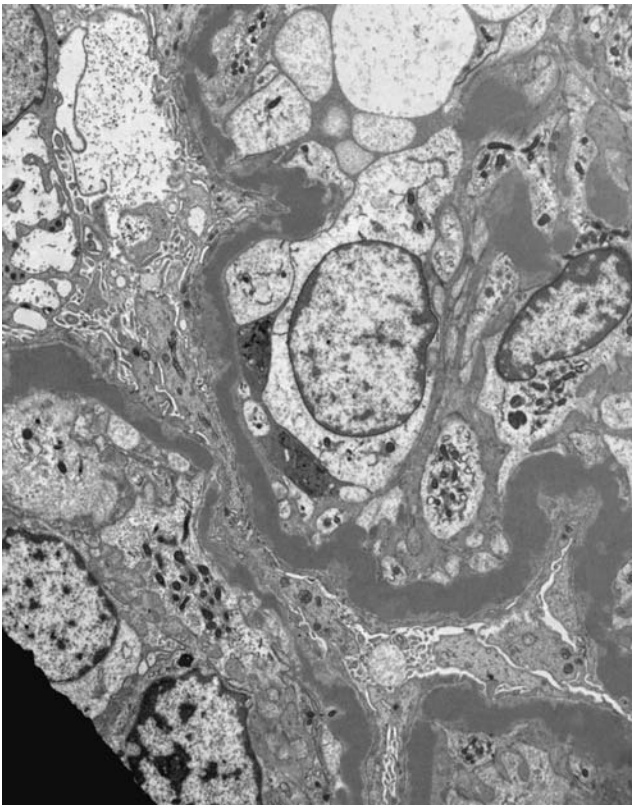

**Fig. 6.18** Electron micrograph of a glomerulus in a renal biopsy specimen from a girl of 13 with proteinuria, progressive renal impairment, a low serum concentration of C3, and C3 nephritic factor in serum. Basement membranes have irregular thickening by material typical of dense deposit disease

one tip change has to be found to alter the diagnosis from minimal change nephropathy, in the glomerular tip lesion, as originally defined, tip changes are usually present in every glomerulus, although this is not apparent without rigorous search of many serial sections.

A problem is that the term glomerular tip lesion has been used with meanings other than the original one. A common usage is to apply the term to all tip changes, whether or not there is the nephrotic syndrome, and irrespective of the condition of the glomerular tuft away from the tubular origin.

If the rest of the tuft is abnormal, the diagnosis depends on the features away from the tip changes. Membranous nephropathy is commonly associated with tip changes, but these should not alter the diagnosis of membranous nephropathy (Figs 6.10 and 6.14).

Another common appearance in the nephrotic syndrome is of tip changes in glomeruli that are abnormal and seem large, with mesangial increase, although the tip changes may be overlooked unless specifically sought. The tip changes

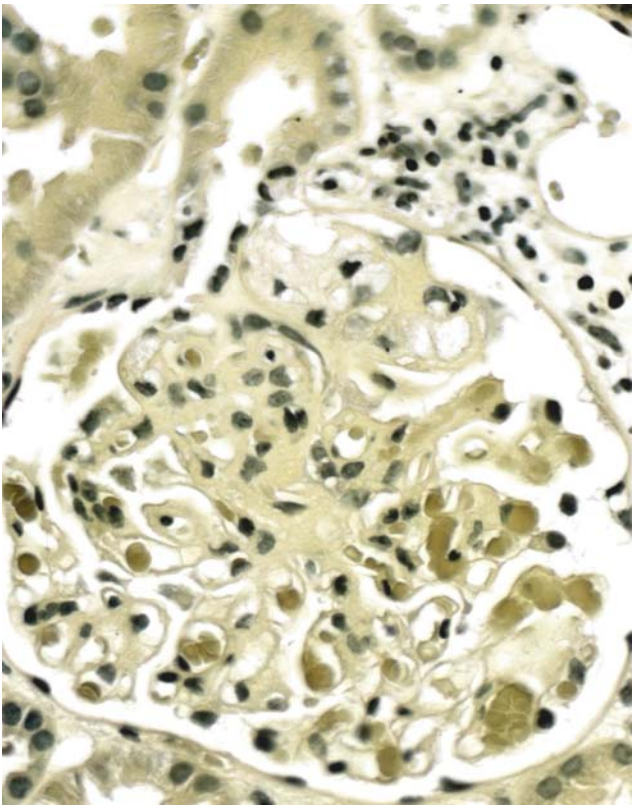

**Fig. 6.19** Glomerulus in a renal biopsy specimen from a man of 37 with the nephrotic syndrome. Next to the tubular opening, adherent to Bowman's capsule, there is a large segmental area of solid material with traces of foamy cells. Many pathologists would call this focal segmental glomerulosclerosis, but this diagnosis can be refined by study of the distribution of abnormalities in glomeruli, and of other features in the kidney

themselves may be large, occupying one-third or more of the glomerulus, and there may be marked acute tubular damage (Figs 6.19, 6.23, 6.25, and 6.26). This condition may evolve into one with more obvious segmental areas of sclerosis, and can be called the early form or early stage of **classic segmental sclerosing glomerulonephritis**. In this name, the adjective classic refers to the traditional clinical usage of the term focal segmental glomerulosclerosis in association with the nephrotic syndrome. To make this more understandable to nephrologists, the terms **early classic focal segmental glomerulosclerosis**, or early focal segmental glomerulosclerosis, could be used.

This condition is less likely to do well clinically than minimal change nephropathy or the glomerular tip lesion as originally defined, but is more likely to do better than expected from the traditional view of focal segmental glomerulosclerosis associated with the nephrotic syndrome, which is that there is almost always progression to renal failure, with no response to treatment.

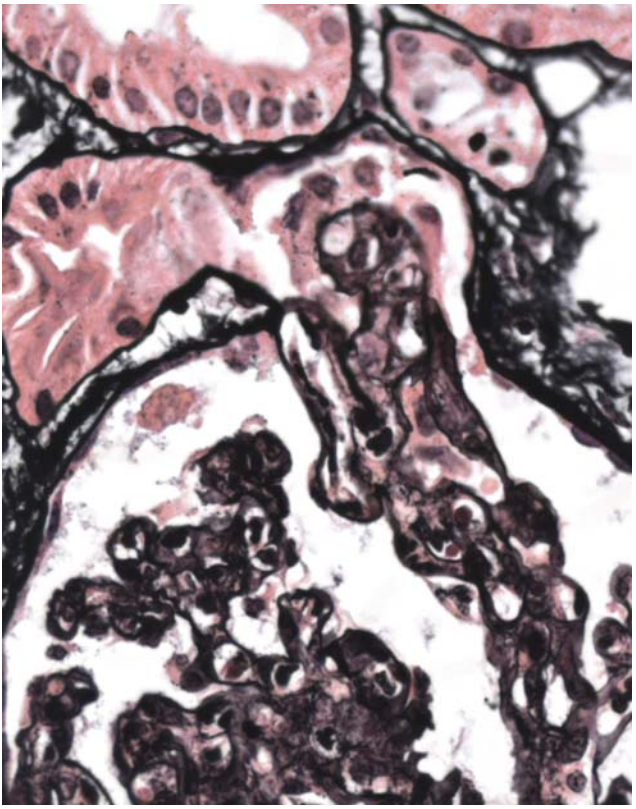

**Fig. 6.20** Glomerulus in a renal biopsy specimen from a man of 28 with acute renal failure, from which he recovered spontaneously shortly after the biopsy. The glomerulus has many neutrophils in capillary loops, and other features of acute postinfective glomerulonephritis. The tuft is prolapsed into the tubular opening. This is an early stage of development of tip changes

Occasionally, in specimens with few glomeruli or with only a few sections, the pathologist may not detect any segmental abnormalities, but may see definite mesangial expansion, usually with glomerular enlargement and IgM deposition in mesangium on immunohistologic study. This should not be called minimal change nephropathy, but there is no satisfactory name. Such specimens will often progress to ones with segmental sclerosing lesions, and may be called an early mesangial proliferative form of focal segmental glomerulosclerosis, or diffuse mesangial hypercellularity, or similar terms.

There may be difficulty for a pathologist to determine whether glomeruli appear normal away from tip changes, or are enlarged, or have mesangial increase, because these are subjective decisions, and the distinction between definitely normal and definitely abnormal is arbitrary. There are some specimens in which the pathologist is in doubt. In these, the best course is to describe the dilemma, and suggest to nephrologists that the clinical course cannot be confidently predicted. Many people will do well, but some may not, with persistence of the nephrotic syndrome and

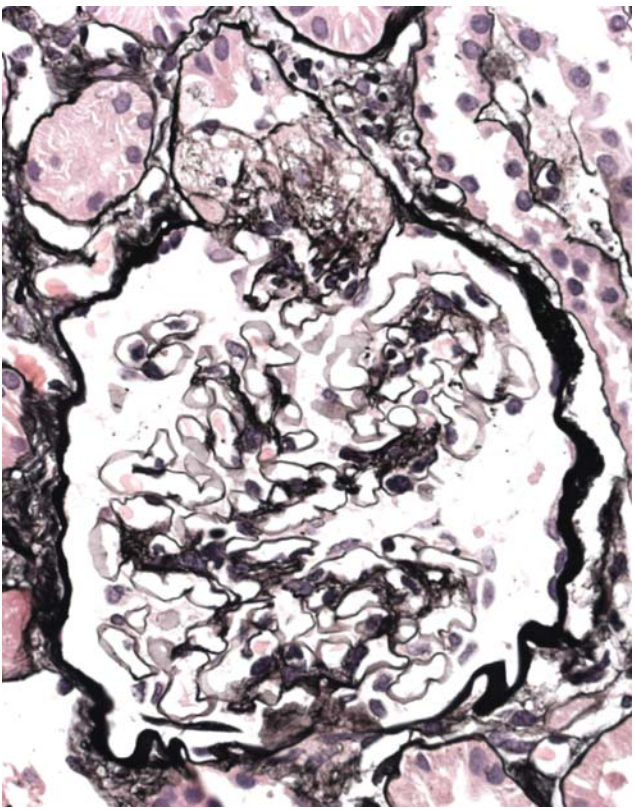

**Fig. 6.21** Glomerulus in a renal biopsy specimen from a woman of 64 with the nephrotic syndrome, from which she recovered spontaneously. Within the tubular opening is a part of the tuft that contains swollen cells with foamy cytoplasm. This is a tip change at an early stage, slightly more advanced than seen in **Fig. 6.20**. The rest of the tuft appears normal, and the diagnosis is glomerular tip lesion

progression to renal failure. Features that suggest there may be a poorer prognosis are any of the following.

1. Large tip changes affecting at least one-third of the tuft.
2. Definite mesangial increase.
3. Acute tubular damage affecting at least one-quarter of proximal tubules.

The more of these features that are seen, the less likely is a good outcome.

One classification of focal segmental glomerulosclerosis, often called the Columbia classification after Columbia University in New York, uses the term tip variant of focal segmental glomerulosclerosis, which corresponds to both the glomerular tip lesion as originally defined, and early classic segmental sclerosing glomerulonephritis. This term may be helpful when the pathologist sees tip changes, but no other segmental abnormalities, and cannot be sure that glomeruli are otherwise normal. Some people have used the term glomerular tip lesion with

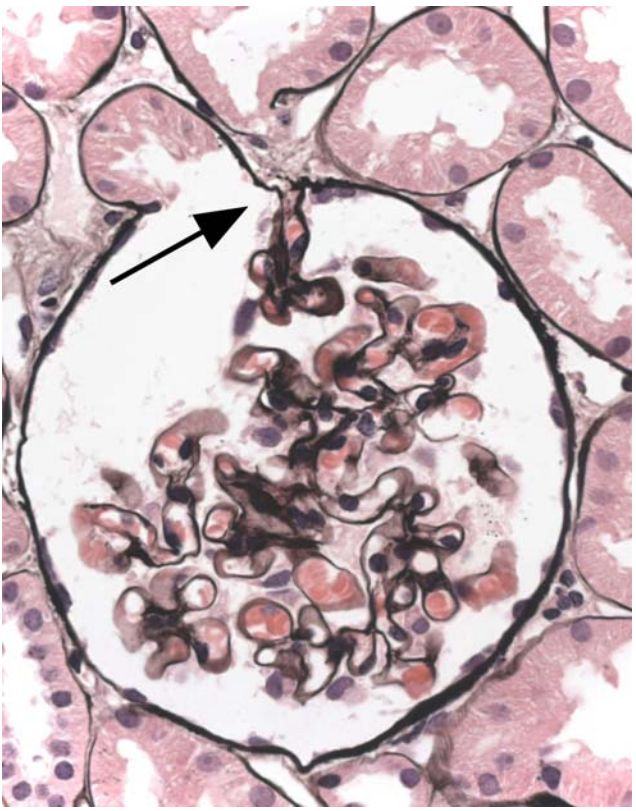

**Fig. 6.22** Glomerulus in a renal biopsy specimen from a man of 27 with the nephrotic syndrome, which had remitted and relapsed a few times over the previous 13 years. There is a thin adhesion, arrowed, between the tuft and Bowman's capsule next to the tubular opening, where the basement membranes of the two have fused. This is one of the late stages of a tip change. Glomeruli otherwise appear normal away from tubular openings, and the diagnosis is glomerular tip lesion

the same meaning as the tip variant of focal segmental glomerulosclerosis, which is different from the original definition of the glomerular tip lesion.

## Segmental Abnormalities Not Only at the Tubular Opening

In the nephrotic syndrome, segmental abnormalities away from the tubular opening develop after those at the opening, and are a sign of a later or more advanced condition. If segmental abnormalities are at various sites in glomeruli, including at the tubular origin, whether the sites are multiple within the same glomerulus or differ between glomeruli, the diagnosis is best given as the late form or the late stage of **classic segmental sclerosing glomerulonephritis** (Figs 6.27 and 6.28). To make this more understandable to nephrologists, the terms **late classic focal segmental glomerulosclerosis**, or late focal segmental glomerulosclerosis, could

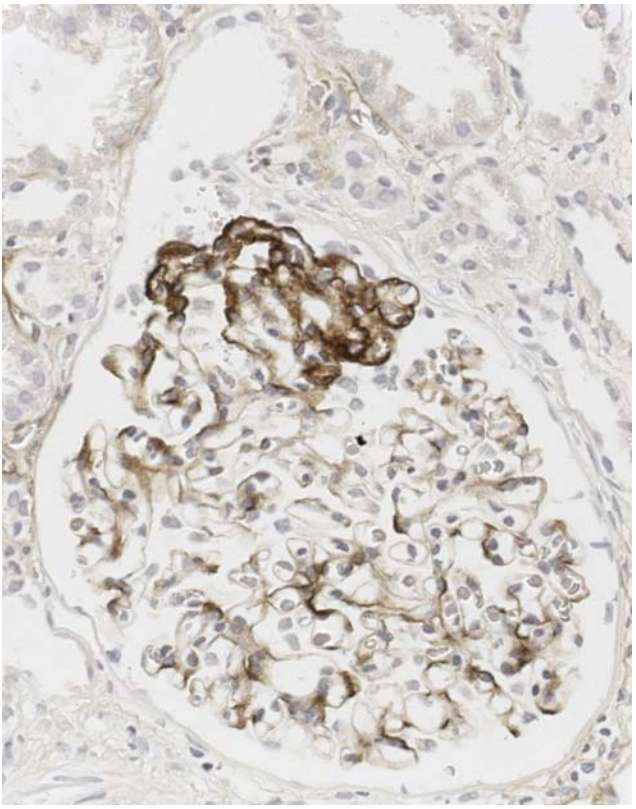

**Fig. 6.23** Glomerulus in a renal biopsy specimen from a woman of 37 with the nephrotic syndrome, examined by an immunoperoxidase method to detect IgM. An early tip change shows heavy deposition of IgM. Otherwise there is mesangial increase with light deposition of IgM. The diagnosis is early classic segmental sclerosing glomerulonephritis, which can also be called early classic focal segmental glomerulosclerosis

be used. Often, the segmental abnormalities are not focal, if sections of enough glomeruli are studied, which is why the segmental feature of the abnormalities is more important to stress.

This type of disorder most closely corresponds with the typical textbook description of focal segmental glomerulosclerosis associated with the nephrotic syndrome. What is not often realised is that this description applies to a condition **late in its course**. This can be confirmed by the high proportion of glomeruli with global sclerosis, and the large amount of tubular atrophy, usually seen in biopsy specimens given the conventional diagnosis. Because the diagnosis is made late, the clinical course usually accords with the conventional view of a condition that does not respond to treatment and progresses to renal failure.

In the Columbia classification, these changes are called focal segmental glomerulosclerosis, not otherwise specified.

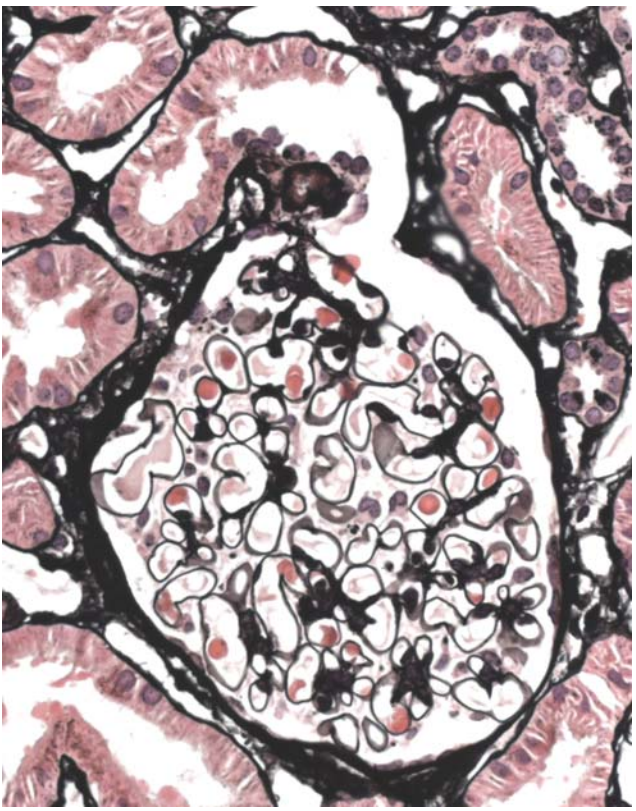

**Fig. 6.24** Glomerulus in a renal biopsy specimen from a woman of 60 with the nephrotic syndrome, from which she recovered without treatment. There is a tip change, and the rest of the tuft appears normal. The diagnosis is glomerular tip lesion

The classic type of segmental sclerosing glomerulonephritis associated with the nephrotic syndrome appears due in some people to a circulating factor, possibly from lymphocytes, that has a toxic effect on glomerular visceral epithelial cells. Part of the evidence for this is that the nephrotic syndrome may recur if someone with this condition receives a renal allograft. Other causes include genetic disorders of various proteins found in glomerular epithelial cells, including podocin and alpha actinin four. Use of the drug **heroin** may produce this type of segmental sclerosing abnormality.

In **adults,** classic segmental sclerosing glomerulonephritis probably affects all glomeruli, although in its late stage there may be more global sclerosis of glomeruli in the deep cortex. In **children,** the glomeruli containing segmental abnormalities may be only in the deep cortex, and may be missed if the corticomedullary junction is not included in the biopsy specimen (Figs 6.29 and 6.30).

Minimal change nephropathy should not progress to a segmental sclerosing glomerular disorder. If this appears to have happened, the diagnosis of minimal

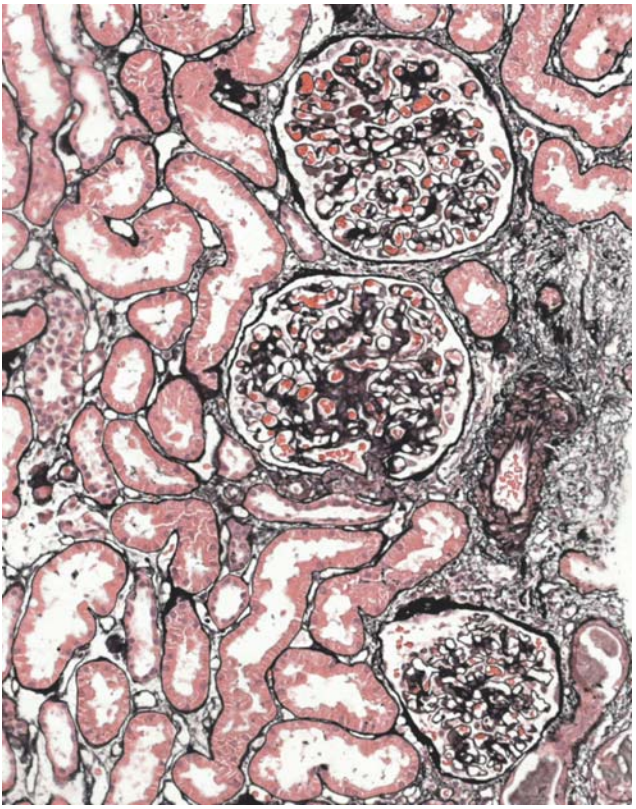

**Fig. 6.25** Cortex in the renal biopsy specimen from the man of 37 that is illustrated in **Fig. 6.19**, which shows a glomerulus with a large tip change. Glomeruli appear large with mesangial increase, but have no segmental abnormalities in this field, because there are no tubular openings. There is acute tubular damage. The diagnosis is early classic segmental sclerosing glomerulonephritis, which can also be called early classic focal segmental glomerulosclerosis

change nephropathy was probably wrong, or there is another explanation, such as effects of long-term use of calcineurin inhibitor drugs.

Clinically, the term malignant focal segmental glomerulosclerosis was used in the past when a segmental sclerosing glomerular disorder progressed rapidly, but a more accurate diagnosis is usually possible now.

## Human Immunodeficiency Viral Infection and its Effects in the Kidney

Many people throughout the world are infected with the human immunodeficiency virus, or HIV. This infection and its severest complication, acquired immunodeficiency syndrome or AIDS, can have several effects on the kidney. One effect presents with the nephrotic syndrome, by its association with a glomerular disorder

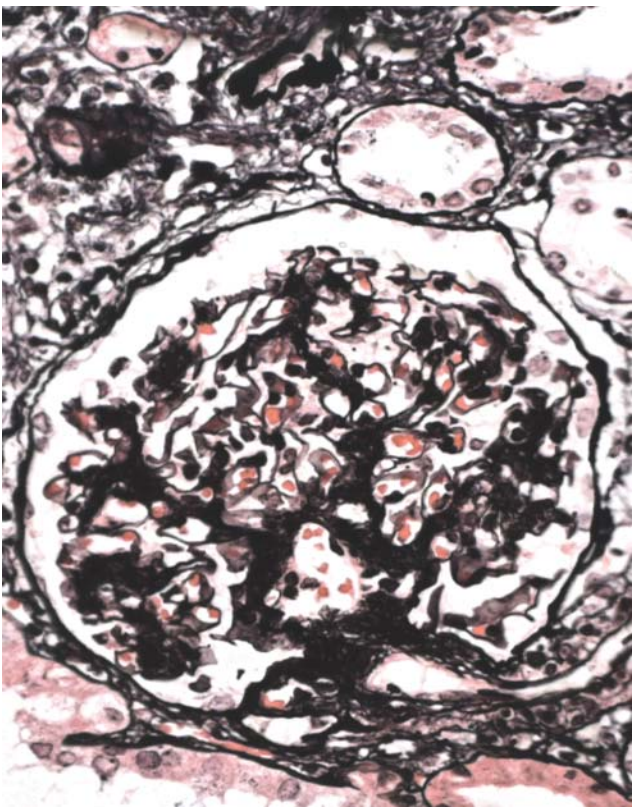

**Fig. 6.26** Glomerulus in a renal biopsy specimen from a girl of 13 with the nephrotic syndrome. The glomerulus appears large and has mesangial increase. Elsewhere in the specimen there is a tip change. The diagnosis is early classic segmental sclerosing glomerulonephritis, which can also be called early classic focal segmental glomerulosclerosis

called **collapsing glomerulopathy**. This is usually included in descriptions of focal segmental glomerulosclerosis, although the changes in glomeruli are usually diffuse, not focal, and global, not segmental.

## Diagnosis of Collapsing Glomerulopathy

The pathologist should think of this diagnosis before a specimen is examined from a person with the nephrotic syndrome and HIV infection, although not all HIV infection will be known before the biopsy or will be revealed to the pathologist, other conditions associated with the nephrotic syndrome may be found in HIV infection, and not all people with collapsing glomerulopathy have HIV infection. There is usually renal failure at the time of biopsy. The drug pamidronate, used to inhibit

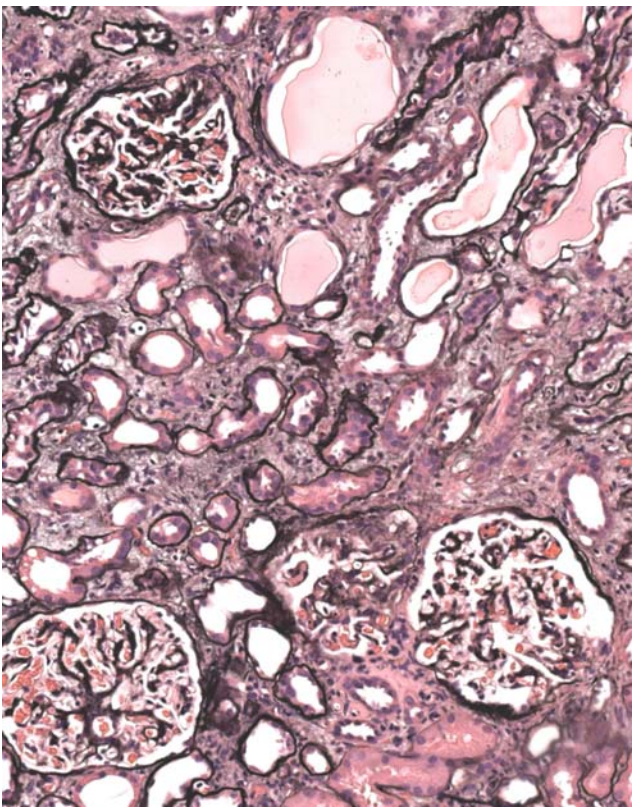

**Fig. 6.27** Cortex in a renal biopsy specimen from a man of 78 with the nephrotic syndrome and renal failure, which clinically appeared acute. There is a moderate amount of tubular atrophy with acute damage in surviving tubules. Glomeruli show various changes with areas of segmental sclerosis. The diagnosis is late classic segmental sclerosing glomerulonephritis, which can also be called late classic focal segmental glomerulosclerosis

osteoclast resorption of bone, is one of the factors other than HIV that may produce collapsing glomerulopathy.

The diagnosis is often suggested by initial inspection of the specimen at low power on the microscope. Some tubules are abnormal, and have striking dilatation, with casts. Other tubules have marked granularity of the cytoplasm. Glomeruli show collapse of capillary loops to different extents, with prominent, vacuolated, granular, visceral epithelial cells on the outside of the collapsed tufts, and material resembling the tubular casts in Bowman's space (Figs 6.31 and 6.32). A characteristic finding in HIV infection on electron microscopy is aggregation of intracytoplasmic tubular structures within the endoplasmic reticulum, called tubulo-reticular bodies, in glomerular endothelial cells (Fig. 6.33). These structures are induced by interferon alpha, and can also be found in conditions other than HIV infection, most notably in lupus nephritis.

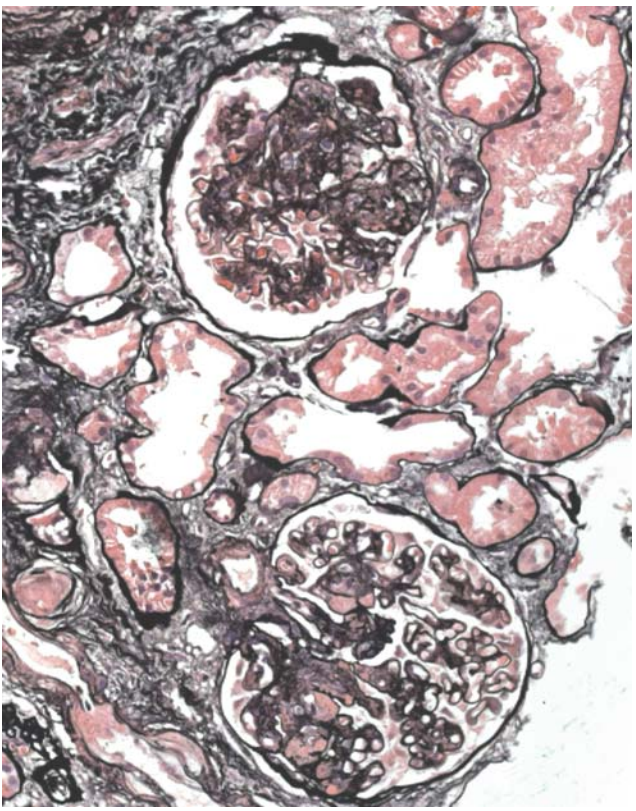

**Fig. 6.28** Cortex in a renal biopsy specimen from a man of 69 with the nephrotic syndrome. Glomeruli have segmental lesions of various sizes and at various sites. The diagnosis is late classic segmental sclerosing glomerulonephritis, which can also be called late classic focal segmental glomerulosclerosis

In the Columbia classification, this abnormality is called the collapsing variant of focal segmental glomerulosclerosis. Another variant, called the cellular variant, seems similar or identical to the collapsing variant.

Usually, collapsing glomerulopathy progresses rapidly to renal failure.

## Other Findings in the Kidney in Human Immunodeficiency Viral Infection

Collapsing glomerulopathy in people with HIV is often called HIV-associated nephropathy. Many renal disorders have been described in these people, who are at risk of other infections and the renal complications of them, but who could also have any renal disorder found in people without HIV.

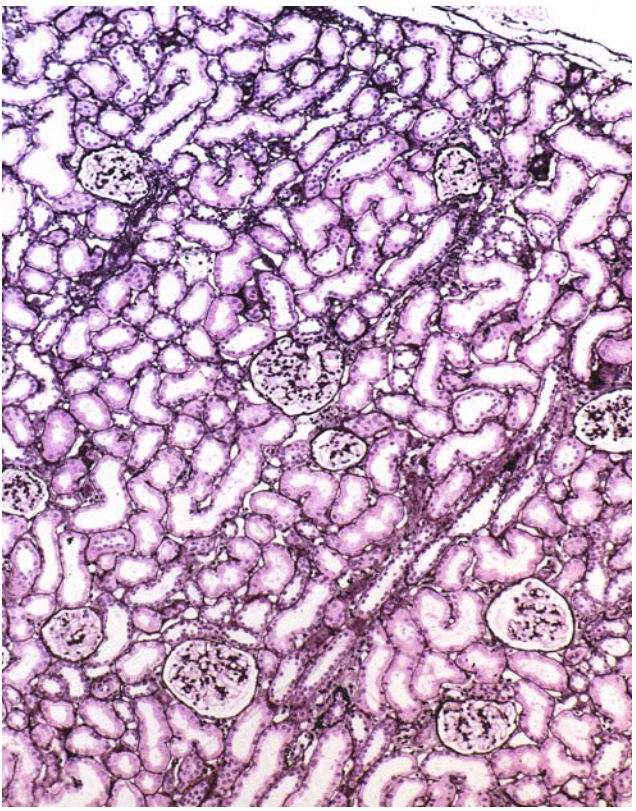

**Fig. 6.29** Outer cortex in a renal biopsy specimen from a girl of 3 with the nephrotic syndrome. Glomeruli are possibly enlarged, but show no other abnormality. In particular, there are no segmental lesions. The inner cortex is illustrated in **Fig. 6.30**

The conditions particularly seen include membranous nephropathy, acute postinfective glomerulonephritis, IgA nephropathy, subendothelial membranoproliferative glomerulonephritis, fibrillary-immunotactoid glomerulopathy, and hemolytic uremic syndrome. These resemble the conditions in people without HIV, although there may be additional features, such as tubulo-reticular bodies, and there can be combinations of the conditions. HIV-infected people may have a condition that resembles lupus nephritis, with heavy deposition of all immunoproteins in several sites in glomeruli, but without serologic and clinical features of systemic lupus erythematosus. Another disorder that has been described overlaps with the lupus-like nephritis, and is apparently intermediate between acute postinfective glomerulonephritis and membranous nephropathy, with mesangial and subepithelial immune deposits.

Drugs used to treat HIV can have effects on the kidney, such as damage to proximal tubular cells.

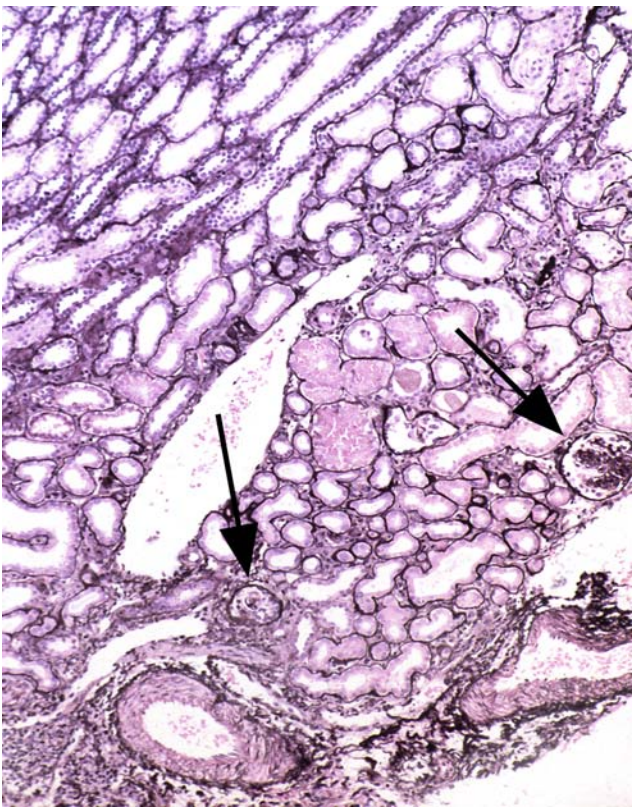

**Fig. 6.30** Inner cortex and arcuate vessels next to the medulla in the renal biopsy specimen from the girl of 3 whose outer cortex is seen in **Fig. 6.29**. Both figures are at the same magnification. A couple of glomeruli have areas of segmental sclerosis, arrowed. This is the typical appearance of the childhood form of late classic segmental sclerosing glomerulonephritis, which can also be called late classic focal segmental glomerulosclerosis

## *Is the Pathologist Told that the Person Biopsied Has Diabetes Mellitus? Is There Evidence of Diabetic Glomerulopathy?*

The pathologist may not be informed that the person biopsied has diabetes mellitus, either by oversight or because the nephrologists are not aware of this, but almost always the pathologist is told.

Diabetic renal disease is a useful term that covers several effects of diabetes mellitus on the kidney, including changes in blood vessels, tubules, and the medulla. Diabetic glomerulopathy is a more specific term for the characteristic changes in glomeruli.

A rule is that although people with diabetes mellitus and clinical renal abnormalities usually have diabetic glomerulopathy, **they may have any other renal disease**, either alone or in combination with diabetic glomerulopathy.

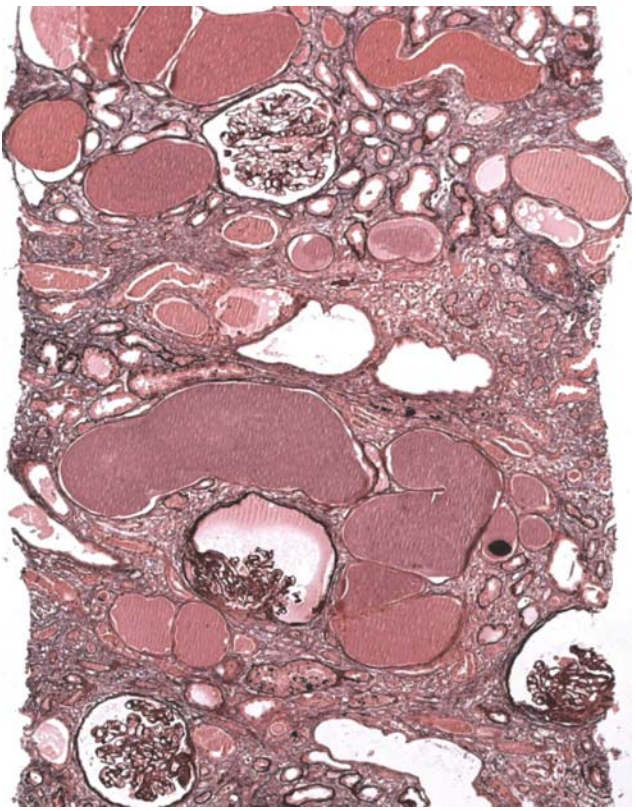

**Fig. 6.31** Cortex in a renal biopsy specimen of a man of 49 with the nephrotic syndrome, acute renal failure, and HIV infection. Many tubules are dilated and contain casts. Glomeruli are shrunken to different extents, and some appear solid. The diagnosis is collapsing glomerulopathy

## Value of Renal Biopsy in Diabetes Mellitus

Renal biopsy establishes whether there is diabetic glomerulopathy or another disorder, the finding of which may affect clinical management. The prevalence of diseases other than diabetic glomerulopathy in biopsy specimens in diabetes mellitus depends upon the policy of nephrologists. If many or most people with diabetes mellitus and a clinical renal disorder have a biopsy, other findings are uncommon. Selective biopsy of people with diabetes mellitus and an atypical clinical renal disorder will show other findings more commonly, but may miss a few in the diabetic population without a biopsy. People with diabetic retinopathy are highly likely to have diabetic glomerulopathy, and many nephrologists consider a renal biopsy unnecessary in these people.

Renal biopsy allows assessment of the extent of chronic damage, and indicates the prognosis for the kidney.

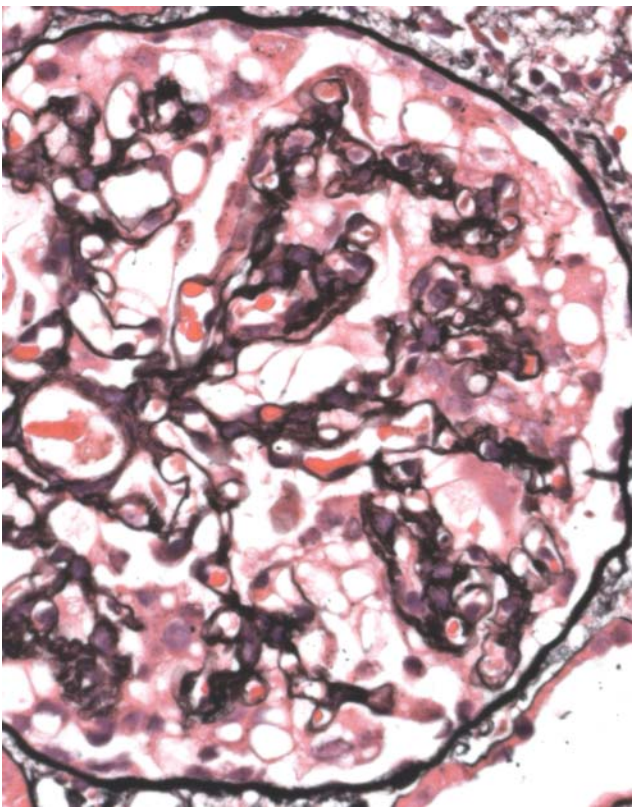

**Fig. 6.32** Glomerulus in a renal biopsy specimen from a woman of 23 with the nephrotic syndrome, but without HIV infection. The glomerulus shows collapse of the tuft as the mesangium has disappeared. Epithelial cells are enlarged and vacuolated. The diagnosis is collapsing glomerulopathy

## Diagnosis of Diabetic Glomerulopathy

Well-established diabetic glomerulopathy is easy to diagnose. There is usually extensive chronic damage in the cortex. Surviving glomeruli appear large, with thickened basement membranes, although not so thick as those in well-established membranous nephropathy. There is strikingly variable increase in mesangial matrix, in which round areas have a peripheral ring of nuclei and are called Kimmelstiel–Wilson nodules (Fig. 6.34). These nodules are sites of healing of microaneurysms (Fig. 6.35). The nodules persist a long time and can be seen in shrunken glomeruli, and even in globally sclerosed glomeruli (Figs 6.36 and 6.37).

Other features are seen in well-established diabetic glomerulopathy, both in glomeruli and in other parts of the kidney. Glomeruli can have areas of hyalinosis stained by eosin, called hyaline caps or lipohyaline caps when they are on the tuft, and called capsular drops when they are on the inner surface of Bowman's capsule (Fig. 6.38). Arterioles often have marked hyalinosis (Fig. 6.39). This change

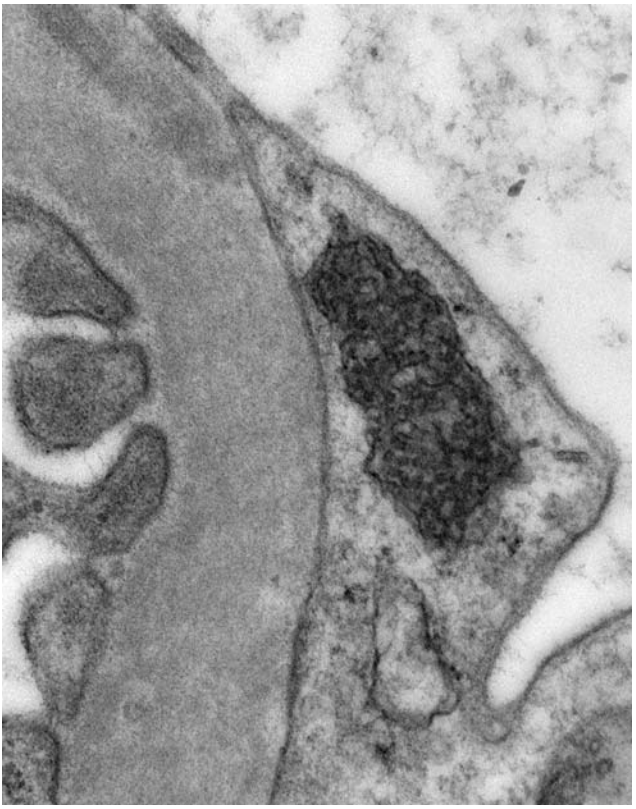

**Fig. 6.33** Electron micrograph showing a tubulo-reticular body in a glomerular endothelial cell. This is frequently found in HIV infection, but is also seen in other conditions, such as lupus nephritis, which is the diagnosis in this renal biopsy specimen, from a woman of 37 with proteinuria

affecting both afferent and efferent arterioles at the hilum of glomeruli is probably only seen in diabetes mellitus (Fig. 6.40). Especially in the old days, when diabetes mellitus was untreated, parts of tubules had accumulation of glycogen, that made the tubular cells appear clear, although this is hardly ever seen now. This is called the Armanni–Ebstein lesion (Fig. 6.41).

Less marked diabetic glomerulopathy is usually still recognisable on light microscopy, even if there are no Kimmelstiel–Wilson nodules. The main feature is increase in mesangial matrix, without evidence of mesangial deposition of immunoproteins, particularly IgA. If there is deposition of IgA, this indicates either pure IgA nephropathy, or the combination of the two conditions, which is commoner than pure IgA nephropathy in diabetes mellitus, and is shown by evidence of typical diabetic features. Glomerular basement membranes in diabetic glomerulopathy may show linear deposition of IgG, but not of complement (Fig. 6.42).

In specimens that appear normal or close to normal, electron microscopy is necessary to show the first sign of diabetic glomerulopathy, which is uniform thickening of glomerular basement membranes (Figs 6.43 and 6.44).

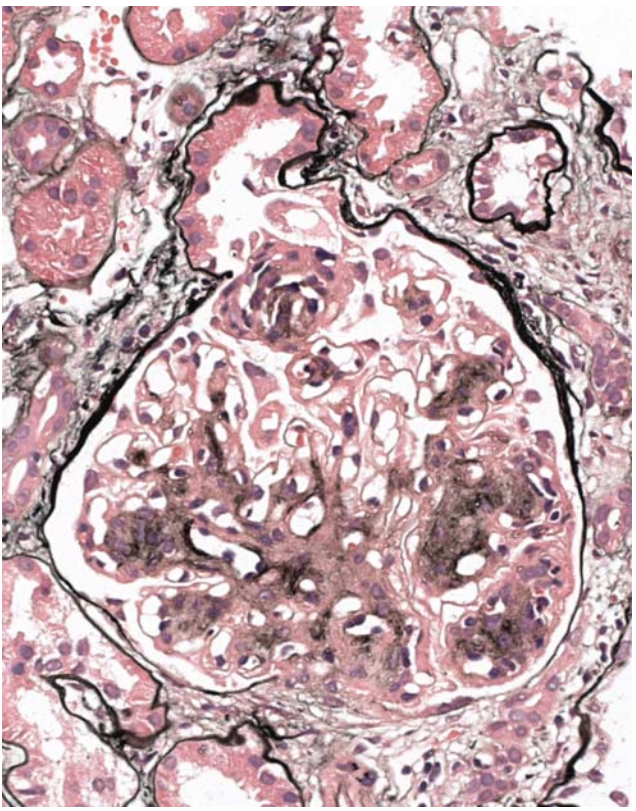

**Fig. 6.34** Glomerulus in a renal biopsy specimen from a woman of 52 with proteinuria in the nephrotic range, chronic renal failure, and a 4-year history of insulin resistant or type two diabetes mellitus. There is expansion of the mesangium with formation of Kimmelstiel–Wilson nodules, typical of diabetic glomerulopathy.

Kimmelstiel, usually pronounced *kimul-steel* in English, and Wilson, pronounced in the usual way, described the postmortem kidneys of eight adults, seven of whom were known to have had diabetes mellitus. They found hyaline masses in the glomerular intercapillary tissue, now called the mesangium. They called this intercapillary glomerulosclerosis, but did not use the word nodule (Kimmelstiel P, Wilson C. Intercapillary lesions in the glomeruli of the kidney. *American Journal of Pathology* 1936; **12:** 83–97). Nodule, coming from the Latin for a little knot, was in use by 1948, and the term Kimmelstiel–Wilson lesion was in use by 1951, although who was the first to think of these is difficult to discover. In Latin, the word diabetes meant a passing through or a siphon, and mellitus meant honeyed or sweet. Paul Kimmelstiel (1900–1970) was born in Hamburg, Germany, and became a pathologist there in the department of Theodor Fahr, who with the physician Franz Volhard was important in the development of understanding of the kidney through their clinicopathologic studies, first published in 1914. Kimmelstiel began to study glomerular lesions, but was forced to leave Germany in 1933 by the Nazis, and went to the United States. Clifford Wilson (1906–1997) qualified in medicine at the London Hospital, United Kingdom. In 1934, he went to Harvard University as a Rockefeller Travelling Fellow and met Kimmelstiel, who was an instructor in the Mallory Institute of Pathology. Later, Kimmelstiel worked as a pathologist in several cities in the United States. Wilson became Professor of Medicine at the London Hospital in 1946, succeeding Arthur William Mickle Ellis (1883–1966). Ellis developed a classification of renal disease that was influential for many years. In this, there were only two numbered types of

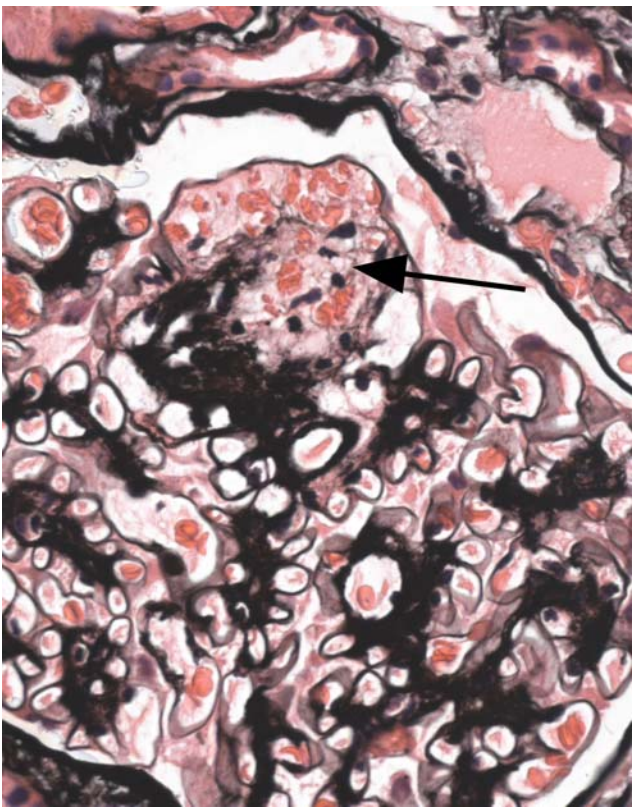

**Fig. 6.35** Glomerulus in a renal biopsy specimen from a man of 58 with proteinuria in the nephrotic range, chronic renal failure, and 10 years of insulin resistant or type two diabetes mellitus. There is an increase in mesangium with a microaneurysm, arrowed. This type of lesion heals to form a Kimmelstiel–Wilson nodule

Usually, if the reason for the biopsy is the nephrotic syndrome and the explanation is diabetic glomerulopathy, this diagnosis is immediately evident. If it is not, another diagnosis is likely, such as membranous nephropathy.

**Fig. 6.34** nephritis, type one of abrupt onset, short duration, and recovery, and type two of insidious onset, long duration, and no recovery. Ellis did not mean that there were only two kinds of renal disease, because he separated other disorders, such as acute focal nephritis, amyloid, and essential hypertension (Ellis A. Natural history of Bright's disease: clinical, histological and experimental observations. *Lancet* 1942; **1:** 1–7, 34–36, 72–76). Ellis's ideas were influenced by Dorothy Stuart Russell (1895–1983), who before she became a famous neuropathologist worked on renal disease, and in 1929 published a classification of kidney disorders that were then called Bright's disease. Pathologists used this to mean chronic, nonsuppurative inflammation of the kidney. Russell predicted the existence of entities not identified in her series, but necessary to complete the neatness of the classification

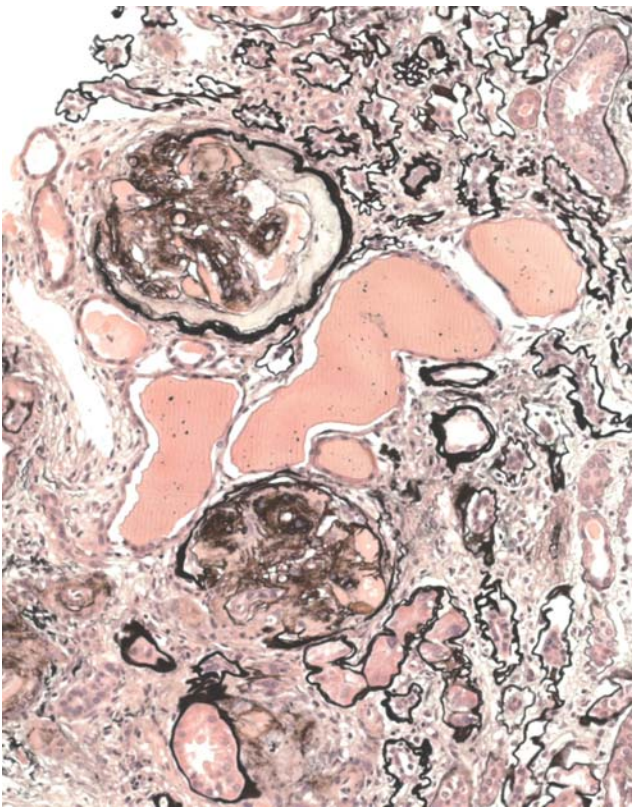

**Fig. 6.36** Cortex in a renal biopsy specimen from a woman of 48 with the nephrotic syndrome, chronic renal failure, and many years of insulin resistant or type two diabetes mellitus. There is extensive chronic renal damage. Glomeruli are globally sclerosed, but advanced changes of diabetic glomerulopathy, including Kimmelstiel–Wilson nodules, are still evident

Diabetic glomerulopathy seems a consequence of persistently high concentration of glucose in the blood, which stimulates increased production and decreased degradation of mesangial matrix and glomerular basement membrane components.

Diabetic glomerulopathy indicates a high risk of progression to renal failure, and also of death from cardiovascular causes, particularly myocardial infarction.

## Differential Diagnosis of Diabetic Glomerulopathy

Nodules in glomeruli can be seen in a few conditions other than diabetic glomerulopathy.

The commonest disorder that has glomerular nodules resembling diabetic glomerulopathy is **light chain glomerulopathy**, or nodular light chain glomerulopathy (Fig. 6.45). Clues to this diagnosis are that the person biopsied is not known

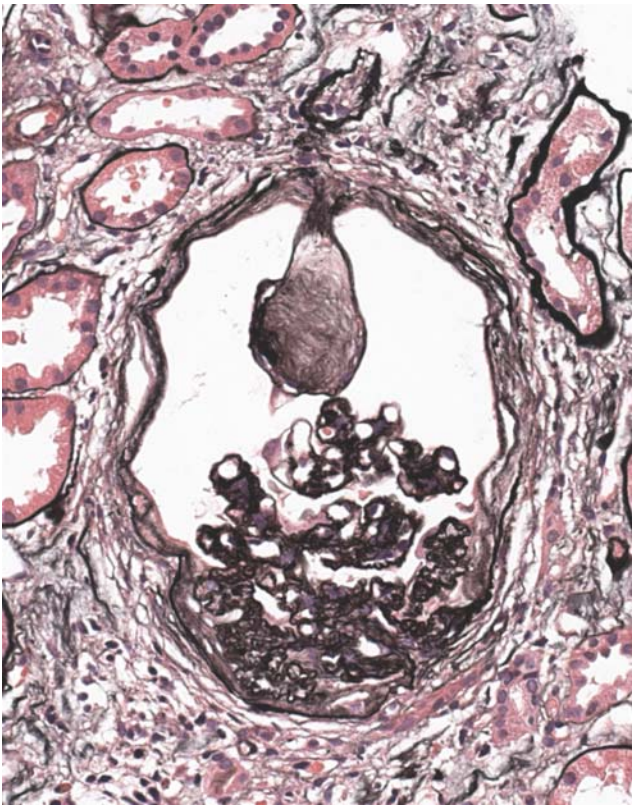

**Fig. 6.37** Glomerulus in a renal biopsy specimen from a woman of 66 with proteinuria in the nephrotic range, and 8 years of insulin resistant or type two diabetes mellitus. There is severe ischemic shrinkage of the tuft, but a Kimmelstiel–Wilson nodule is still seen, adherent to Bowman's capsule just at the origin of the tubule

to have diabetes mellitus, and has a disorder of immunoglobulins, although this may not have been detected before the biopsy. Immunohistologic staining to detect kappa and lambda light chains should show deposition of only one type in glomeruli and in tubular basement membranes (Figs 6.46 and 6.47). Kappa chains are much more often found than lambda.

The nodules in light chain glomerulopathy are usually all approximately the same size within a glomerulus, and most glomeruli look the same, although in diabetic glomerulopathy there is often much variation within a glomerulus and between glomeruli. There is usually heavy deposition of complement in nodules on immunohistologic study in light chain glomerulopathy, but not in diabetic glomerulopathy. Electron microscopy usually shows a line of deposited material in the inner or subendothelial aspect of glomerular basement membranes (Fig. 6.48).

**Amyloid** may give a similar nodular appearance, but the Congo red stain identifies this (Fig. 6.49).

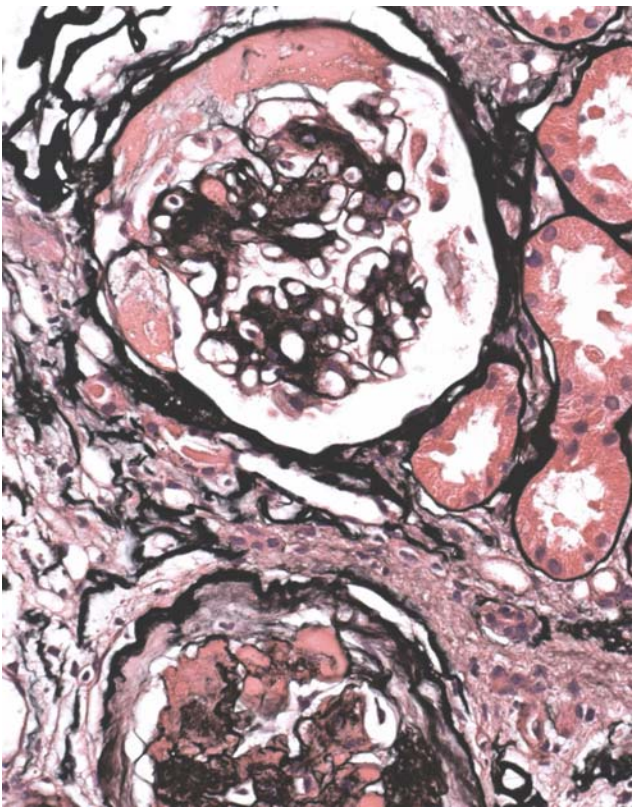

**Fig. 6.38** Glomerulus in a renal biopsy specimen from a woman of 58 with proteinuria, chronic renal failure, and insulin resistant or type two diabetes mellitus. Hyaline material is seen in capillary loops, including in a globally sclerosed glomerulus, and there is a large capsular drop on the inside of Bowman's capsule of the surviving glomerulus

Nodules may occur in advanced stages of **subendothelial membranoproliferative or mesangiocapillary glomerulonephritis**, also called membranoproliferative or mesangiocapillary glomerulonephritis type one (Fig. 6.50). In this condition, staining with periodic acid-methenamine silver shows doubled glomerular basement membranes, which are not seen in diabetic glomerulopathy.

## *Is the Pathologist Told that the Person Biopsied Has Systemic Lupus Erythematosus? Is There a Possibility of Lupus Nephritis?*

Almost always, systemic lupus erythematosus is diagnosed clinically before renal biopsy. If not, before a specimen is examined, the pathologist should think of lupus nephritis as a possible diagnosis in any young woman with the nephrotic syndrome, or indeed any other indication for a renal biopsy.

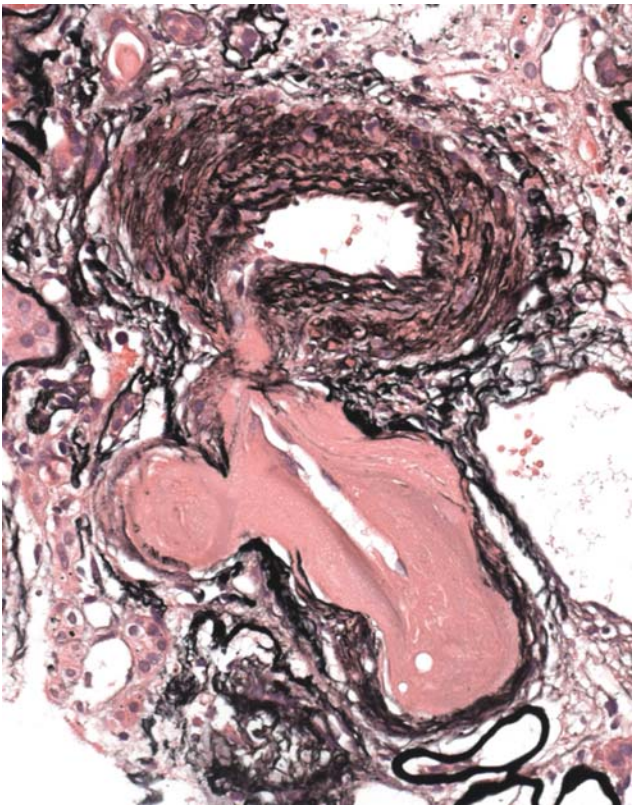

**Fig. 6.39** Cortex in the renal biopsy specimen from the woman of 58 with diabetic glomerulopathy that is illustrated in **Fig. 6.38**. Arterioles have severe hyalinosis

Lupus nephritis is easy to diagnose, but is made complicated and difficult for pathologists in most texts. This is because there are elaborate systems of classification.

## Value of Renal Biopsy in Systemic Lupus Erythematosus

A renal biopsy is hardly ever done in someone with lupus, but without clinical renal disease. The value when there is clinical renal disease is to confirm that there is lupus nephritis, although any other finding is rare, to show the type of renal disease, and to allow an assessment of the severity and proportions of active and late changes, which may be used in decisions about clinical management. A prognostic feature is the amount of chronic damage, assessed by methods such as measurement of the index of chronic damage (Fig. 5.6).

Repeat renal biopsy is perhaps commoner in lupus than in any other condition, if there is reactivation of clinical renal disease, or another change in its clinical

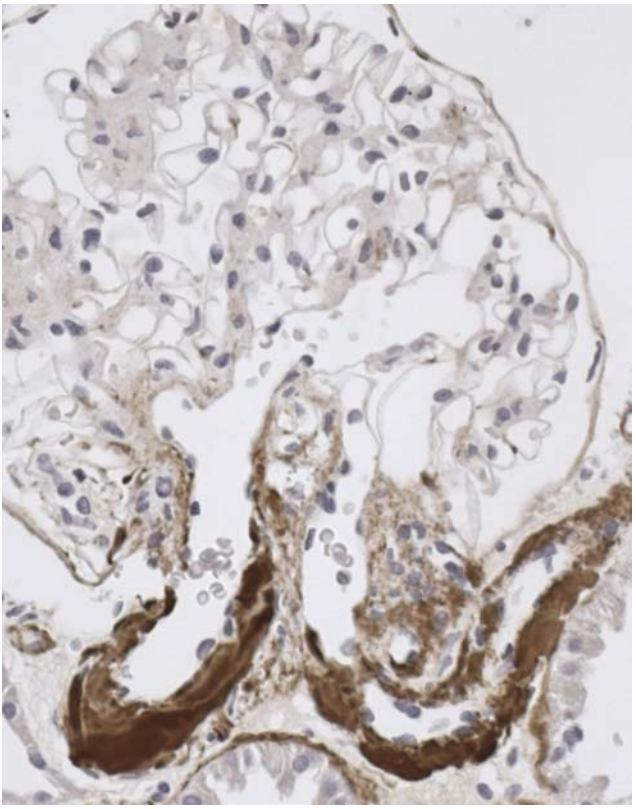

**Fig. 6.40** Glomerulus in a renal biopsy specimen from a woman of 54 with the nephrotic syndrome and insulin resistant or type two diabetes mellitus. An immunoperoxidase method to detect C9 shows that both arterioles at the glomerular hilum have hyalinosis, a feature of diabetic renal disease

characteristics. Lupus nephritis can change appearances between biopsies, and the new pathological findings influence management.

## Diagnosis of Lupus Nephritis

Lupus nephritis can give **almost any glomerular abnormality**, and **almost any combination of abnormalities**. A combination of glomerular disorders in a specimen from a person not reported to have systemic lupus erythematosus should make the pathologist think about lupus nephritis as a possible diagnosis. Similar changes may be seen in mixed connective tissue disorders, in which there are various clinical features of systemic lupus erythematosus, scleroderma or systemic sclerosis, and polymyositis.

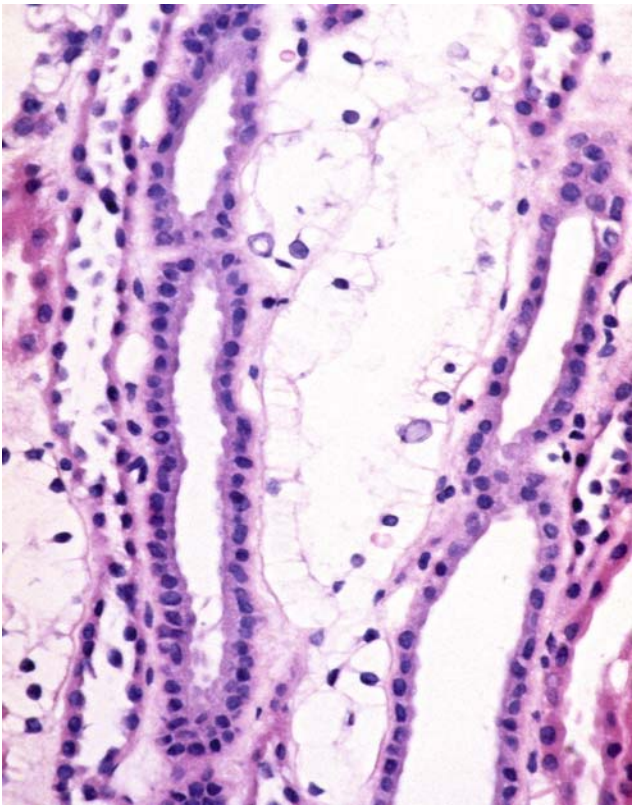

**Fig. 6.41** Outer medulla in a renal biopsy from a girl of 12 with proteinuria and 8 years of insulin deficient or type one diabetes mellitus that was poorly controlled. Some tubules, probably straight parts of proximal tubules, are lined by clear cells that contain glycogen. This is the Armanni–Ebstein lesion, named after Luciano Armanni (1839–1903), pronounced *ar-man-ee*, a pathologist in Naples, Italy, who was diabetic himself later in life, and first saw the abnormality in autopsy kidneys in 1872, and Wilhelm Ebstein (1836–1912), pronounced *eb-stine*, a German physician, who independently saw this in 1882

The pathologist should assess the extent of chronic damage, which may be anywhere between none and widespread (Figs 6.51 and 6.52). Common findings in glomeruli in lupus nephritis are membranous nephropathy, mesangial expansion to various extents, subendothelial membranoproliferative or mesangiocapillary pattern with doubled basement membranes, and segmental lesions of vasculitic type (Figs 6.53–6.57). When the renal disease is active, there is often an interstitial infiltrate of mixed inflammatory cells, with evidence of acute damage to tubules (Fig. 6.57). Blood vessels occasionally show changes of small vessel vasculopathy, also called thrombotic microangiopathy, with thrombosis and fibrinoid necrosis in arterioles, and loose concentric intimal thickening in small arteries (Fig. 6.58).

Immunohistology in lupus nephritis often shows heavy deposition of all immunoproteins in glomeruli, in a distribution that depends upon the pattern of structural

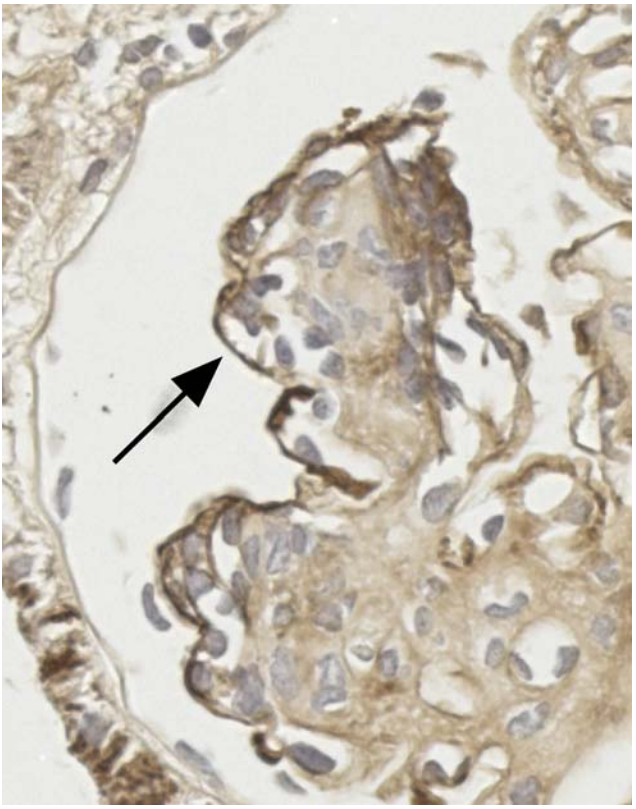

**Fig. 6.42** Glomerulus in the renal biopsy specimen from the woman of 52 whose diabetic glomerulopathy is illustrated in **Fig. 6.34**. An immunoperoxidase method to detect IgG shows linear deposition of IgG in glomerular basement membranes (arrowed), sometimes found in diabetic glomerulopathy. Granules of IgG are seen in proximal tubular cells, a finding in glomerular proteinuria

changes (Figs 6.59–6.62). IgG is usually evident. Mesangial deposition of IgG is a clue to the diagnosis of lupus nephritis, because few other conditions give this. The finding of IgA in membranous nephropathy is another clue that there is lupus nephritis. If the disease is late or serologically inactive, there may be little or no deposition of immunoproteins.

Electron microscopy in lupus nephritis confirms the distribution of immune deposits in glomeruli. Tubulo-reticular bodies are often found in glomerular endothelial cells (Fig. 6.33).

There are many immunologic abnormalities in systemic lupus erythematosus, but the cause is not known. One problem may be that fragments of apoptotic cells are not removed in the normal way, but stimulate an immune response to nuclear antigens, particularly nucleosomes, which are positively charged histone proteins complexed to deoxyribonucleic acid. Circulating histones or nucleosomes may attach to the negatively charged glomerular basement membrane, and allow antibodies against these antigens to fix in glomeruli.

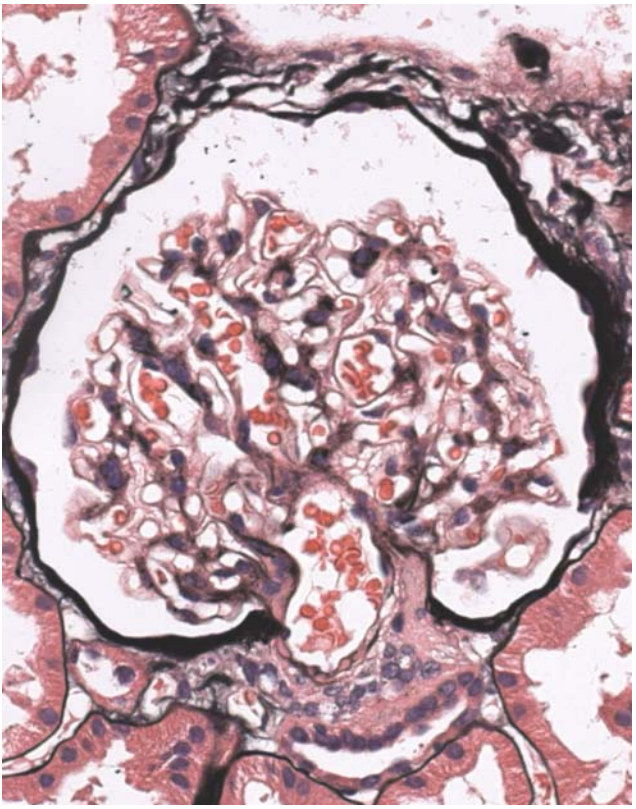

**Fig. 6.43** Glomerulus in a renal biopsy specimen from a woman of 18 with proteinuria and 7 years of insulin deficient or type one diabetes mellitus. The glomerulus is close to normal, but has a little mesangial expansion which suggests early diabetic glomerulopathy, confirmed by electron microscopy, as in **Fig. 6.44**

A pathologist should always give a description of the changes in lupus nephritis, even if a classification system is used. The description should always apply, although the classification will change.

## Classification of Lupus Nephritis

There have been a few numerical systems of classification of lupus nephritis, mainly published by the World Health Organization, WHO. Derived from these was a system published in 2003 by the International Society of Nephrology and the Renal Pathology Society ISN/RPS. The intention of these schemes is to ensure uniformity of reporting of lupus nephritis. Any numerical system has difficulties, and the main problems are these.

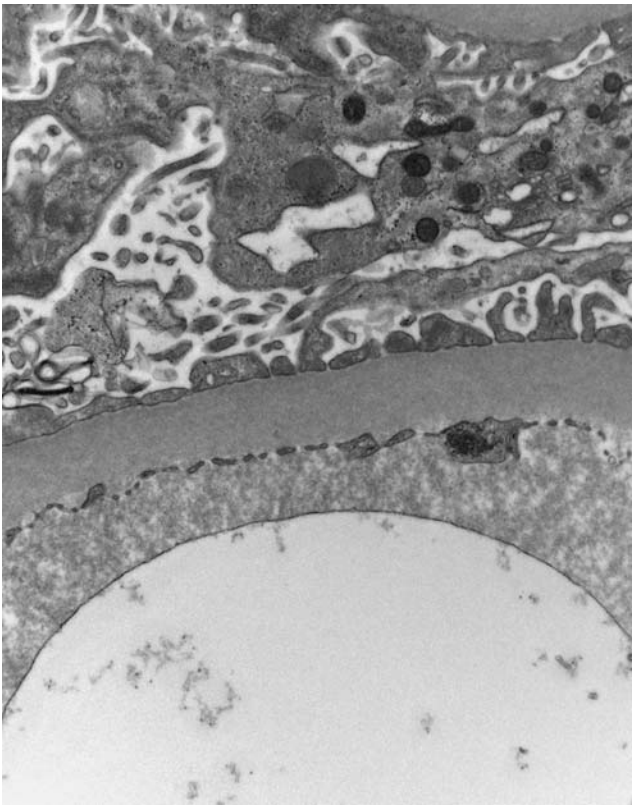

**Fig. 6.44** Electron micrograph of part of the glomerular basement membrane in a renal biopsy specimen from a woman of 46 with the nephrotic syndrome, and insulin deficient or type one diabetes mellitus for 7 years. The membrane is from 700 to 900 nm thick, which is more than twice the normal thickness. This is confirmation of early diabetic glomerulopathy. A normal glomerular basement membrane at the same magnification is illustrated in **Fig. 6.6**

1. Systems come and go. The WHO system changed every few years, and has been superseded. Changes in classification may mean that pathologists and physicians are not using the same system, and that findings of trials of treatment, for example, based on old systems, may not be applicable to new systems.
2. A pathologist cannot work out from first principles what a number in a numerical system means. Without other knowledge, the meaning is obscure of such terms as type one diabetes mellitus or class three lupus nephritis.
3. Glomeruli often show more than one abnormality in lupus nephritis, and there can be marked variation between glomeruli in a specimen. One number may not accurately reflect the combination of changes, and a pathologist may not be able to reconstruct the appearances of a particular specimen just from this number. This is true even when a system allows more than one number to be used.
4. Systems are not reliably used by pathologists, and have imperfect reproducibility. The ISN/RPS system has better reproducibility in some respects than WHO schemes, but is still not used consistently.

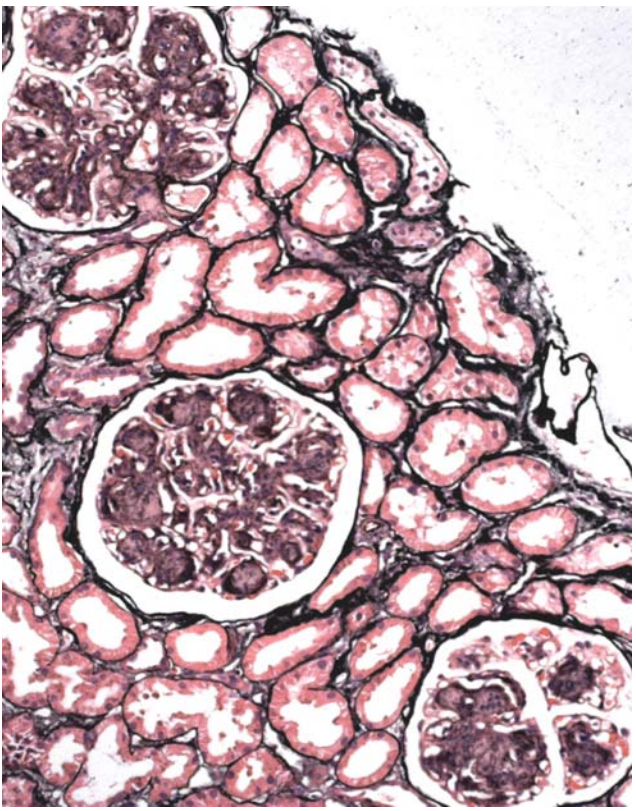

**Fig. 6.45** Cortex in a renal biopsy specimen from a man of 60 with the nephrotic syndrome. Appearances resemble diabetic glomerulopathy, but the diagnosis is light chain glomerulopathy. The man was not diabetic, and had myeloma, which was found after the biopsy. There was a Bence Jones protein in the urine, consisting of dimeric monoclonal kappa light chains, with an IgG kappa paraprotein in the serum. Although monoclonal light chains in the urine are called Bence Jones proteins, pronounced *benss* and *jones* in the usual way, the name should be Jones proteins, or even MacIntyre proteins. Henry Bence Jones (1813–1873) did not hyphenate his name and was called Jones. He qualified in medicine at St George's Hospital in London, United Kingdom, where he became a physician, and specialised in what would now be called clinical chemistry. In 1847 and 1848, he reported an unusual protein in the urine of a man aged 45, under the care of Dr Thomas Watson and Dr William MacIntyre. The properties of the urine were discovered by MacIntyre in 1845, but not published by him until 1850. Myeloma was named in 1873, and its relation to Jones's proteinuria was noted in 1889. About four-fifths of people with myeloma have this type of proteinuria, but few have the glomerulopathy

5. A numerical system has the implication that there is a progression in severity or in time from low numbers to high numbers. This is by analogy with staging systems in cancer. Some pathologists assume that the highest numbers in a classification are the worst conditions.
6. Only glomerular changes are considered when a class number is given to a biopsy specimen with lupus nephritis, although another feature, for example a small vessel vasculopathy, may be much more important.

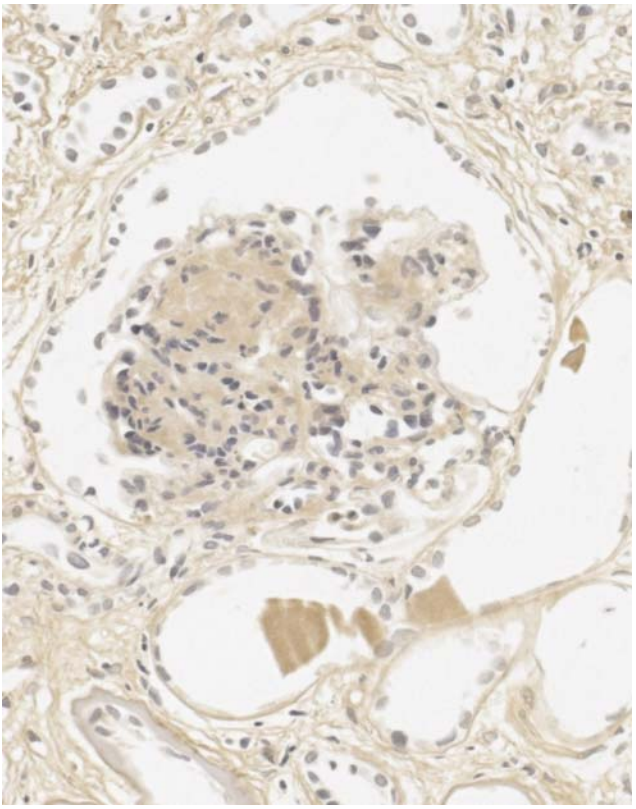

**Fig. 6.46** Glomerulus in a renal biopsy specimen from a man of 61 with acute renal failure and myeloma, with monoclonal lambda light chains in serum and urine. There is a nodular appearance. Immunoperoxidase staining to detect kappa light chains shows no significant deposition in the kidney

## International Society of Nephrology/Renal Pathology Society 2003 Classification of Lupus Nephritis

No pathologist should know classification systems. If they are used, the pathologist should refer to the guidelines for them, such as those following, and should specify in a report which system is used.

The 2003 RPS/ISN classification is given here, with an explanation of each class:

Class one – **Minimal mesangial lupus nephritis**: Glomeruli appear normal on light microscopy, but have mesangial immune deposits on immunohistology. If glomeruli have no abnormality at all, there is no lupus nephritis, and no class number is used.

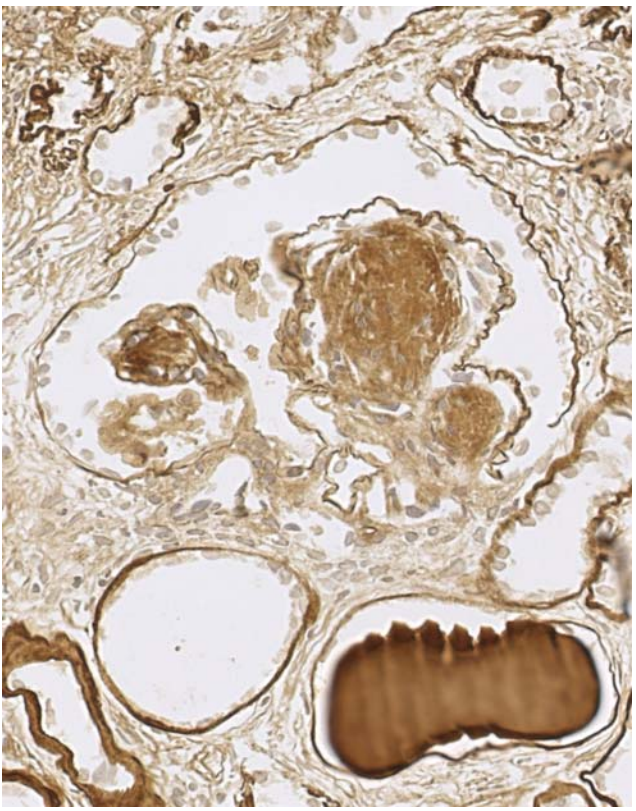

**Fig. 6.47** Glomerulus in the renal biopsy specimen from the man of 61 shown in **Fig. 6.46**. Immunoperoxidase staining to detect lambda light chains shows heavy deposition in mesangium, glomerular basement membranes, tubular basement membranes, and in casts. This confirms light chain glomerulopathy

Class two – **Mesangial proliferative lupus nephritis**: Mesangial hypercellularity or expansion of mesangial matrix is seen with mesangial immune deposits (Figs 6.53 and 6.60).

Class three – **Focal lupus nephritis**: Focal is defined here to mean that fewer than half of all the glomeruli in a specimen are affected by lesions. These are usually segmental but occasionally global, and are of vasculitic type, active or healed. In the active stage, these show different combinations of endocapillary thrombosis or aggregates of immune complexes, hypercellularity and degeneration of cells in capillary loops, disruption of glomerular basement membranes, and cells in Bowman's space (Fig. 6.54). These lesions heal to give segmental areas of sclerosis that are sharply outlined, and cross part of the glomerular tuft and Bowman's space. Class 3(A) means active lesions, 3(C) means healed, chronic, inactive lesions, and 3(A/C) means a mixture. The proportion of glomeruli affected by active or healed lesions is

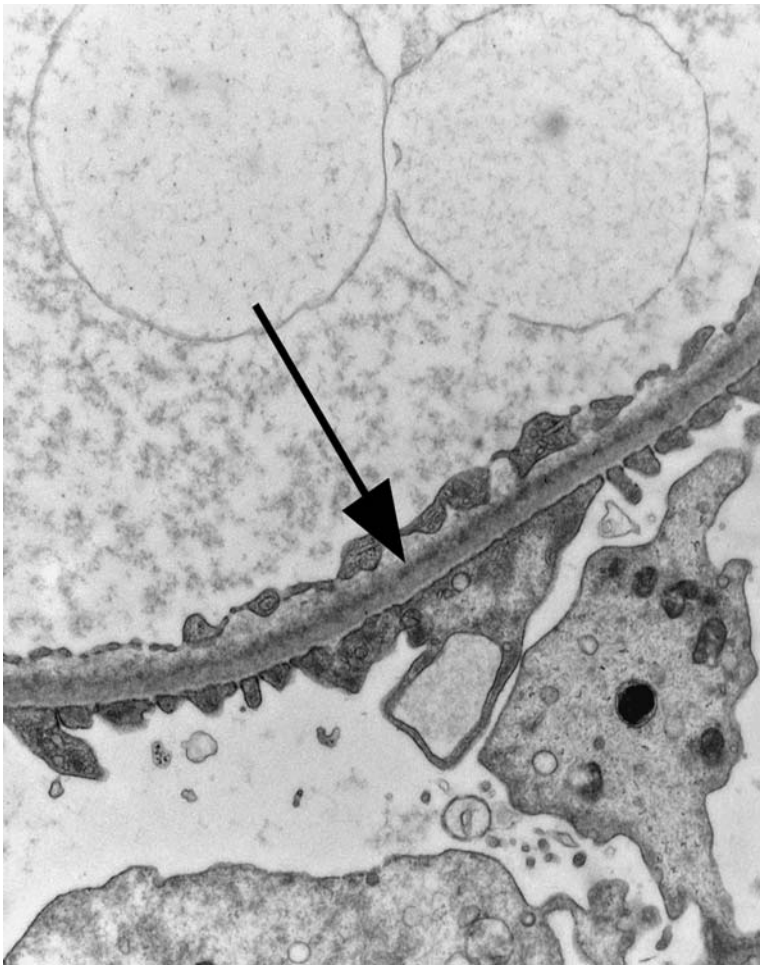

**Fig. 6.48** Electron micrograph of a glomerular basement membrane in a renal biopsy specimen from a woman of 44 with proteinuria and renal failure. There is a line of deposited material (arrowed), which indicates a light chain glomerulopathy. After the biopsy, monoclonal kappa chains were found in serum and urine

reported. Class three is often associated with segmental areas of subendothelial immune deposits, and may have mesangial alteration, even affecting all glomeruli.

Class four – **Diffuse lupus nephritis**: Segmental or global lesions affect at least half of all the glomeruli in a specimen. Segmental in this class is defined as a lesion sparing half of the tuft. Class 4S has more widespread lesions than class three, but is otherwise similar, and is divided into similar subtypes, 4S(A), 4S(A/C), and 4S(C). The global form, class 4G, usually has endocapillary and mesangial hypercellularity, often with a subendothelial

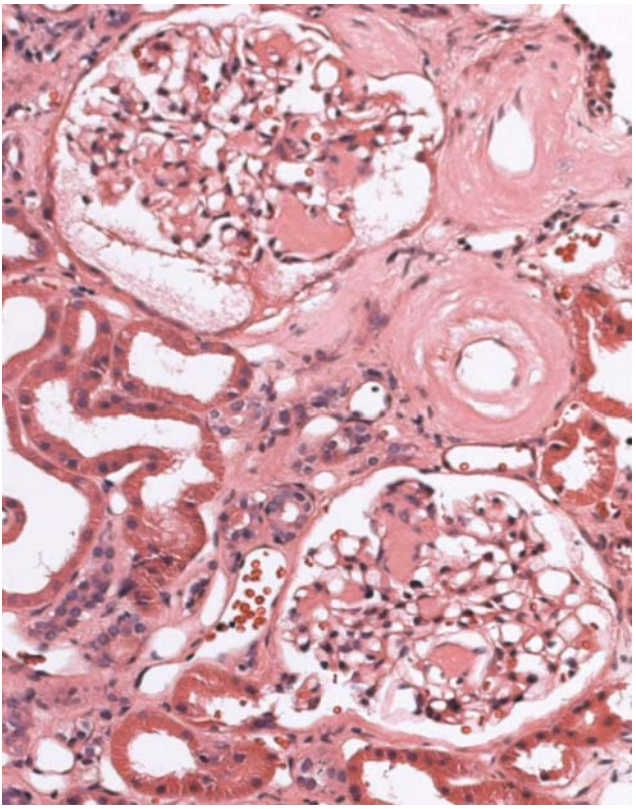

**Fig. 6.49** Cortex in a renal biopsy specimen from a man of 67 with chronic renal failure and myeloma. Glomeruli contain nodules that are shown by Congo red staining to contain amyloid

membranoproliferative or mesangiocapillary pattern (Figs 6.55–6.57, 6.61, and 6.62). There are usually widespread subendothelial immune deposits, and sometimes these are the main abnormality. Class 4G may show healing to give segmental or global areas of sclerosis, and the subtypes are 4G(A), 4G(A/C), and 4G(C).

Class five – **Membranous lupus nephritis**: Subepithelial immune deposits are seen, with or without mesangial alteration (Figs 6.51 and 6.59). This can occur with either class three or class four, but class five is only reported as well as the other class if at least half of the surface area of glomerular capillary loops in at least half of glomeruli shows membranous nephropathy (Figs 6.55 and 6.62).

Class six – **Advanced, globally sclerosed lupus nephritis**: At least nine-tenths of glomeruli are globally sclerosed (Fig. 6.52).

A test of the ISN/RPS 2003 classification showed that class four was by far the commonest class used, and was diagnosed much more often than in a WHO

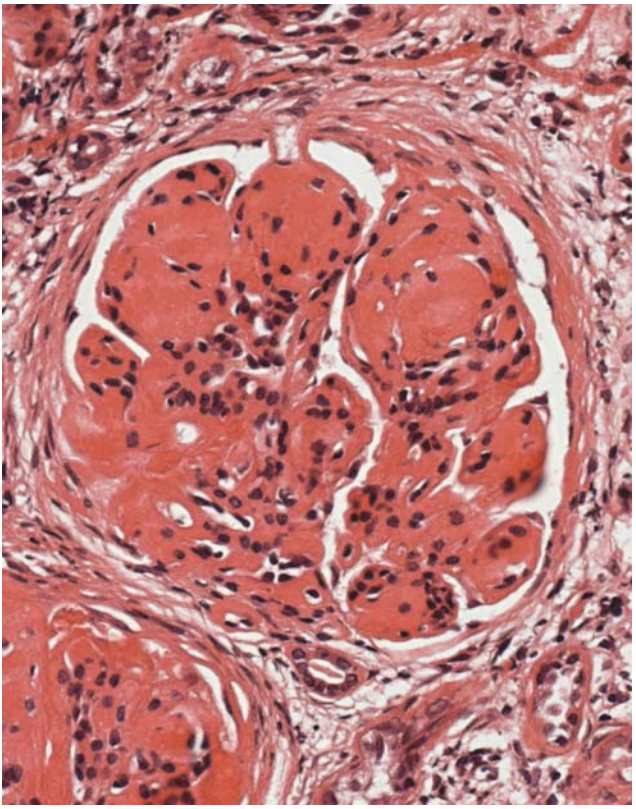

**Fig. 6.50** Glomerulus in a renal biopsy specimen from a man of 22 with hematuria and proteinuria. There are nodules. Periodic acid-methenamine silver staining shows double basement membranes, with other features of subendothelial membranoproliferative glomerulonephritis. Subendothelial membranoproliferative glomerulonephritis was found to be the diagnosis in two of the three kidneys in the Gordon Museum at Guy's Hospital in London, United Kingdom, that had been described by Bright, who for many years was honoured by the term Bright's disease that was applied to clinical renal disorders (**Fig.** 6.34). Richard Bright (1789–1858), whose surname is pronounced in the usual way, was born in Bristol, United Kingdom, qualified in medicine in Edinburgh, and became a physician at Guy's Hospital at the same time as Addison and Hodgkin, who also had diseases named after them. In 1827, Bright published a book called "Reports of medical cases selected with a view of illustrating the symptoms and cure of diseases by a reference to morbid anatomy". He showed the association of edema, then called anasarca or dropsy or dropsical affection, with proteinuria and disorders of the kidney, and separated edema due to renal disorders from edema due to diseases of the heart and liver. The third kidney in the Gordon Museum showed amyloid secondary to pulmonary tuberculosis

classification. There was poor reproducibility between pathologists of assessment of activity and chronicity. Active features in glomeruli are endocapillary hypercellularity, infiltration of leukocytes, disruption of nuclei called karyorrhexis, thrombosis, rupture of basement membranes, cells in Bowman's space, subendothelial immune deposits, and intraluminal immune aggregates. Chronic features in glomeruli are

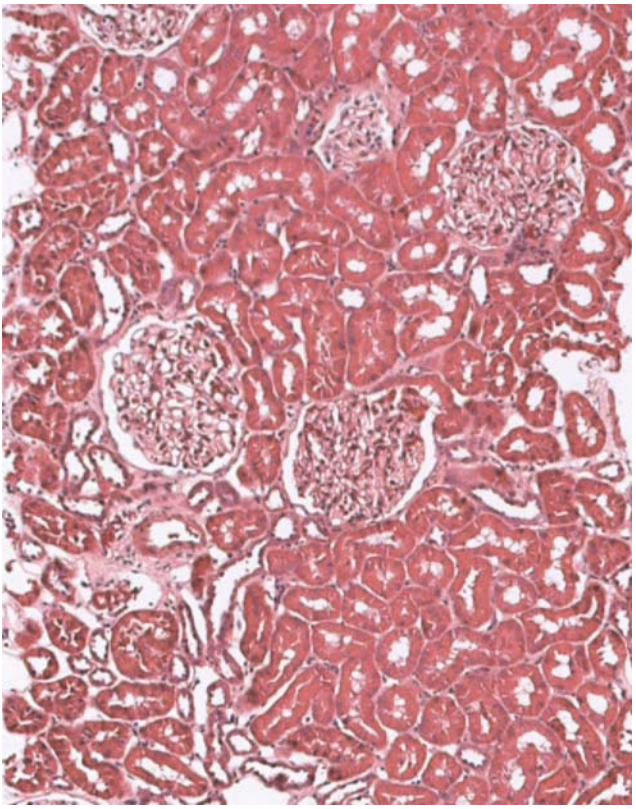

**Fig. 6.51** Cortex in a renal biopsy specimen from a woman of 21 with the nephrotic syndrome, and clinical reactivation of systemic lupus erythematosus that had been treated for 2 years. There is no acute or chronic tubular damage. Glomeruli have pure membranous nephropathy as a sign of lupus nephritis. In Latin, the word lupus meant a wolf. In English, the word was used for many centuries to mean a skin ulcer. This was well defined by Barrough in 1590: "Lupus is a malignant ulcer quickly consuming the neather parts; and it is very hungry like unto a woolfe". Different types of ulcer became recognised, such as lupus vulgaris caused by tuberculosis. The name systemic lupus erythematosus had this basis rather than other suggested origins, such as the supposed resemblance of the facial rash to a wolf's face. Systemic lupus erythematosus is thought to have caused renal failure and death in the American writers Jack London (1876–1916) and Flannery O'Connor (1925–1964), and the ruler of the Philippines, Ferdinand Marcos (1917–1989), who died after two renal allografts

segmental or global sclerosis, fibrosed adhesions between tuft and Bowman's capsule, and fibrosis in Bowman's space.

Active lupus nephritis usually responds to immunosuppression, although some types are more difficult to treat, particularly segmental vasculitic lesions, in classes three and four, and global membranoproliferative changes, in class four. Late changes in any class, as in any renal disorder, are not likely to improve.

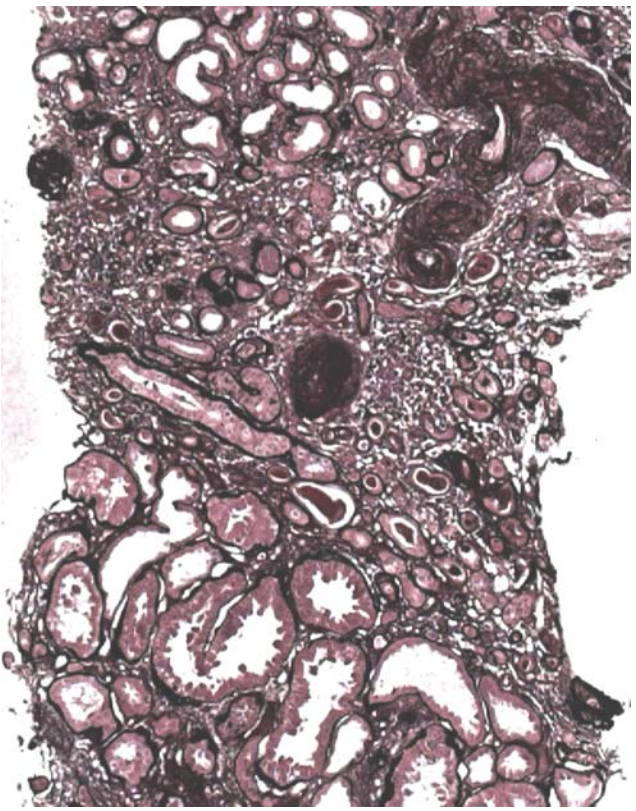

**Fig. 6.52** Cortex in a renal biopsy specimen from a woman of 52 with hematuria, proteinuria, chronic renal failure, and a 12-year history of systemic lupus erythematosus. There is severe late damage, with global sclerosis of nearly every glomerulus

### *Are Glomeruli Abnormal? Is There Amyloid?*

Amyloid is often an unexpected finding in renal biopsy specimens, and may be missed if the diagnosis is not considered, and no specific stain is requested. Because of this, and because amyloid is one of the few things that a simple stain can identify, there is justification to use Congo red as a routine stain on every renal biopsy specimen (Fig. 6.63).

## Diagnosis of Amyloid

Amyloid is easy to diagnose. The diagnosis can be made on one glomerulus, or even if there are no glomeruli in the specimen (Fig. 4.5).

There are various appearances on light microscopy, but usually there is expansion of mesangium and glomerular basement membranes by acellular material that stains

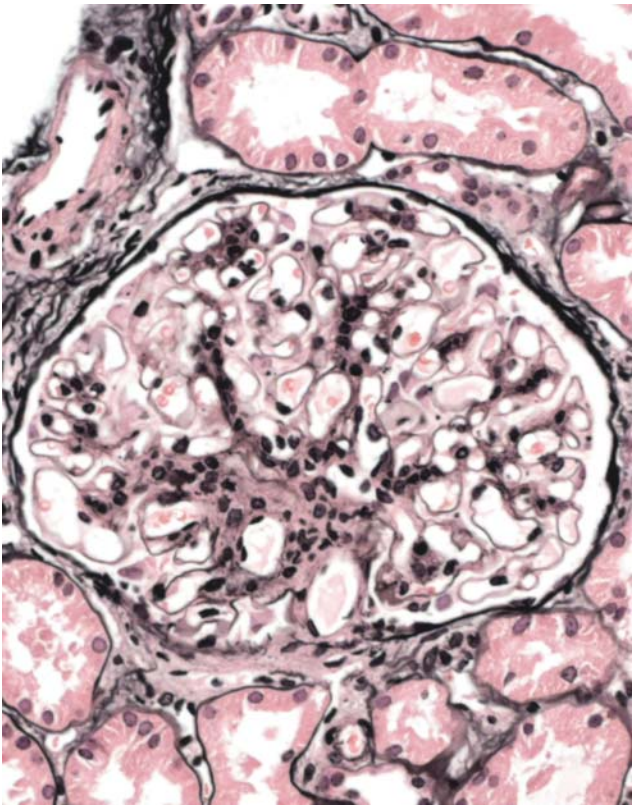

**Fig. 6.53** Glomerulus in a renal biopsy specimen from a woman of 39 with hematuria, proteinuria, and a short history of systemic lupus erythematosus. There is lupus nephritis, seen as mild mesangial expansion

palely with eosin (Fig. 6.64). This may stain black with periodic acid-methenamine silver. Often there are spikes or bristles projecting from the outside of glomerular capillary loops on sections stained with periodic acid-methenamine silver. These do not look like the spikes in membranous nephropathy, because in amyloid the projections are longer and coarser, and are found in groups rather than uniformly throughout glomeruli (Fig. 6.65). Material similar to that in glomeruli is often seen in walls of small blood vessels, tubular basement membranes, and interstitial tissues.

The diagnosis is given by Congo red staining. A control section known to contain amyloid should always be included when sections are stained by Congo red.

Amyloid appears various shades of red on orthodox light microscopy, depending on the amount of amyloid, thickness of sections, and technique of Congo red staining (Fig. 6.63). Sections thicker than the usual 3 μm are helpful in the study of amyloid, especially if there is not much in a specimen (Figs 6.66 and 6.67). Small amounts of amyloid can be missed, and the diagnosis in the nephrotic syndrome may be thought to be minimal change nephropathy.

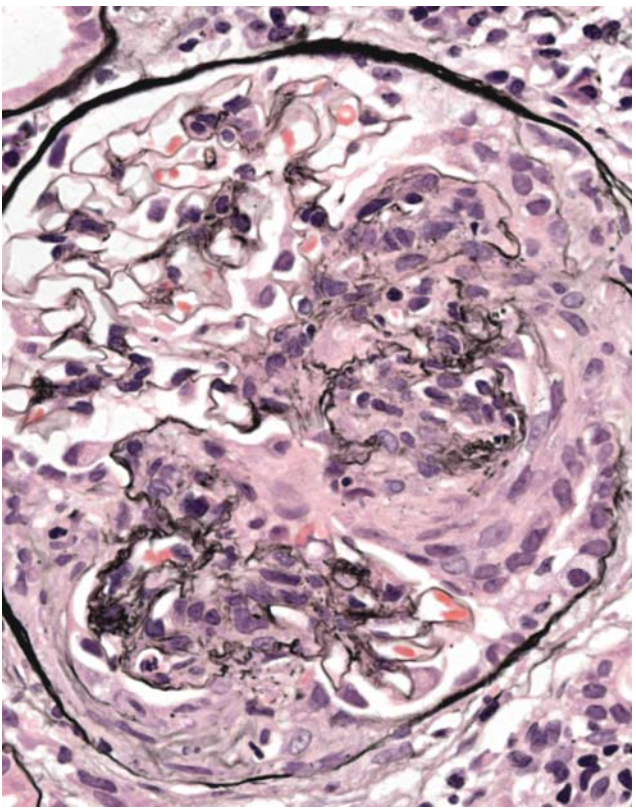

**Fig. 6.54** Glomerulus in a renal biopsy specimen from a woman of 40 with the nephrotic syndrome, hematuria, hypertension, acute renal failure, and systemic lupus erythematosus for over 10 years, but previously without any renal disorder. There is lupus nephritis, seen as a sharply outlined segmental lesion of vasculitic type, with disruption of basement membranes in capillary loops, and cells in Bowman's space

Not all material that stains with Congo red is amyloid. For instance, the internal elastic lamina of arteries stains in normal arteries. Polarising microscopy is necessary to confirm amyloid in sections stained by Congo red. Amyloid can be diagnosed satisfactorily by light microscopy, and electron microscopy is not essential for the diagnosis.

## Principles of Polarising Microscopy

To confirm amyloid, microscopic examination is needed with **polarising filters** below and above the section, called polariser and analyser. When one filter is rotated, the background changes from light to dark, with the maximum darkness when the planes of polarisation of the filters are at right angles to each other, and the filters

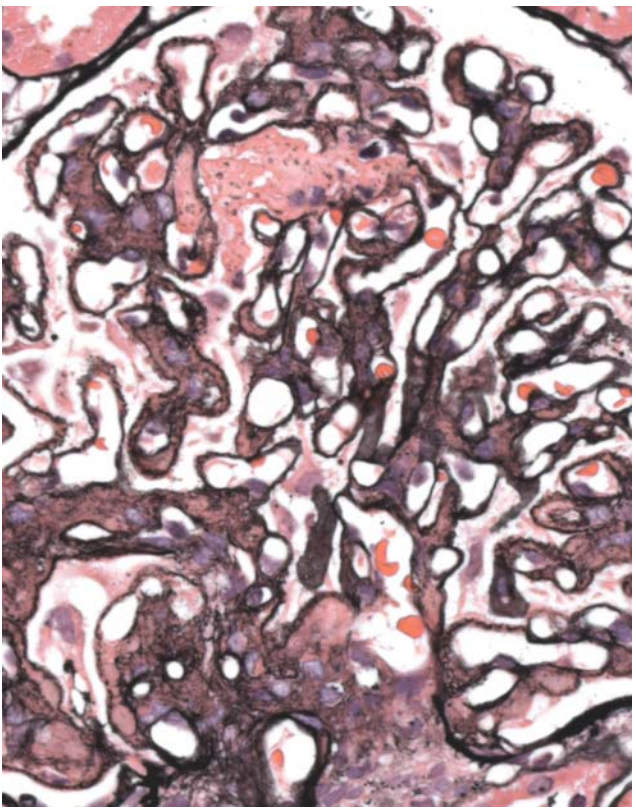

**Fig. 6.55** Glomerulus in a renal biopsy specimen from a woman of 23 with hematuria, proteinuria, and clinical reactivation of systemic lupus erythematosus that had been treated for 4 years. There is lupus nephritis, seen as a combination of membranoproliferative pattern with doubled basement membranes, membranous pattern, and early segmental vasculitic pattern, with thrombosis and disruption of a capillary loop

are said to be crossed. At this point and near it, birefringent structures lying at about 45° to the planes of polarisation appear bright against the dark background.

**Birefringent** means that a structure has two refractive indices for transmitted light. The refractive index is the ratio of velocity of light in a vacuum, or in air, to velocity in the material. A birefringent structure has asymmetry of its component parts. Light polarised in one plane interacts with components orientated in that plane, and its velocity is reduced or retarded more than light polarised at right angles. At 45° to the plane of polarisation, a birefringent structure resolves the linearly polarised light beam into two components, or vectors, at right angles to each other. As these vectors pass through the material, one is retarded more than the other. When these components emerge from the structure, their velocity returns to that in air, and they merge to produce elliptically polarised light. This means that the light waves, if viewed end on along their direction of travel, are no longer vibrating in

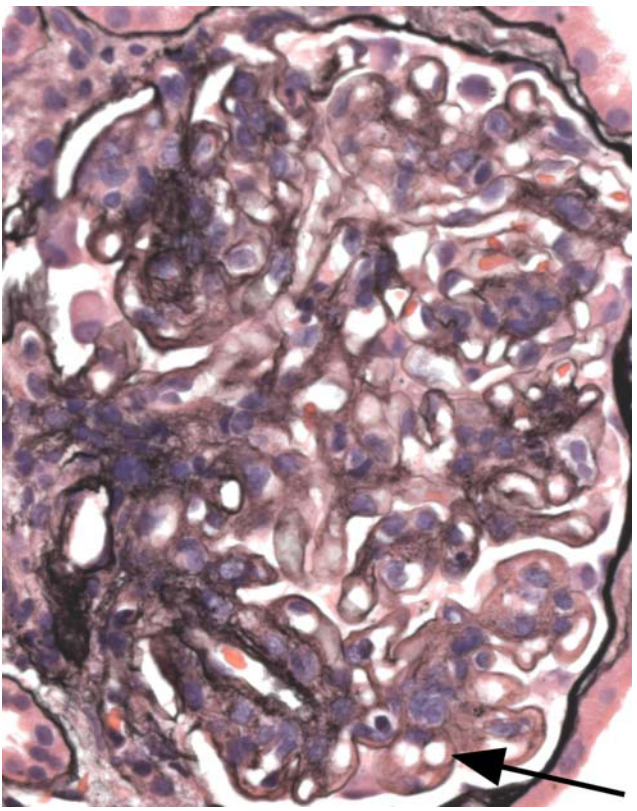

**Fig. 6.56** Glomerulus in a renal biopsy specimen from a woman of 45 with the nephrotic syndrome, acute renal failure, and clinical reactivation of systemic lupus erythematosus that had been treated for 9 years. There is lupus nephritis, with the appearance of subendothelial membranoproliferative glomerulonephritis, including subendothelial immune deposits (arrowed) that are called wire loops, because they resemble the tools used in microbiology to spread organisms on culture dishes

just one plane, but the tip of the combined vector rotates to trace an ellipse. Part of the light can now pass through a crossed analyser, and the structure appears bright against a dark background.

This explains why materials, such as starch particles or some other crystalline structures, have an appearance of Maltese crosses when examined between crossed polariser and analyser. There are four quadrants, in each of which there is maximal effect of the birefringence on polarised light (Fig. 6.68).

Characteristic of amyloid stained by Congo red is the appearance of various colours under these conditions (Figs 6.69–6.72). These may be called **anomalous colours**, because they include colours other than the red seen under unpolarised illumination. The only colour usually reported is green, often called “apple green birefringence”, although yellow and blue, or shades between these and green, are commonly seen. These colours alternate when the slide is rotated.

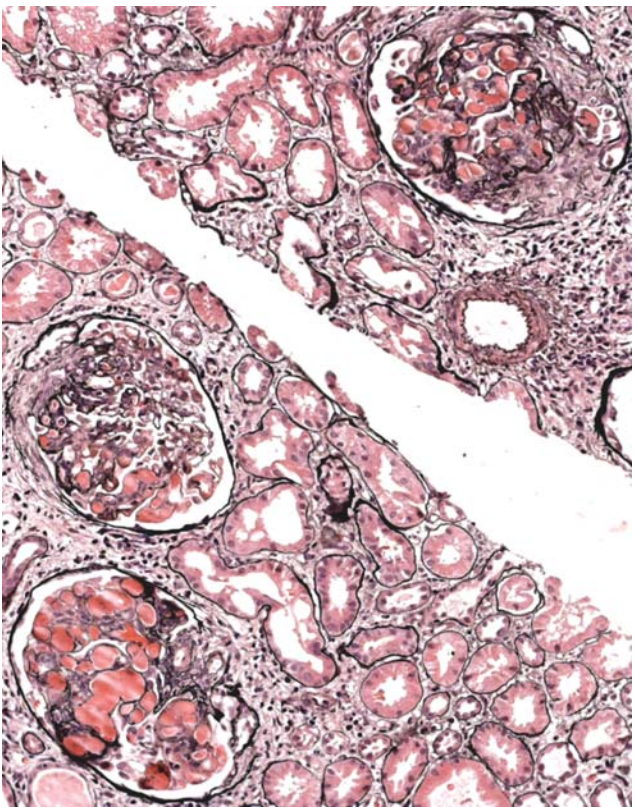

**Fig. 6.57** Cortex in a renal biopsy specimen from a woman of 22 with the nephrotic syndrome, renal failure that appeared acute, and clinical reactivation of systemic lupus erythematosus that had been treated briefly 1 year before. There is lupus nephritis with acute interstitial nephritis, various amounts of mesangial expansion, active and healing glomerular vasculitic lesions, and large intracapillary masses in glomeruli that are often called hyaline thrombi, although they are immune aggregates rather than thromboses

The explanation of anomalous colours is that molecules of Congo red are orientated on fibrils of amyloid, so that they absorb and retard light polarised in one plane, but not light polarised at right angles. This means that amyloid stained by Congo red is birefringent. The birefringence is not the same for every wavelength of light. Birefringence is maximal around the absorption peak of Congo red, which is in the blue–green part of the spectrum. Wavelengths shorter than the peak are transmitted with one direction of rotation of elliptically polarised light, giving blue, and longer wavelengths have an opposite direction of rotation, giving yellow.

When conditions are perfect for polarising microscopy, blue and yellow are both transmitted, and the net appearance is green. When conditions are not perfect, additional birefringence in the optical system may remove one of the colours, partly or completely, by the process called compensation, and shades of blue or yellow

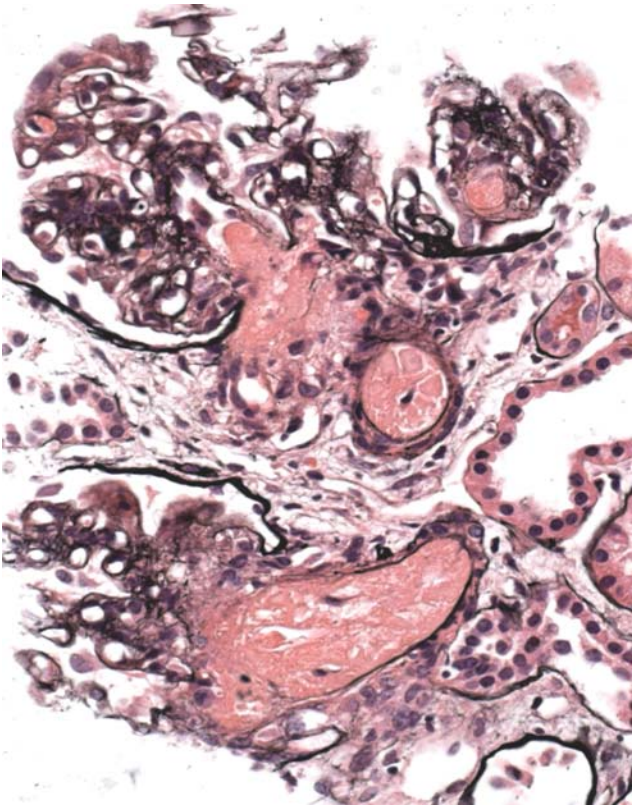

**Fig. 6.58** Cortex in a renal biopsy specimen from a woman of 19 with acute renal failure, hematuria, proteinuria, and relapse of systemic lupus erythematosus that had been treated for 5 years. There is lupus nephritis with a small vessel vasculopathy, also called thrombotic microangiopathy, seen as thrombosis and fibrinoid necrosis in arterioles

appear. Which one is removed depends on the relative orientation of the amyloid and the compensating agent. The extraneous birefringence could be in microscope lenses, the glass slide, or the coverslip.

Birefringence alone does not completely account for the anomalous colours, because as light passes through Congo red, there is absorption, particularly in the blue–green. The net effect of birefringence and absorption accounts for the colours seen in Congo red at 45° to the polariser, between crossed polariser and analyser.

As the polariser or analyser is rotated from this position, other colours appear. This test is useful in practice, to confirm amyloid. Increasing rotation in one direction gives yellow, orange, bright red, and dull red, in some areas of orientated amyloid. The other direction gives light green, white, and colourless in these areas. Specimens show both changes at the same time, because amyloid has many different orientations in a section.

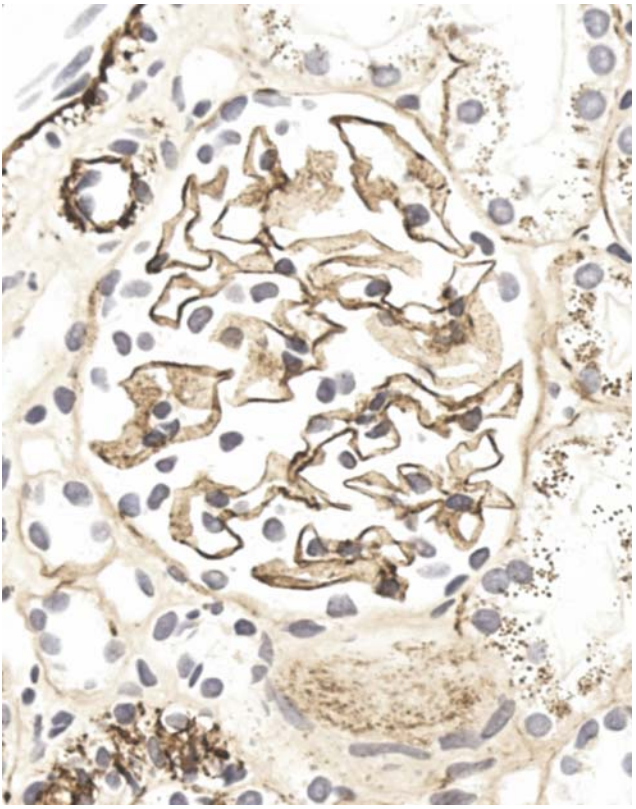

**Fig. 6.59** Glomerulus in a renal biopsy specimen from a woman of 44 with proteinuria in the nephrotic range, and reactivation of systemic lupus erythematosus that had been quiescent for many years. An immunoperoxidase stain to detect C9 shows the appearances of membranous nephropathy, with uniform, tiny granules on the outside of every capillary loop

These colours are produced by the combination of progressive decline in birefringence, and progressively strengthened effects of absorption on directly transmitted light. More light is transmitted directly as the polariser and analyser are uncrossed. Light passing directly through orientated molecules of Congo red in one plane is absorbed, and the appearance is of white lacking blue–green, which is red, against a white background. Light at right angles to this plane is not absorbed, and there is white, or no colour.

This change in appearance, related to a difference in the plane of illumination with polarised light, is called **dichroism**. Dichroism is detected in a material with use of a polariser only, without an analyser, or vice versa. Rotation of the slide, or the polariser or analyser, will show areas that change intensity of colour. Amyloid stained by Congo red is dichroic, but this is usually difficult to detect, because there are only small areas in a section where the amyloid has a uniform orientation.

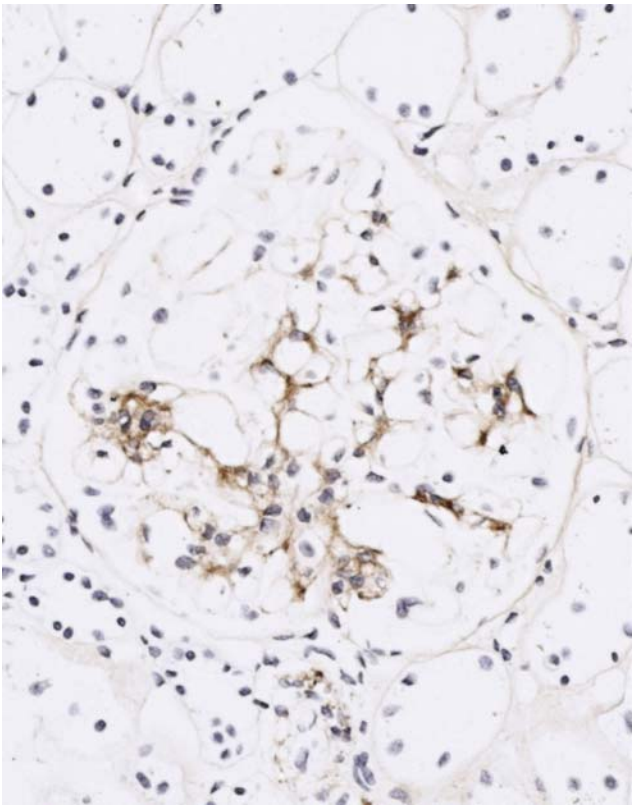

**Fig. 6.60** Glomerulus in the renal biopsy specimen from the woman of 39 with lupus nephritis, which is illustrated in **Fig. 6.53**. An immunoperoxidase stain to detect IgG shows only mesangial deposition

## Determination of the Type of Amyloid

Amyloid is not one substance, but a group of misfolded proteins with the similar property of formation of extracellular insoluble fibrils, which bind serum amyloid P glycoprotein. The commonest type found in the kidney is **AL amyloid**, derived from a monoclonal immunoglobulin light chain, and this is much more commonly lambda than kappa. The finding of amyloid consistent with AL type is often the first indication that there may be paraproteinemia, although this may be difficult to detect.

The second commonest type is **AA amyloid**. This is derived from serum amyloid A protein, which is an apolipoprotein of high-density lipoproteins, and is an acute phase reactant produced by the liver in many inflammatory conditions. AA amyloid is often associated with rheumatoid arthritis and other rheumatologic disorders, but also occurs in chronic infections, such as tuberculosis, bronchiectasis, osteomyelitis, and persistent abscesses, such as those found in the skin of some

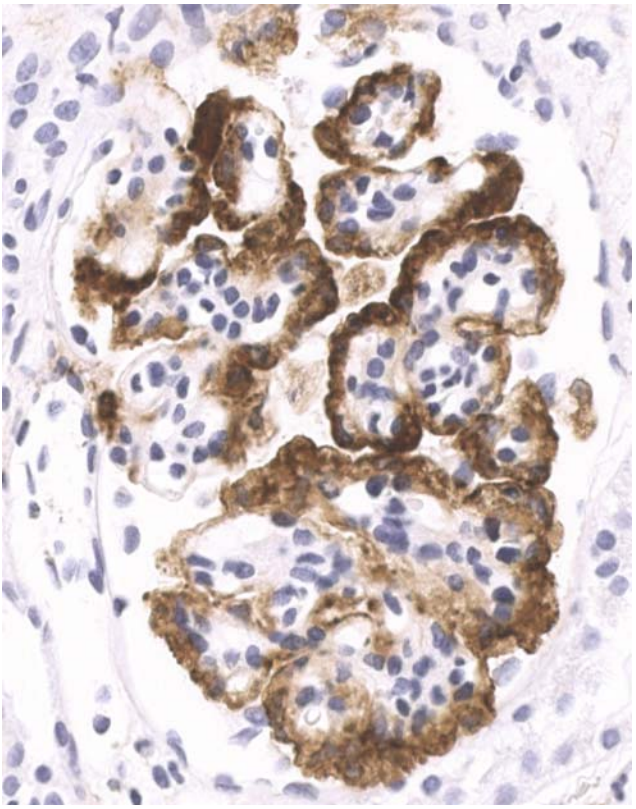

**Fig. 6.61** Glomerulus in a renal biopsy specimen from a man of 32 with the nephrotic syndrome, renal failure, and reactivation of systemic lupus erythematosus that had been quiescent for 2 years. An immunoperoxidase stain to detect C9 shows heavy subendothelial deposition.

intravenous drug users. This type also occurs in people with leprosy and schistosomiasis in tropical countries. Two inflammatory disorders which do not usually have a rise in concentration of serum amyloid A protein, and are not associated with amyloidosis, are systemic lupus erythematosus and ulcerative colitis. Persistent infections outside the kidney explain the common finding of AA amyloid in cattle and dogs.

AA amyloid is also found in familial mediterranean fever, and other inherited periodic fever disorders, in which it may respond to treatment. Other **familial** types of amyloid are associated with genetic abnormalities of fibrinogen Aalpha chain, lysozyme, transthyretin, apolipoprotein A1, gelsolin, and other proteins, but these are all rare. The commonest type found in the kidney is fibrinogen. Investigation of these types is not usually possible in most laboratories. Some other types of amyloid do not affect the kidney, or are not investigated by renal biopsy, such as the amyloid derived from beta two microglobulin found in people on hemodialysis,

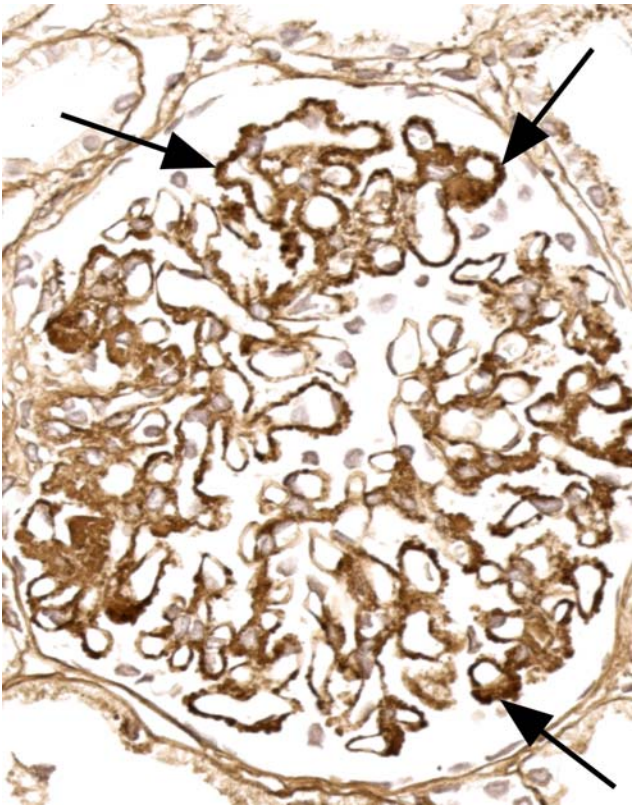

**Fig. 6.62** Glomerulus in the renal biopsy specimen of the woman of 23 with lupus nephritis that is illustrated in **Fig. 6.55**. An immunoperoxidase stain to detect IgG shows deposition in mesangium, on the outside of many capillary loops in a membranous pattern, and inside a few capillary loops, arrowed

or the cerebral amyloid derived from amyloid precursor protein in Alzheimer's disease.

When amyloid is discovered, the pathologist should try to define the type. This will help clinical investigation and management. If AL amyloid is found, appropriate immunologic investigations should be arranged by nephrologists. The prognosis of renal amyloidosis depends upon first, the extent of chronic renal damage, which is an indicator of the length of survival until renal replacement therapy is needed, and second, the underlying disorder, which has more relation to the death rate. AL amyloid has a higher mortality rate than other types, related to the underlying neoplastic disease and the damage to other organs, particularly the heart.

Immunohistology using an antibody to amyloid A protein usually confirms or excludes AA amyloid unequivocally (Figs 6.73 and 6.74). Antibodies to kappa and lambda light chains are not so straightforward, because they do not always react with the abnormal light chains in AL amyloid, but if available they should be used

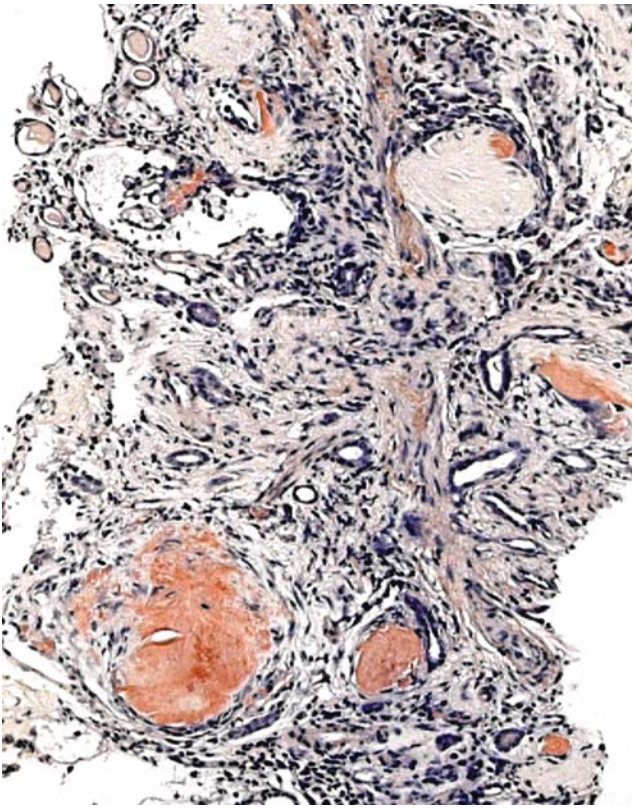

**Fig. 6.63** Cortex in a biopsy specimen of a renal allograft in a woman of 38, 12 years after transplantation for chronic renal failure that developed in childhood due to a segmental sclerosing glomerular disorder. Examination of a section stained with Congo red shows deposits of amyloid. This was unexpected. The amyloid was shown to be AL type, and further clinical investigation showed that the woman had myeloma

(Figs 6.75 and 6.76). Amyloid that does not react with an antibody to amyloid A protein, nor with antibodies to light chains, should be reported as non-AA amyloid, most likely AL, or consistent with AL, unless the pathologist is able to show that there is one of the rarer types.

Occasionally, especially when immunohistology is unavailable, another method of differentiation between AA amyloid and other types may be used. This is examination of thick sections by Congo red staining, with and without pretreatment of sections with potassium permanganate. Potassium permanganate always reduces the extent of Congo red staining, but if all staining is abolished, the amyloid is probably AA type. If any staining remains, the type is probably AL, but could be one of the rare types. This method is cruder than immunohistology, and may be unreliable when there are small amounts of amyloid.

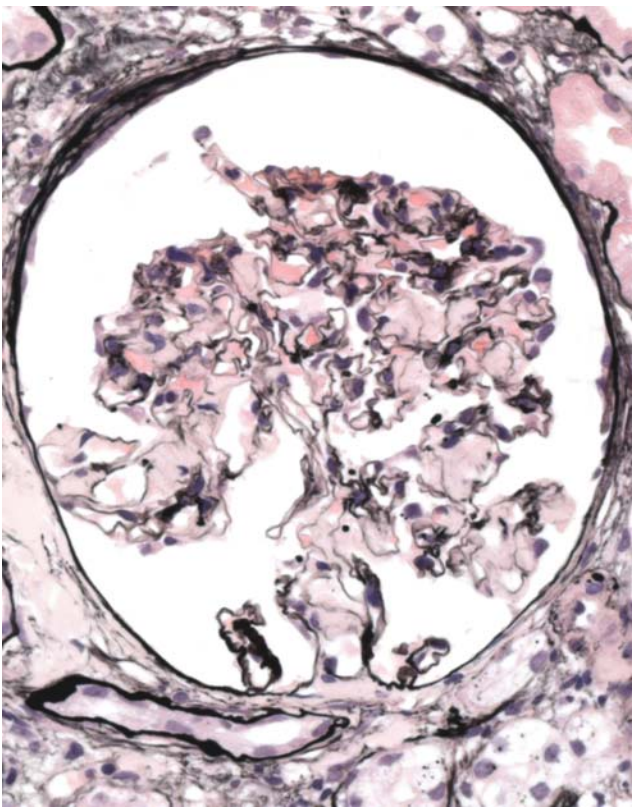

**Fig. 6.64** Glomerulus in a renal biopsy specimen from a man of 71 with the nephrotic syndrome. The mesangium contains material that is not stained by periodic acid-methenamine silver. The diagnosis was shown to be amyloid of AL type. After the biopsy, a paraprotein was found in serum and urine

## Differential Diagnosis of Amyloid

Diagnosis of amyloid is usually straightforward. Provided the staining with Congo red is reliable, there should be little difficulty.

An uncommon group of disorders that can resemble amyloid is differentiated by a lack of reactivity with Congo red. These disorders include **fibrillary glomerulopathy** and **immunotactoid glomerulopathy**, although these names are used inconsistently, and one name or the other, or **fibrillary-immunotactoid glomerulopathy**, may be sometimes applied to conditions with deposition of extracellular microfibrils or microtubules, without reactivity with Congo red, and in the absence of cryoglobulins, systemic lupus erythematosus, or diabetes mellitus.

These disorders can have various appearances on orthodox light microscopy, but usually there is mesangial expansion which resembles amyloid, but does not

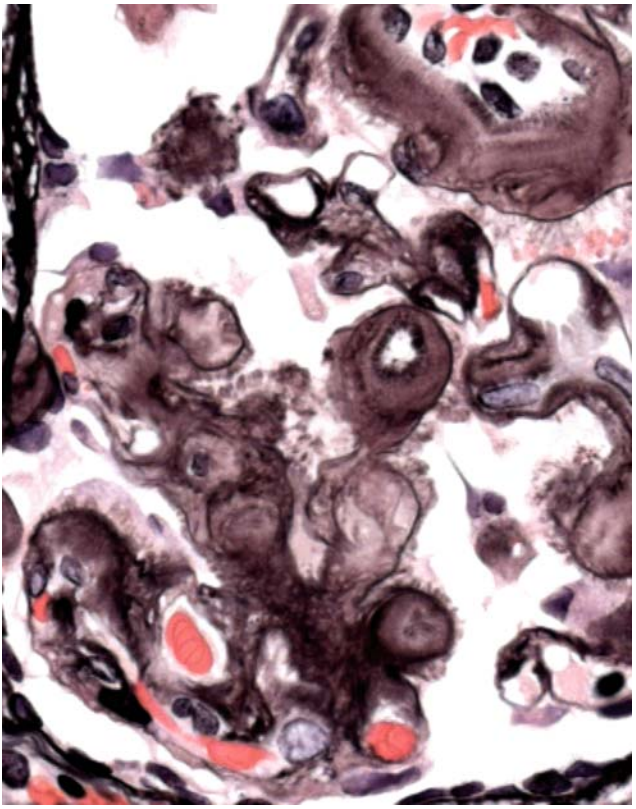

**Fig. 6.65** Glomerulus in a renal biopsy specimen from a man of 66 with the nephrotic syndrome, and a paraprotein in serum and urine. The mesangium contains material stained by periodic acid-methenamine silver, with groups of coarse bristles projecting from basement membranes in places. A further investigation is shown in **Fig. 6.74**

stain with Congo red (Fig. 6.77). Immunohistologic study shows IgG and complement in mesangium, and sometimes elsewhere. The deposits are usually polyclonal, containing both kappa and lambda light chains, but monoclonal deposits may be found, particularly in the immunotactoid type. Electron microscopy shows filamentous or microtubular deposits in mesangium and glomerular basement membranes. The appearance and size of the deposits is used to differentiate fibrillary glomerulopathy from immunotactoid glomerulopathy, in which there is the appearance of microtubular structures (Fig. 6.78). Fibrils in fibrillary glomerulopathy are about 10–30 nm thick, and microtubules in immunotactoid glomerulopathy are about 20–50 nm thick. In comparison, fibrils in amyloid are about 8–12 nm thick.

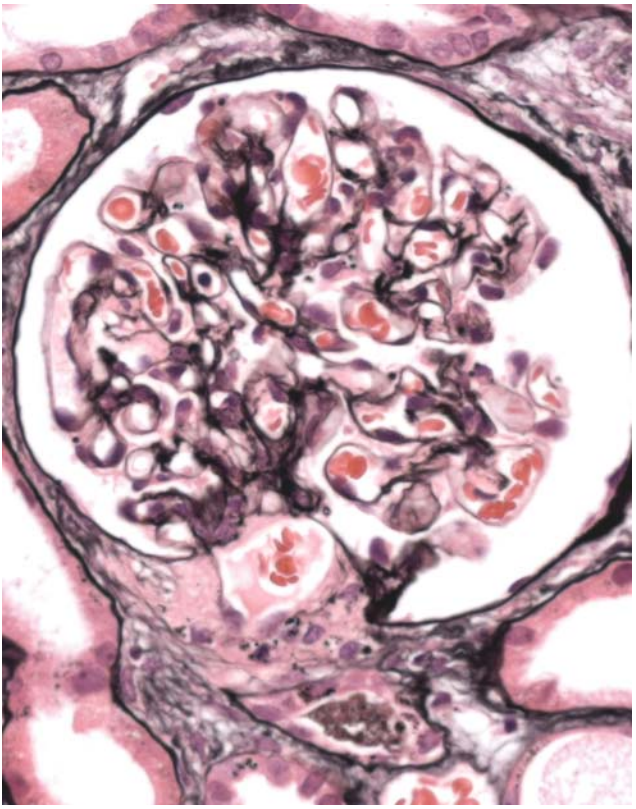

**Fig. 6.66** Glomerulus in a renal biopsy specimen from a man of 65 with the nephrotic syndrome and acute renal failure. This is close to normal on periodic acid-methenamine silver staining. Congo red staining is shown in **Fig. 6.67**

## *Have Minimal Change Nephropathy, Membranous Nephropathy, Segmental Sclerosing Disorders, Diabetic Glomerulopathy, Lupus Nephritis, Amyloid, and Conditions that Could be Confused with Them Been Excluded?*

Particularly in developing countries there are two other glomerular disorders that can commonly produce the nephrotic syndrome.

Both give the appearance on low power microscopy of glomerular hypercellularity, which affects the whole of each glomerulus uniformly. These global and diffuse disorders are **acute postinfective glomerulonephritis,** and **subendothelial membranoproliferative** or **mesangiocapillary glomerulonephritis**, which is also sometimes called membranoproliferative or mesangiocapillary glomerulonephritis type one.

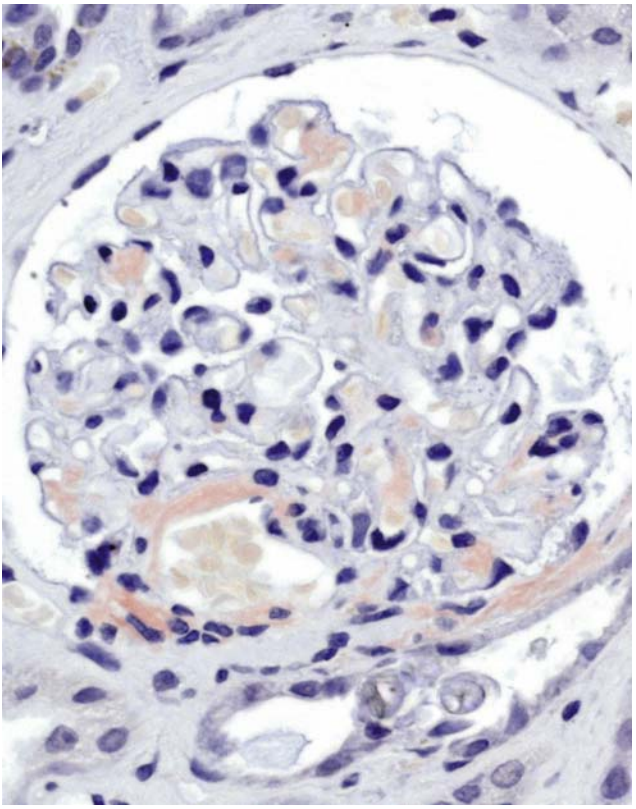

**Fig. 6.67** Glomerulus in the renal biopsy specimen from the man of 65 illustrated in **Fig. 6.66**. Congo red staining shows deposits of amyloid in mesangium, and also in an arteriolar wall and adjacent Bowman's capsule. Further investigations are shown in **Figs 6.75** and **6.76**

**Acute postinfective glomerulonephritis** typically presents several days after an infection as acute nephritis, with edema, proteinuria, hematuria, hypertension, and acute renal failure. Serum complement component C3 has a reduced concentration. The commonest cause is infection of the pharynx or skin by *Streptococcus pyogenes*. This is why the term acute poststreptococcal glomerulonephritis is sometimes used, although infection with other microorganisms can precede the disorder. These include *Staphylococcus aureus*, Gram-negative bacilli, and, less commonly, virtually every other pathogenic organism. The presentation may be atypical, and the nephrotic syndrome may predominate.

Acute postinfective glomerulonephritis is probably not due to deposition of circulating immune complexes, but to an antibody response to antigens deposited in glomeruli early in the course of an infection. Most people with this disorder recover to normal.

**Fig. 6.68** Tubules in a renal biopsy specimen from a woman of 65 with myeloma kidney, or light chain cast nephropathy, stained by Congo red, and examined between crossed polariser and analyser. There is a Maltese cross appearance produced by birefringence, although the cast material is not amyloid. There are anomalous colours, blue–green and yellow

**Subendothelial membranoproliferative glomerulonephritis** may also follow an infection, or more usually occurs during the course of a persistent infection, such as infection with hepatitis B or C viruses, malaria, schistosomiasis, syphilis, infective endocarditis, longstanding abscesses, or infected shunts draining cerebral ventricles. This can also be seen associated with sickle cell disease, various neoplasms such as chronic lymphocytic leukemia, and several other conditions. There is usually a mixture of clinical renal abnormalities.

Subendothelial membranoproliferative glomerulonephritis is probably due to deposition of immune complexes in glomeruli, either because there is prolonged heavy generation of immune complexes, or because immune complexes cannot be cleared when there are deficiencies of complement components. Various complement components, particularly C3, may have a reduced concentration in serum. Remission is unlikely. Generally, there is gradual progression to renal failure.

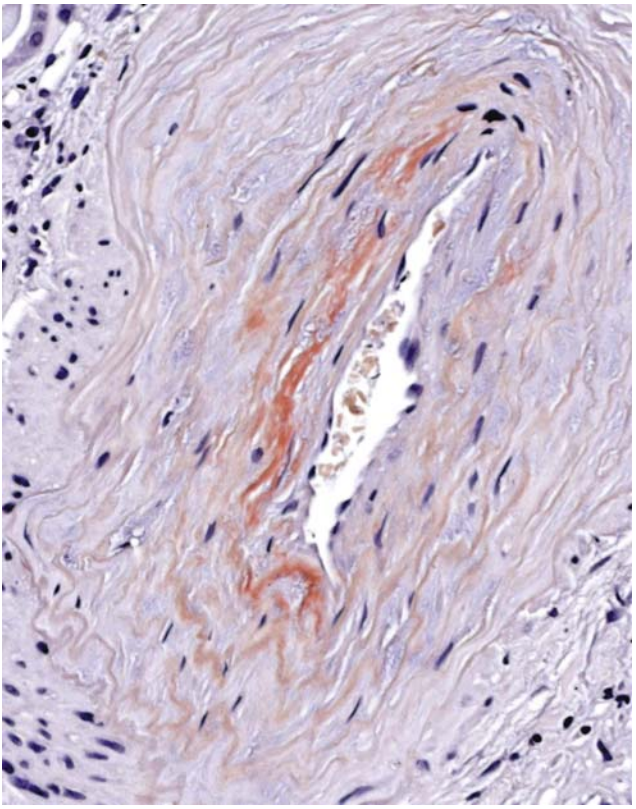

**Fig. 6.69** Artery in a renal biopsy specimen from a man of 85 with proteinuria, hematuria, and acute renal failure, stained by Congo red, which shows amyloid. **Fig. 6.70** shows its appearance between crossed polariser and analyser

## Differentiation Between Acute Postinfective Glomerulonephritis and Subendothelial Membranoproliferative Glomerulonephritis

Both disorders give global and diffuse glomerular hypercellularity, and both may have an infiltrate of neutrophils in the tuft at early stages. One of the features that helps the pathologist to distinguish between them is the appearance of glomerular basement membranes on sections stained by periodic acid-methenamine silver. In acute postinfective glomerulonephritis, these appear single, but in subendothelial membranoproliferative glomerulonephritis, these appear double, with interposition of mesangial cells between the two membranes (Figs 6.20, 6.79, and 6.80). The glomerular tuft in subendothelial membranoproliferative glomerulonephritis may appear in distinct lobules, and there may be mesangial nodules (Fig. 6.50).

On immunohistologic study, acute postinfective glomerulonephritis has irregular coarse granules, particularly of complement and sometimes of IgG, mainly on the outside of glomerular capillary loops, unlike the uniform fine granules

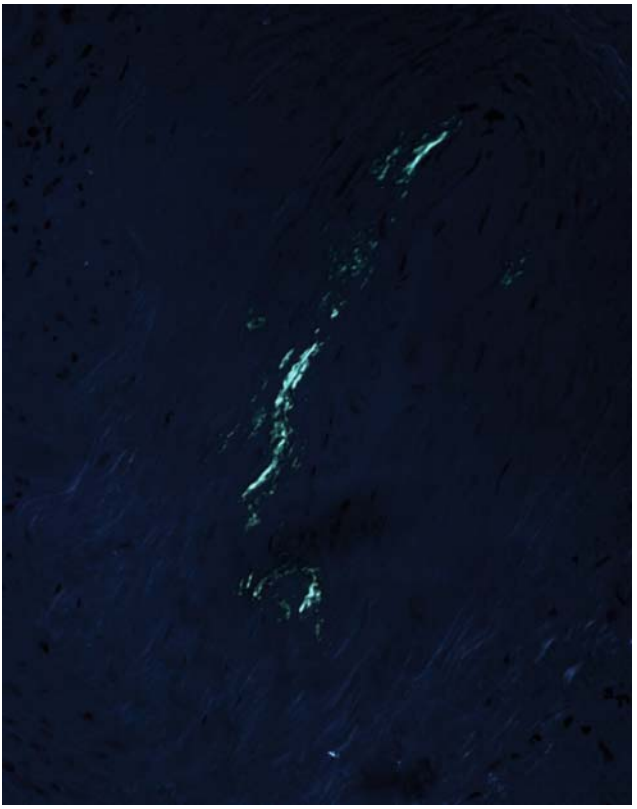

**Fig. 6.70** The microscopic field in **Fig. 6.69**, stained by Congo red, between crossed polariser and analyser, showing an anomalous green colour. Pure green is not always seen under these conditions, despite a widespread belief that it is

seen in membranous nephropathy (Fig. 6.81). Subendothelial membranoproliferative glomerulonephritis has large deposits, particularly of complement but often of IgG and IgM as well, in various proportions on the inner aspect of capillary loops, and sometimes in mesangium (Fig. 6.82). Electron microscopy confirms the distribution of immune deposits, and shows whether glomerular basement membranes are single or double, in which case, there is interposition of mesangial cells (Figs 6.83 and 6.84).

## Other Findings in the Nephrotic Syndrome

Other glomerular disorders may present with the nephrotic syndrome, but these are unusual. In particular, IgA nephropathy, which is often the commonest single finding in any series of renal biopsy specimens, hardly ever presents in this way. The finding of mesangial IgA deposits, but no other abnormality on light microscopy, in a child with the nephrotic syndrome, suggests a diagnosis of coincidental minimal change nephropathy and IgA nephropathy. Henoch–Schönlein nephritis, which

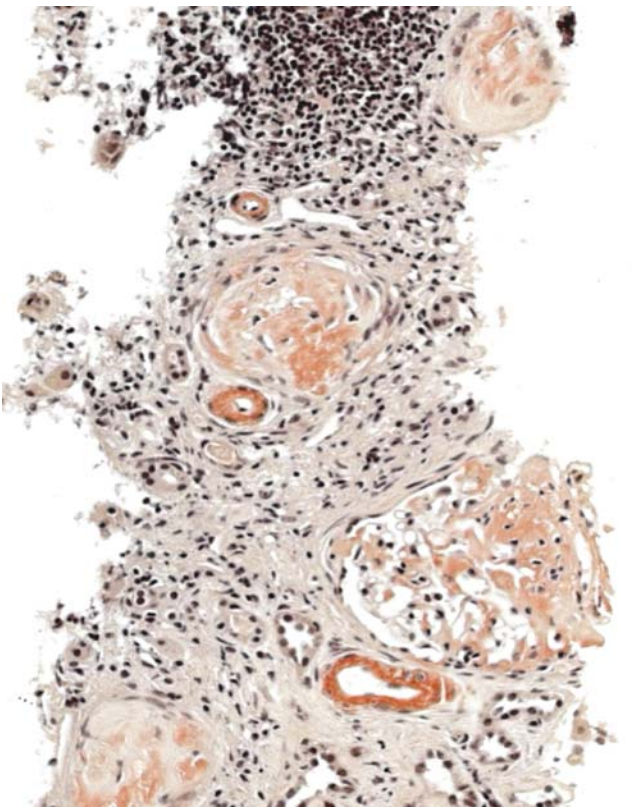

**Fig. 6.71** Cortex in a renal biopsy specimen from a man of 68 with the nephrotic syndrome, chronic renal failure, a paraprotein in serum, and paraplegia, after a road traffic accident 12 years previously. Congo red staining shows amyloid in glomeruli and walls of blood vessels. **Fig. 6.72** shows the appearance between crossed polariser and analyser

is the combination of IgA nephropathy and vasculitic glomerulonephritis, usually presents with acute renal failure, but may be associated with proteinuria in the nephrotic range at the time of presentation.

The nephrotic syndrome in young children may have findings not seen at other ages. The term **congenital and infantile nephrotic syndrome** covers several conditions associated with the nephrotic syndrome in young children. **Congenital** strictly means present at birth, but congenital nephrotic syndrome is used for onset of the syndrome between birth and 3 months. Onset after 3 months and up to 1 year is called **infantile** nephrotic syndrome. The commoner of these is congenital. By far, the commonest finding is the Finnish type of congenital nephrotic syndrome, an autosomal recessive condition in which the protein nephrin is abnormal in glomerular epithelial cells. Diffuse mesangial sclerosis is the next most frequent, and may be associated with mutation of the Wilms' tumor gene, *WT1*. Specimens are mostly seen in specialised centres, and are often difficult to interpret, particularly if the biopsy is within a few months of birth. The diagnosis is reached by a combination of investigations, which may include genetic studies.

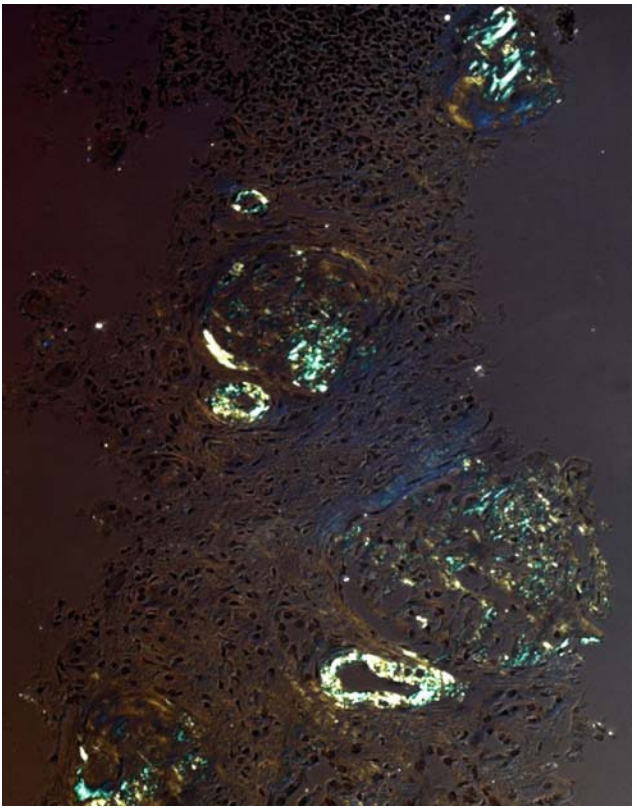

**Fig. 6.72** The microscopic field in **Fig. 6.71** stained by Congo red, between crossed polariser and analyser, showing anomalous colours, blue–green and yellow. A further investigation is shown in **Fig. 6.73**

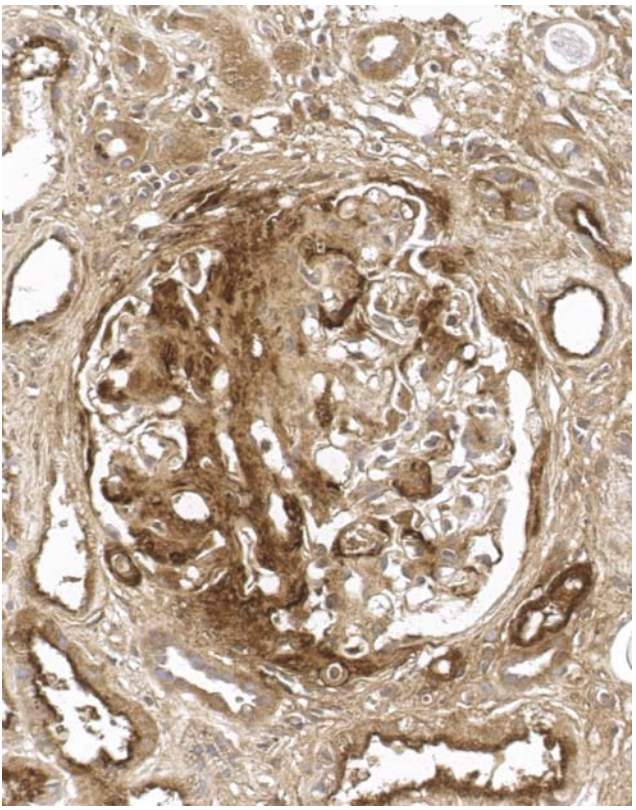

**Fig. 6.73** Glomerulus in the renal biopsy specimen from the man of 68 that is illustrated in **Figs** 6.71 and **6.72**. Immunoperoxidase study to detect amyloid A protein shows heavy deposition in the glomerulus. The staining in tubular epithelium is seen in every kidney, and is ignored. Despite the paraprotein, the diagnosis was amyloid of AA type. This was attributed to a persistent inflammatory response to bed sores of long duration

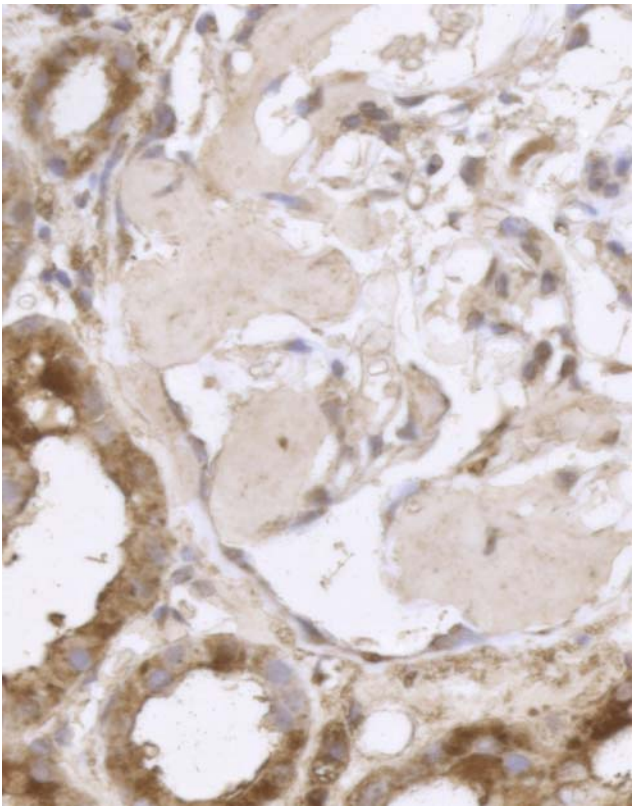

**Fig. 6.74** Glomerulus in the renal biopsy specimen from the man of 66 with amyloid, illustrated in **Fig. 6.65**. Immunoperoxidase study to detect amyloid A protein shows no deposition in the glomerulus. Although there was no definite deposition of kappa or lambda light chains in glomeruli, the diagnosis was non-AA amyloid, consistent with AL type

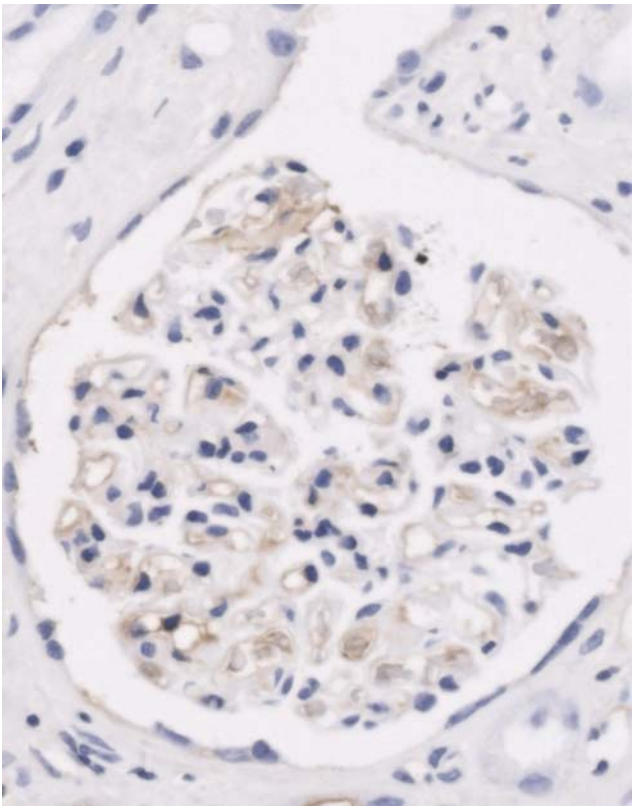

**Fig. 6.75** Glomerulus in the renal biopsy specimen from the man of 65 with amyloid, which is illustrated in **Figs 6.66** and **6.67**, stained by an immunoperoxidase method using an antibody to kappa light chains. This shows no significant deposition. **Fig. 6.76** shows the comparable immunostaining for lambda light chains

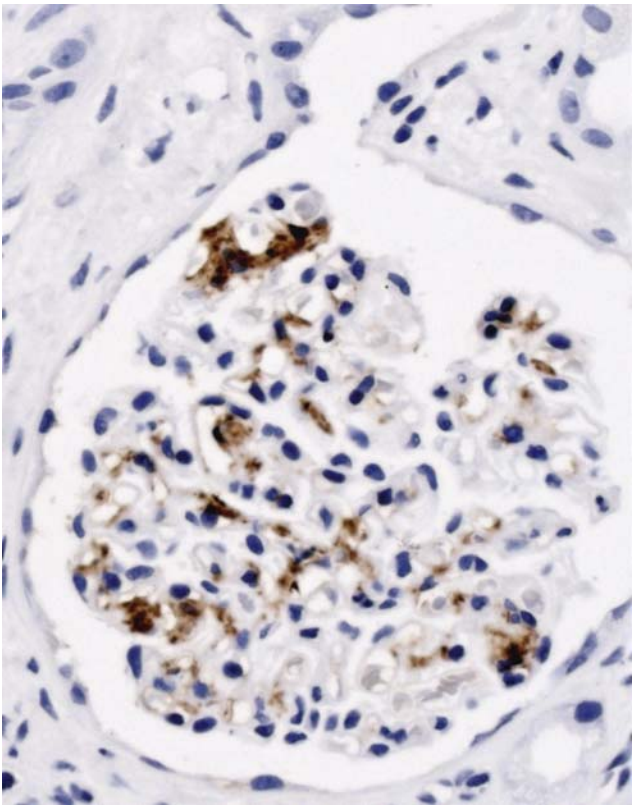

**Fig. 6.76** Another section of the same glomerulus as **Fig. 6.75**, immunostained for lambda light chains. There is deposition in the mesangium, which indicates AL amyloid. After the biopsy, an IgG lambda paraprotein and monoclonal lambda light chains were found in the man's serum

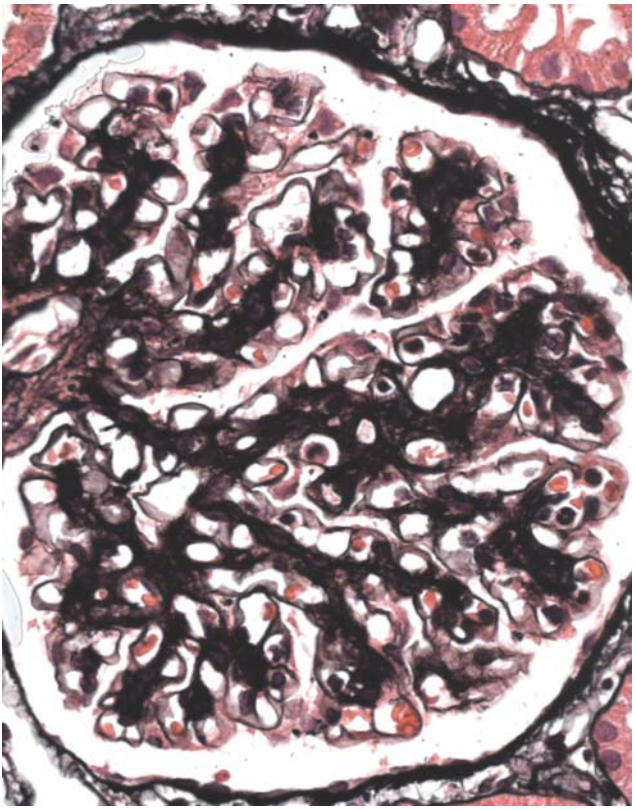

**Fig. 6.77** Glomerulus in a renal biopsy specimen from a man of 36 with heavy proteinuria and episodes of hematuria. There is mesangial expansion, but no reactivity with Congo red. Electron microscopy shows fibrillary deposits in mesangium, with the appearance of fibrillary glomerulopathy

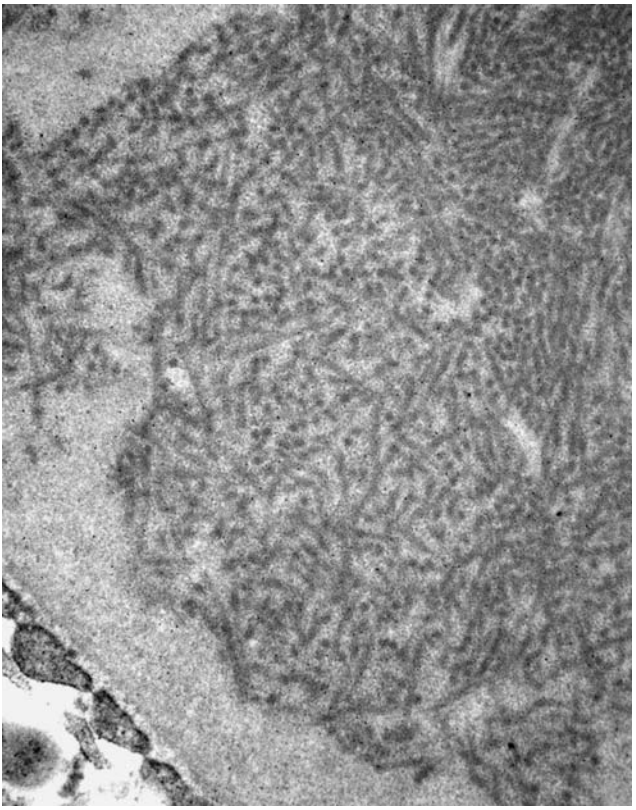

**Fig. 6.78** Electron micrograph of part of a glomerulus in a renal biopsy specimen from a man of 37, with HIV infection and the nephrotic syndrome. There are microtubular structures in the mesangium, indicating immunotactoid glomerulopathy

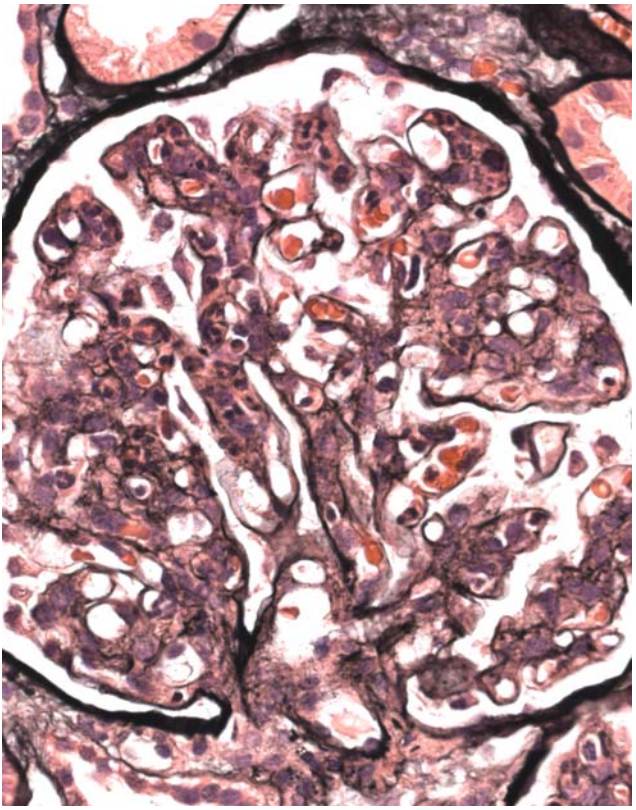

**Fig. 6.79** Glomerulus in a renal biopsy specimen from a man of 31 with the nephrotic syndrome and acute renal failure, after an illness with fever. The glomerulus appears hypercellular, with swollen endocapillary cells and a heavy infiltrate of neutrophils. Basement membranes are normal. The diagnosis is acute postinfective glomerulonephritis. The man recovered to normal

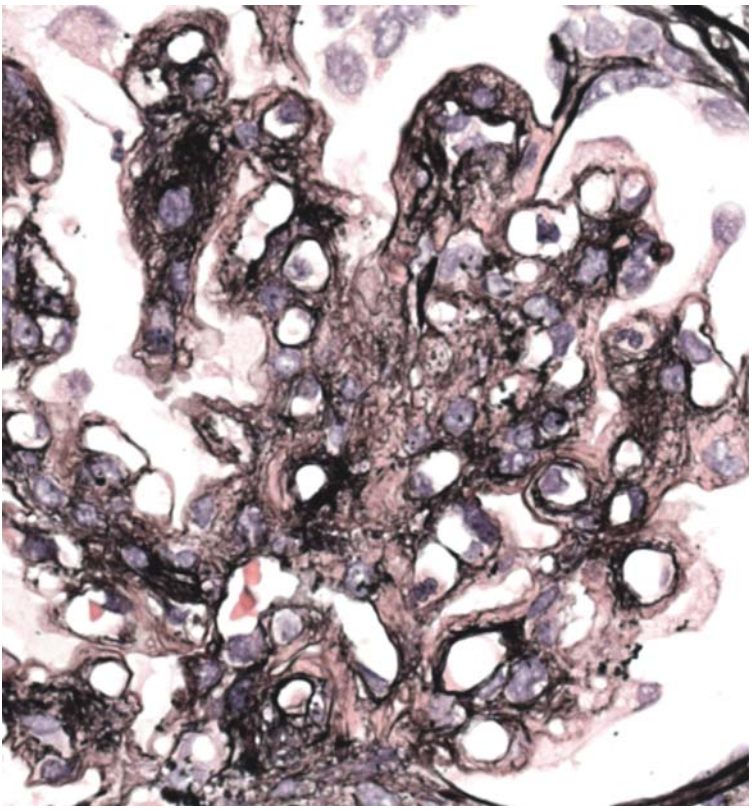

**Fig. 6.80** Glomerulus in a renal biopsy specimen from a man of 45 with the nephrotic syndrome, hematuria, and chronic renal failure. There is mesangial expansion, and most basement membranes appear double on the section stained by periodic acid-methenamine silver. The diagnosis is subendothelial membranoproliferative glomerulonephritis

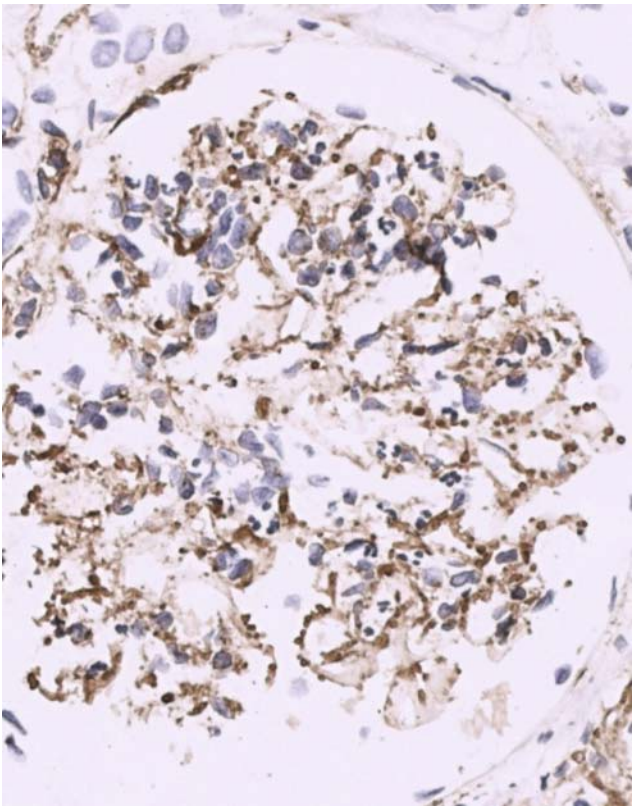

**Fig. 6.81** Glomerulus in a section stained by an immunoperoxidase method to detect C9, in a renal biopsy specimen from a man of 67 with acute postinfective glomerulonephritis. There are coarse granules of complement scattered irregularly on the outside of capillary loops, with finer deposits in mesangium

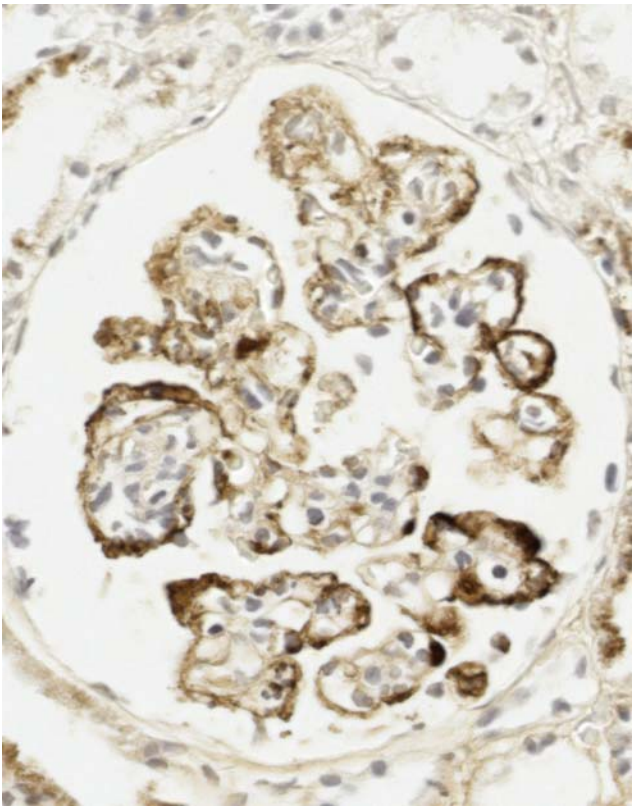

**Fig. 6.82** Glomerulus in a renal biopsy specimen from a woman of 64 with the nephrotic syndrome and chronic lymphocytic leukemia, stained by an immunoperoxidase method to detect IgG. There are large areas of subendothelial deposition, which confirms subendothelial membranoproliferative glomerulonephritis

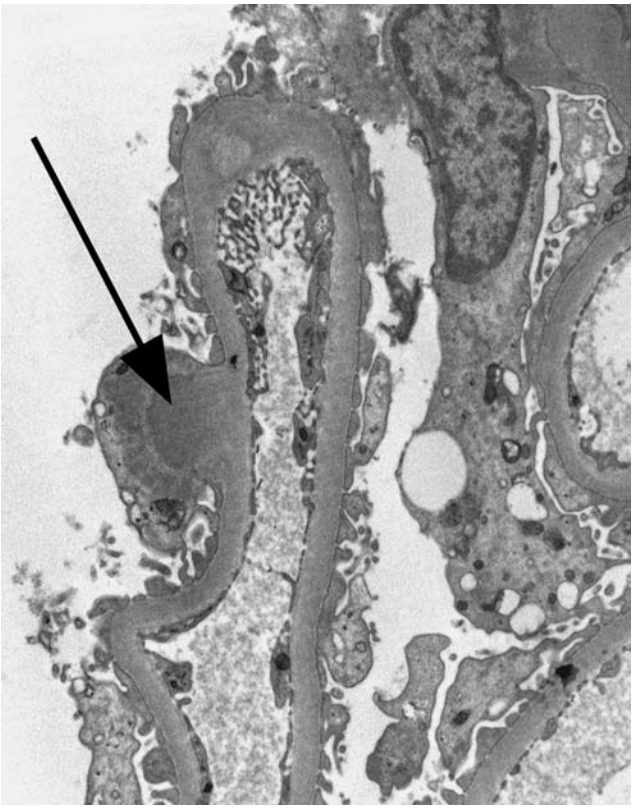

**Fig. 6.83** Electron micrograph of a glomerulus in a renal biopsy specimen from a man of 38 with acute postinfective glomerulonephritis, showing a large subepithelial deposit (arrowed)

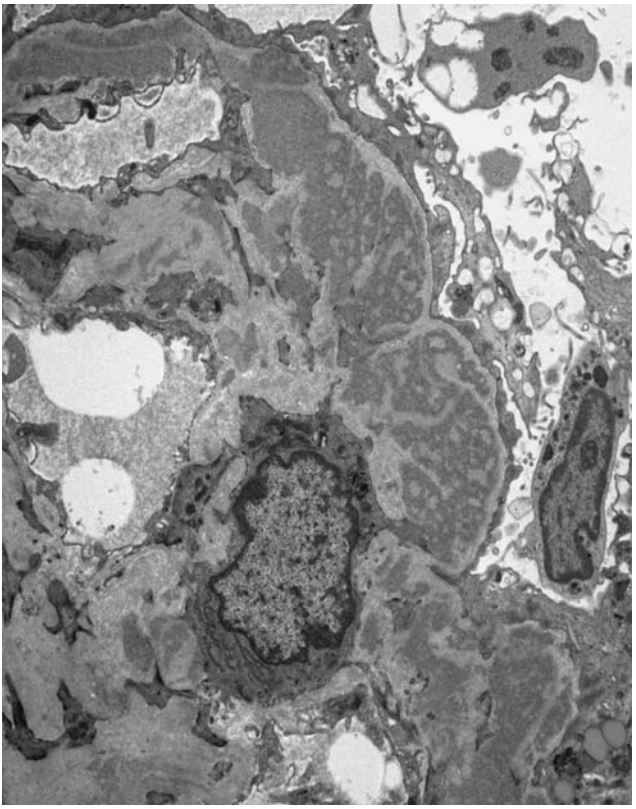

**Fig. 6.84** Electron micrograph of a glomerulus in a renal biopsy specimen from a man of 44 with subendothelial membranoproliferative glomerulonephritis, showing many large subendothelial deposits

## Summary: Nephrotic Syndrome

The nephrotic syndrome always indicates a glomerular disorder.

Extent of tubular damage should be assessed in the nephrotic syndrome. Severe acute tubular damage may be a sign of renal vein thrombosis.

In adults with the nephrotic syndrome, membranous nephropathy, segmental sclerosing disorders, and minimal change nephropathy are usually the commonest findings.

Diabetic glomerulopathy, lupus nephritis, and amyloid often account for nearly all other biopsy specimens in adults with the nephrotic syndrome. Acute postinfective glomerulonephritis and subendothelial membranoproliferative glomerulonephritis may be found, especially in developing countries.

In those children with the nephrotic syndrome who have a biopsy, most have either minimal change nephropathy or a segmental sclerosing disorder.

# Further Reading: Nephrotic Syndrome

D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. *American Journal of Kidney Diseases* 2004; **43**: 368–382. This gives the Columbia classification of segmental sclerosing glomerular disorders.

D'Agati VD, Jennette JC, Silva FG. Non-Neoplastic Kidney Diseases. Atlas of Nontumor Pathology, first series, fascicle 4. Washington, DC:American Registry of Pathology and Armed Forces Institute of Pathology, 2005. Chapters 3, 5–7, 9–11, 13, 17.

Howie AJ, Pankhurst T, Sarioglu S, Turhan N, Adu D. Evolution of nephrotic-associated focal segmental glomerulosclerosis and relation to the glomerular tip lesion. *Kidney International* 2005; **67**: 987–1001.

Jennette JC, Olson JL, Schwartz MM, Silva FG. Heptinstall's Pathology of the Kidney. Sixth ed. Philadelphia:Lippincott Williams and Wilkins, 2007. Chapters 4–9, 12, 18, 19.

# Chapter 7
# Indication for Biopsy: Acute Renal Failure

## Introduction to Acute Renal Failure

This means that so far as can be determined clinically, renal excretory function was normal until the last few days or weeks, when renal function was noted to be abnormal. This acute reduction of glomerular filtration rate may also be called **acute renal impairment**, or **acute kidney injury**.

In most people with acute renal failure, the symptoms and signs are those of the underlying condition that explains the renal dysfunction, rather than specifically of the dysfunction, which may just give the symptom of not feeling completely well. Renal failure is assessed by investigations such as serum creatinine concentration, which is an indirect measure of the glomerular filtration rate. This means that renal failure, although it may be suspected clinically, is a condition that is diagnosed by **clinical chemistry**.

Renal function is a continuous variable, and there are arbitrary divisions between normal function and abnormal function, and between mild renal impairment and severe renal impairment that few would disagree should be called frank acute renal failure. The pathologist should not be concerned with these problems, but should approach any renal biopsy specimen in the way suggested here, if the request form gives the information of acute renal impairment, or acute renal failure, or similar terms, such as acute rise in serum creatinine concentration.

Few people are known to have had definitely normal renal function before they are found to have abnormal function. Nephrologists rely on clues from the clinical history, and other features such as size of the kidneys, which should be normal in acute renal failure, to decide whether this dysfunction is acute or chronic, but occasionally they may be in doubt. A sudden deterioration of renal function can occur in people with pre-existing, stable, longstanding renal impairment, as well as in those with previously normal renal function. This shows that there is no simple definition of acute renal failure.

If the request form mentions renal failure but not whether this is acute or chronic, or hints that the failure could be acute or chronic, the pathologist should approach interpretation with the assumption that the failure is acute. Assessment of the amount of chronic, irreversible damage in the biopsy specimen should immediately

A. J. Howie, *Handbook of Renal Biopsy Pathology.*

clarify whether there is longstanding renal failure, rather than acute dysfunction, or whether there is a mixture of both (Figs 4.4 and 7.1).

In acute renal failure, the person biopsied may have small urine output, called oliguria, or no urine output, called anuria, and may be on dialysis. There may be hematuria, proteinuria that may be heavy enough to give the nephrotic syndrome, and hypertension that clinically may be in the accelerated phase. If the nephrotic syndrome is present, the biopsy specimen should be assessed in the way suggested in Chapter 6.

Renal biopsy specimens are always abnormal in acute renal failure, and the pathologist should almost always be able to give a satisfactory diagnosis.

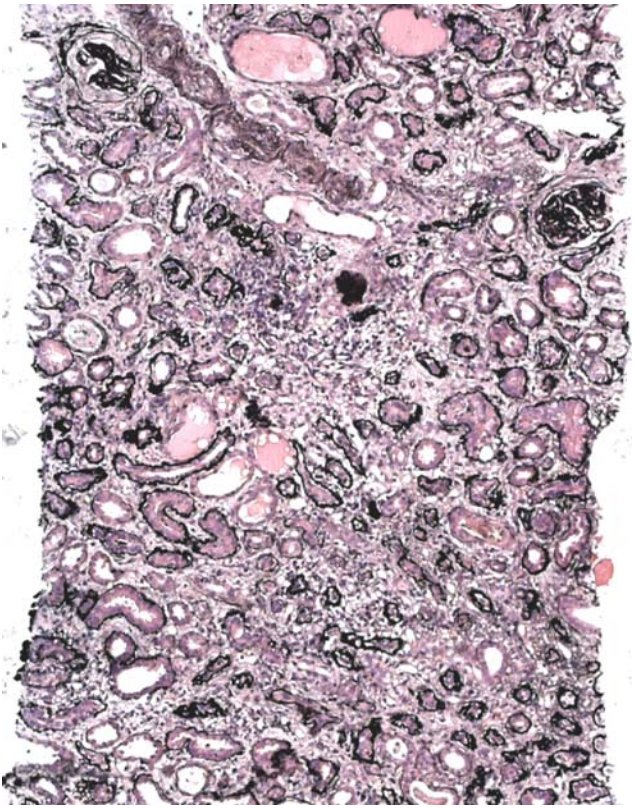

**Fig. 7.1** Cortex in a renal biopsy specimen from a man of 30 with severe hypertension, two kidneys of normal size, and renal failure that clinically appeared acute. There is advanced early tubular atrophy, and much of the damage appears chronic and irreversible, rather than acute and potentially reversible. Glomeruli have evidence of IgA nephropathy, and there is a small vessel vasculopathy, also called thrombotic microangiopathy, consistent with effects of accelerated hypertension. Renal function did not recover

**Most people with acute renal failure do not have a renal biopsy**. This is usually because the cause seems adequately explained by findings in the clinical history, clinical examination, and investigations.

## Causes of Acute Renal Failure

Traditionally, causes of acute renal failure are divided into prerenal, renal or intrarenal, and postrenal. Prerenal means reduced blood flow to the kidney, renal means direct damage to the kidney, and postrenal means obstruction of the urinary tract. Reality is more complicated than this. For instance, reduced blood flow and obstruction of the urinary tract will lead to damage to the kidney.

Causes are different between the sexes, at different ages, and in different parts of the world. **Neonates** may have acute renal failure from effects of dehydration, hypotension from congenital heart disease, and other conditions. Developmental disorders of the urinary tract may give renal failure, but this is more likely chronic than acute, and in severe disorders the child is stillborn. **Children** are most likely to have acute renal failure from diarrhea-associated hemolytic uremic syndrome, but there are many other causes, including many of those that are found in adults. **Adults** can have acute renal failure from many causes, including hypotension from blood loss, dehydration, septic shock or left ventricular dysfunction, toxic damage for instance from gentamicin, and urinary tract obstruction, for example from prostatic enlargement in old men, although there is likely to be chronic renal damage in people who present with urinary tract obstruction. Contrast media injected intravascularly for radiologic investigations can induce acute renal failure, but there is usually pre-existing chronic renal damage.

In developing countries, acute renal failure may be a complication of infective diarrheal illnesses, obstetric problems, intravascular hemolysis from glucose-6-phosphate dehydrogenase deficiency, hemolytic and other complications of malaria, and many other disorders.

## Value of a Renal Biopsy in Acute Renal Failure

Renal biopsy is used to investigate acute renal failure when the explanation is not considered adequately explained by clinical findings. The biopsy specimen gives information that will help nephrologists in clinical management. A diagnosis may be given that requires further clinical investigation, such as myeloma. The most important help is in the decision whether to begin aggressive treatment of an underlying disease, such as vasculitis. **Acute renal failure may recover**, provided the changes in the kidney are reversible, and the underlying cause is treatable and treated.

Renal biopsy in acute renal failure should be considered **an urgent matter**. This is one of the few circumstances when the pathologist can have an immediate

influence on clinical management. For instance, if renal vasculitis is unrecognised and untreated, survival rates are worse than for almost all cancers.

**A General Rule: Renal function is more closely correlated with structural changes in tubules than with any other changes. Acute renal failure is associated with acute abnormalities in tubules.**

One reason for this is a consequence of the fact that the kidney, particularly the cortex, has a large blood flow that is necessary for its function. The kidney mass is about half a hundredth of the body mass, about 300 g in a person weighing 60 kg, and yet the renal blood flow is almost one-quarter of the cardiac output.

Renal blood flow can be reduced severely in the short term to maintain the blood supply to the heart, lungs, and brain, in severe hemorrhage, for example. This necessarily reduces the glomerular filtration rate, and also has an effect on tubules. These have a high metabolic rate, and are sensitive to a reduction in blood flow, which is **ischemia**. If the blood volume and renal blood supply are restored quickly, there may be no tubular damage, and renal function can return to normal. If there has been ischemic tubular damage, there are mechanisms that prevent effective glomerular filtration until the tubules recover. These mechanisms also explain the acute renal failure that follows an initial **toxic** effect on tubules, for instance from gentamicin and other aminoglycoside antibiotics, some antineoplastic drugs such as cisplatin, some types of immunoglobulin light chains, and accidental or deliberate poisoning with many chemical agents, such as carbon tetrachloride. There can be a mixture of ischemic and toxic initiating events, for example, in acute renal failure associated with crush injury to skeletal muscle.

## Acute Abnormalities in Tubules

Acute abnormalities in tubules can have various appearances.

At the worst, there is **infarction** of some of the kidney or all of it, and all structures are affected. This means that tubules, glomeruli, interstitial tissues, and blood vessels are necrotic and appear poorly stained, sometimes with surviving areas next to dead areas (Fig. 7.2). The **mildest acute abnormalities** can be impossible to detect on sections stained by hematoxylin and eosin. There may be patchy loss of the brush border of proximal tubules, which can be shown by periodic acid Schiff staining or immunohistologic methods.

Between these limits, there can be changes in tubules such as vacuolation that may be fine or coarse, irregularity of epithelial thickness, loss of cells to leave bare basement membranes, and accumulation of material in the lumen that may be cells, cellular debris, or acellular casts (Figs 6.1, 6.3, 7.3, and 7.4). Not all tubules necessarily show the same features, and some can appear normal while others appear abnormal. Most of these changes can be seen in acute tubular damage of any cause, and they rarely by themselves indicate a precise cause. Single, large vacuoles in many tubular cells are consistent with prolonged hypokalemia, but may

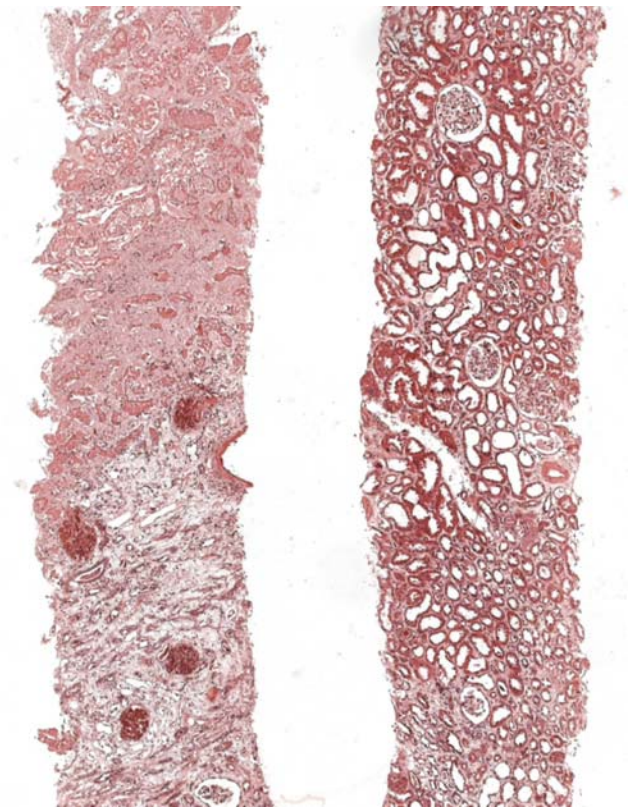

**Fig. 7.2** Two pieces of cortex in a renal biopsy specimen from a woman of 75 with acute renal failure and atrial fibrillation. One piece is mostly necrotic, while the other has acute tubular damage. There was assumed to be embolisation of left atrial thrombus into branches of the renal artery, but there was no direct evidence of this in the specimen. With appropriate treatment, there was partial recovery of renal function

occur in other circumstances, and probably reflect local conditions in the affected tubules.

Interstitial tissues often appear increased in acute renal failure, and a common explanation is edema (Fig. 7.3). This may still be seen after recovery from acute renal failure (Fig. 7.5).

The range of possible abnormalities reflects the range of renal function, which does not have just two states, definitely normal and definitely abnormal, but can vary along a continuous scale. Renal failure is not all or none, but has a gradation of severity.

Provided acutely abnormal tubules are not in an infarcted area of cortex, **they may recover to normal**. Infarcted areas and atrophic tubules will never recover.

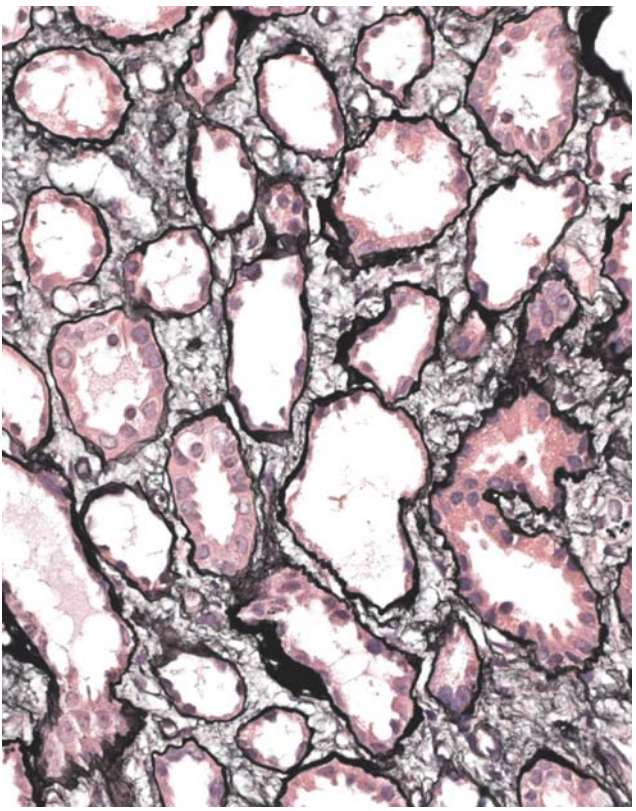

**Fig. 7.3** Cortex in a right renal biopsy specimen from a man of 67 with acute renal failure, after surgery to relieve obstruction of the left renal pelvis. Most tubules are acutely damaged, with irregular flattening of the epithelium. There is interstitial edema. The cause of the acute tubular damage is not apparent in the specimen, but was later thought to be septicemia

The term often used for tubular changes in acute renal failure is acute tubular necrosis. This is not strictly accurate, and not particularly useful for pathologists, because identifiable necrosis of tubular cells is hardly ever seen. Tubular cells may be lost from tubules by apoptosis, or by being shed into the tubular fluid, to be passed in urine. Lost cells are replaced by division of remaining cells, and there may be nuclear abnormalities during this regenerative stage (Fig. 7.6). A better term than acute tubular necrosis is **acute tubular damage**, which covers the range of abnormalities short of infarction of the cortex. Acute tubular injury is also used.

**Because nearly every biopsy specimen taken to investigate acute renal failure shows acute tubular damage, this should not be given as a diagnosis, unless it is the only abnormality.** This means that in many biopsy specimens, the explanation of acute tubular damage is evident, and should be given as the diagnosis.

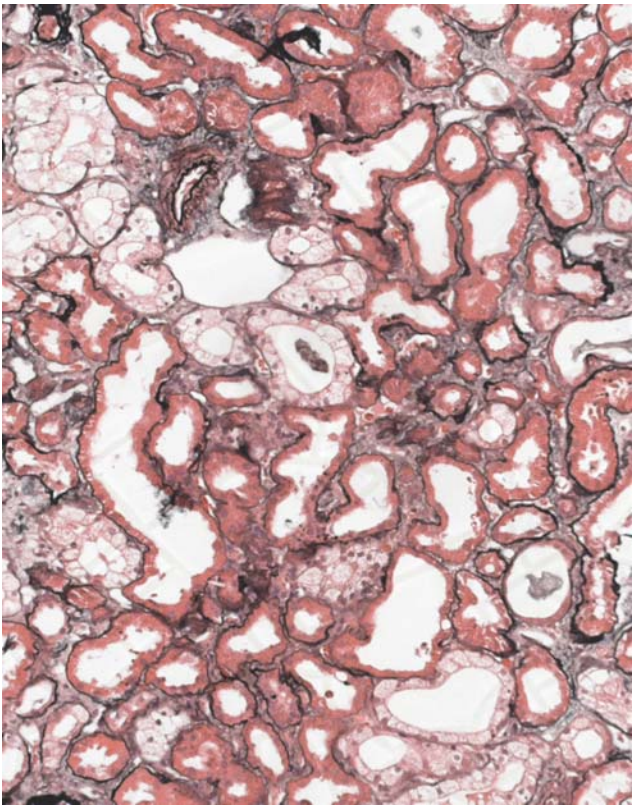

**Fig. 7.4** Cortex in a renal biopsy specimen from a man of 42 with acute renal failure, after heart transplantation with many complications. Some tubules appear normal, some have fine vacuolation of the epithelium, and a few are atrophic. The fine vacuolation may be an effect of a calcineurin inhibitor used as an immunosuppressant, but similar changes can be seen in people with acute tubular damage, not treated with this type of drug (**Fig. 5.9**)

## Approach to the Diagnosis in Acute Renal Failure

### *Is There Necrosis in the Kidney?*

In a biopsy specimen taken to investigate acute renal failure, the first thing for the pathologist to assess is whether there is **necrosis** of the kidney, particularly of the cortex. This means death of all structures, meaning tubules, glomeruli, interstitial tissues, and blood vessels, not necessarily uniformly throughout the specimen (Fig. 7.2). This is a rare finding, but has serious implications for prognosis, because if there is necrosis of most or all of both kidneys, renal function will never recover.

The most likely causes of necrosis are these:

1. A **thrombosing condition**, such as disseminated intravascular coagulation, with thrombi in glomerular capillaries or arterioles or larger vessels, or a **small vessel**

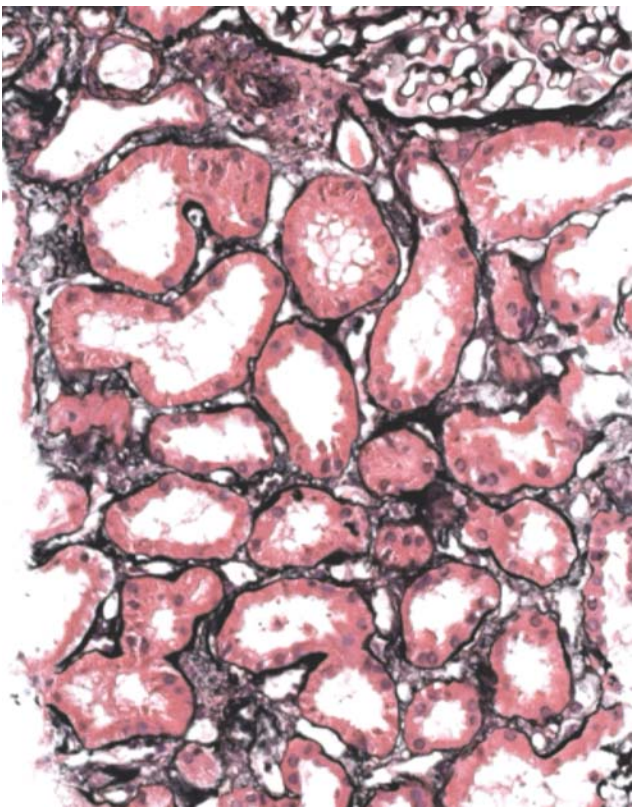

**Fig. 7.5** Cortex in a renal biopsy specimen from a woman of 57 who had recovered from acute renal failure by the time of biopsy. Most tubules appear normal, but there is interstitial edema

**vasculopathy**, also called thrombotic microangiopathy, in which there are acute abnormalities in vessels, particularly loose, concentric, intimal thickening in small arteries, and fibrinoid necrosis of arterioles (Figs 6.58 and 7.7–7.9). Various disorders, such as the group called thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, can give these appearances, and usually the pathologist cannot differentiate between the disorders.

2. Infarction caused by **blockage of a large artery**, which is not often included in the specimen. Embolic material in arteries is a clue to this diagnosis, but is much more commonly seen in specimens of chronically ischemic kidneys without necrosis (Fig. 7.10).
3. The condition **renal cortical necrosis**, caused by acute, severe underperfusion of the kidney, without blockage of arteries. Renal cortical necrosis may be incomplete, and there may be surviving tubules and other structures among necrotic tissues. If there are no clues such as this feature or hints of a small vessel

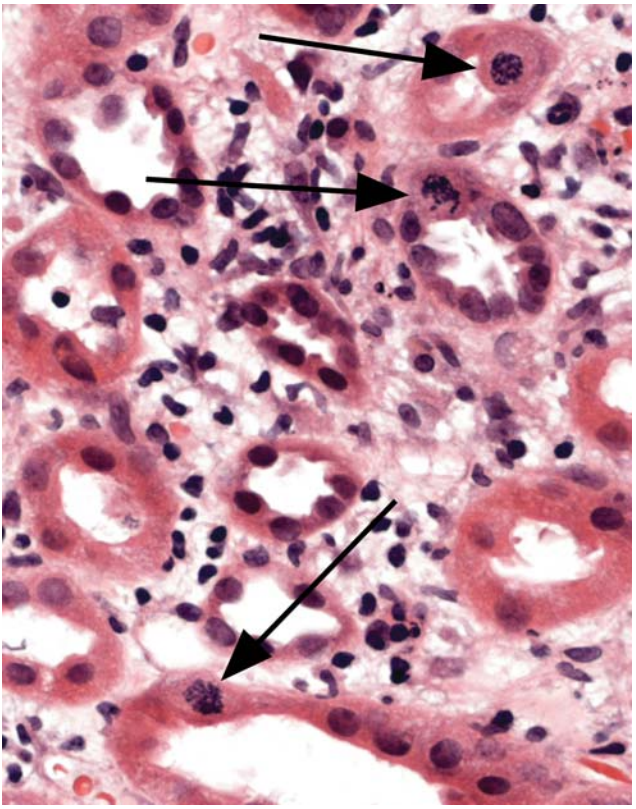

**Fig. 7.6** Medulla in a biopsy specimen of a renal allograft present for 9 days in a man of 48. Tubules are recovering from acute damage, and three mitotic figures are arrowed

vasculopathy, also called thrombotic microangiopathy, or embolic material in arteries, the pathologist may not be able to determine the cause of necrosis in a specimen.

## *Is There the Expected Number of Tubules in the Kidney?*

In the usual specimen in which there is no necrosis, the pathologist should decide whether there is the **expected number of tubules**, when allowance is made for the age of the person biopsied. Assessment of the amount of tubules and atrophy is done by inspection at low power on the microscope. In an old person, there may be patches of atrophic tubules that should not be seen in a young person. Occasionally, there may be such extensive atrophy that despite the clinical presentation with acute renal failure, the pathologist can say that there is a relatively longstanding renal disorder that is unlikely to recover, rather than an acute one that may recover (Fig. 7.1). A combination of acute damage and chronic changes can also occur (Fig. 6.27).

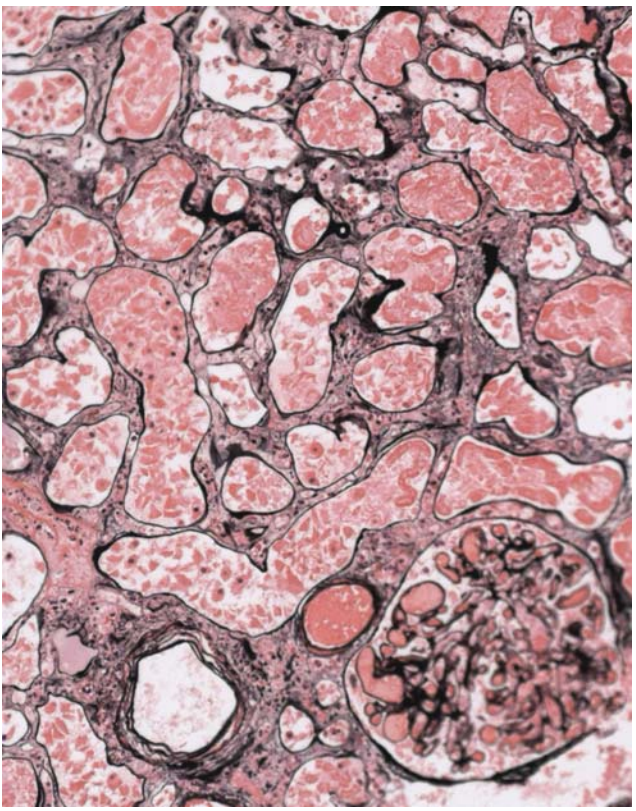

**Fig. 7.7** Cortex in a renal biopsy specimen from a man of 72 with acute renal failure. There is necrosis, with thrombosis of glomeruli and arterioles. Clinically, the eventual diagnosis was thrombotic thrombocytopenic purpura

### *Are There Clues to the Cause of Acute Tubular Damage?*

In acute renal failure that appears genuinely acute to the pathologist, there are tubules in normal numbers or nearly normal numbers, even though they may be more widely separated then normal, and they are expected to be structurally abnormal. The next problem for the pathologist is to decide whether there are changes in the specimen that give clues to the cause of the tubular damage. These clues can be in the tubules themselves, or in glomeruli, interstitial tissues, or blood vessels.

## Common Findings in Renal Biopsy Specimens in Acute Renal Failure

The pathologist should examine the specimen to see if there is evidence of one of the common conditions expected in renal biopsy specimens in acute renal failure.

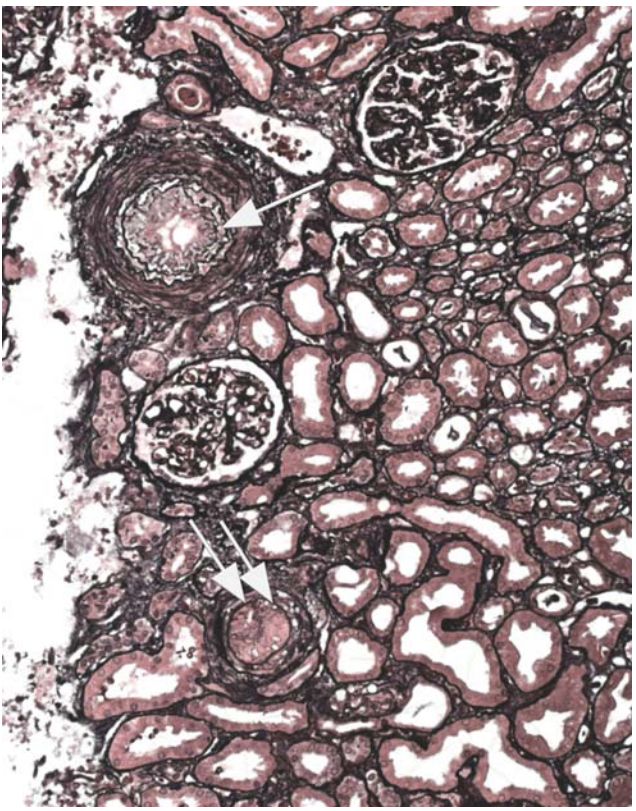

**Fig. 7.8** Cortex in a renal biopsy specimen from a woman of 44 with acute renal failure. There is a small vessel vasculopathy, also called thrombotic microangiopathy, with loose concentric intimal thickening in a small artery (single arrow), and thrombus in another (double arrow). Clinically, the diagnosis was a mixed connective tissue disorder, with features of scleroderma and systemic lupus erythematosus

These conditions are not the same as those that are common in all people with acute renal failure, because most do not have a biopsy.

In **adults**, the commonest finding, generally in more than a quarter of specimens, is vasculitis. Other findings, in descending order of commonness, are pure acute tubular damage not explained by anything in the specimen, acute interstitial nephritis, small vessel vasculopathy, also called thrombotic microangiopathy, myeloma kidney, and acute postinfective glomerulonephritis. Other disorders together generally account for less than a tenth of specimens.

In **children**, over half the specimens have one of three conditions, Henoch–Schönlein nephritis, hemolytic uremic syndrome, and acute interstitial nephritis. Other likely findings are lupus nephritis, pure acute tubular damage not explained by anything in the specimen, and acute postinfective glomerulonephritis, with a

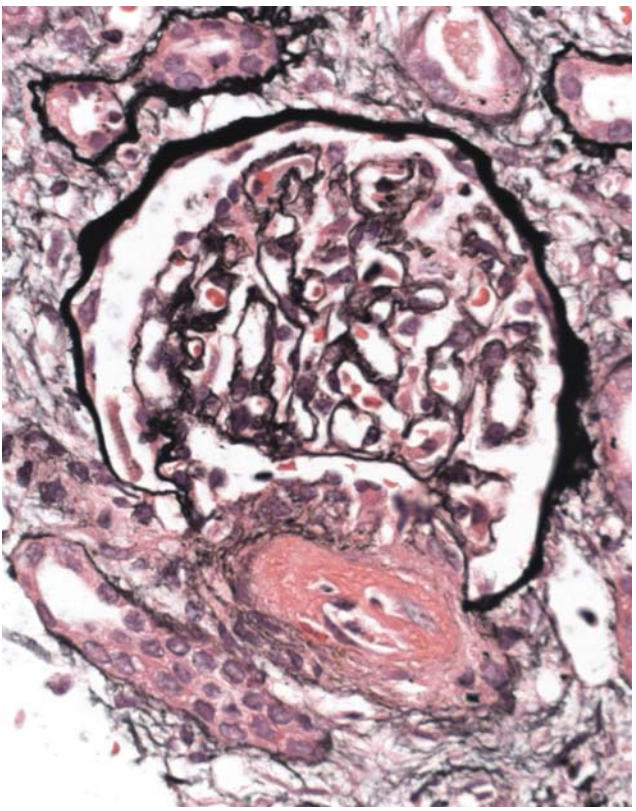

**Fig. 7.9** Cortex in a renal biopsy specimen from a woman of 29 with acute renal failure, 2 years after a liver transplant. An arteriole has fibrinoid necrosis of its wall. The explanation was hemolytic uremic syndrome, possibly due to cyclosporine treatment

range of disorders in the few remaining specimens. Myeloma kidney is not seen in children. Vasculitic conditions other than Henoch–Schönlein nephritis occur, but are rare.

Exceptionally, as well as frank necrosis of the cortex, a few other uncommon disorders can be detected on low power microscopy used by the pathologist to assess the relative amounts of acute and chronic tubular damage. These include infiltration by a lymphoma or other neoplasm (Fig. 7.11).

## *Is There Evidence of Renal Vasculitis?*

Because the most likely finding in adults who are biopsied in acute renal failure is vasculitis, this should always be considered as a possibility in specimens taken for this indication.

Vasculitis is often a multisystem illness, and there may be clinical clues such as fever, arthralgia, myalgia, weight loss, upper respiratory tract symptoms, neurologic

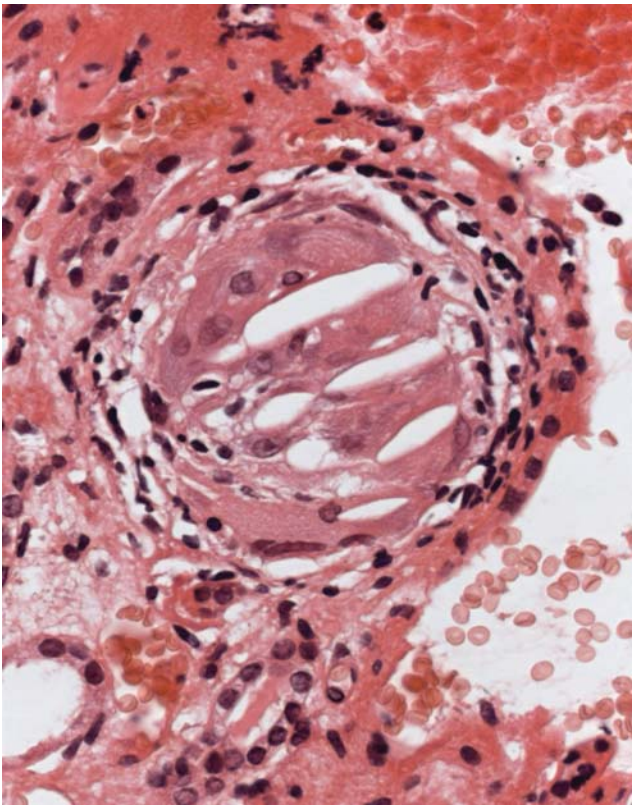

**Fig. 7.10** A small cortical artery in a renal biopsy specimen from a man of 72, showing blockage of the artery by material including cells and clefts, from which cholesterol has been dissolved during processing of the material. These are the appearances of an atherosclerotic or thrombo-atherosclerotic embolus

signs, and a rash. Hematuria and proteinuria are common, but not the nephrotic syndrome.

Vasculitis in the kidney almost always takes the form of a glomerular abnormality that can be called **vasculitic glomerulonephritis**. Other names for this are used, but are less satisfactory. They include focal segmental thrombosing and necrotising glomerulonephritis, glomerulonephritis associated with antineutrophil cytoplasmic antibodies or ANCA-associated glomerulonephritis, glomerulonephritis with crescents or crescentic glomerulonephritis, pauci immune glomerulonephritis, pauci immune crescentic glomerulonephritis, and rapidly progressive glomerulonephritis.

## Diagnosis of Vasculitic Glomerulonephritis

Vasculitic glomerulonephritis can range in severity from a small segmental abnormality in one glomerulus to complete destruction of all glomeruli, with all stages in between. This means it can be focal and segmental, as some names for this disorder

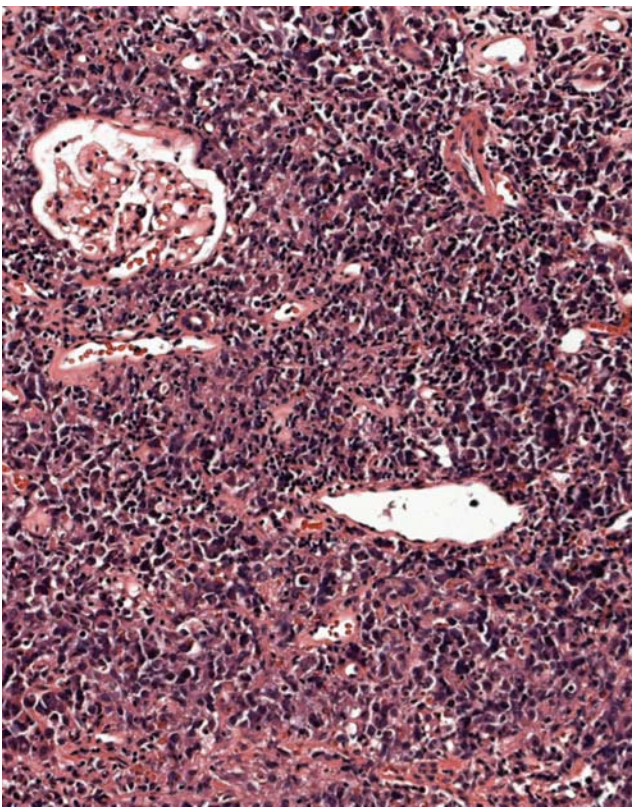

**Fig. 7.11** Cortex in a renal biopsy specimen from a woman of 77 with insulin resistant or type two diabetes mellitus, and acute on chronic renal failure. There is a dense infiltrate of lymphoid cells. This is a non-Hodgkin's lymphoma

describe it, but it can also be focal and global, or diffuse and segmental, or diffuse and global.

This is one of the conditions of the kidney in which **one abnormal glomerulus is enough to give the diagnosis** (Fig. 7.12).

Vasculitic glomerulonephritis is not a static condition, but changes with time.

The earliest stage recognisable by a pathologist is segmental thrombosis in a glomerulus, with disruption of capillary loops, seen on sections stained with periodic acid-methenamine silver (Fig. 7.13). The next stage is accumulation of fibrin and cells in Bowman's space over the affected capillary loops (Figs 7.14 and 7.15). The cells are a mixture of macrophages and epithelial cells, sometimes with neutrophils and giant cells. Sometimes Bowman's capsule is disrupted. Then there is gradual deposition of fibrous tissue and disappearance of cells (Fig. 7.16). The final stage is a scar which is sharply defined, includes part of the glomerular tuft and part of the original Bowman's space, and is adherent to Bowman's capsule (Fig. 7.17).

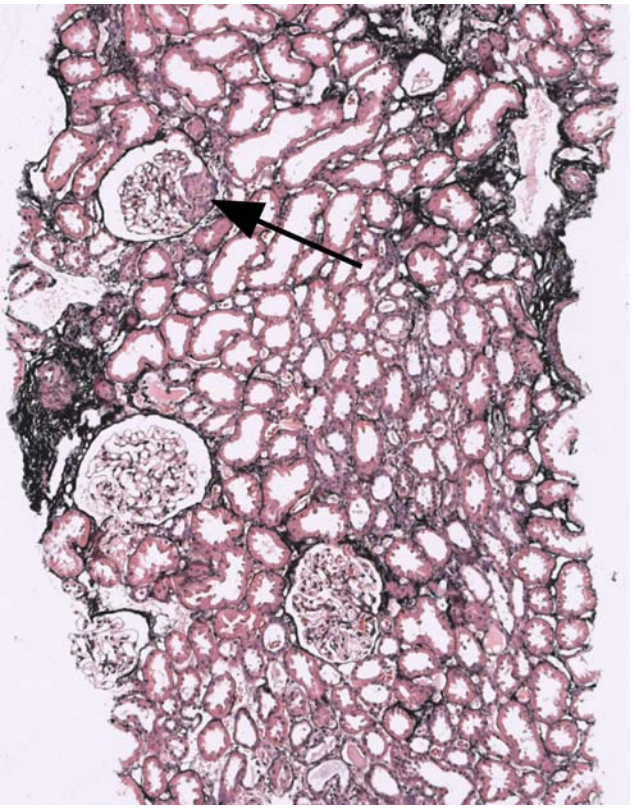

**Fig. 7.12** Cortex in a renal biopsy specimen from a man of 47 with a multisystem illness, a weakly positive antineutrophil cytoplasmic antibody, hematuria, proteinuria, and normal renal function. One glomerulus has a small, acute, segmental vasculitic lesion (arrowed). This is enough to give the diagnosis of renal vasculitis

The glomerular abnormality in vasculitic glomerulonephritis can be of any size from one capillary loop to the whole of the glomerulus (Fig. 7.16). Segmental abnormalities are usually well outlined, with edges that are easily defined (Figs 7.12–7.15, and 7.17). This feature is a help in identification of vasculitic changes, especially late ones, because other segmental abnormalities have indistinct outlines, and do not cross Bowman's space, although the tuft may adhere to Bowman's capsule.

The word crescent is often used in vasculitic disorders, as in the term glomerulonephritis with crescents, but this has difficulties. Generally, this is taken to mean a group of cells in Bowman's space. A problem for the pathologist is to know how many cells are needed before a group can be called a crescent. Some definitions do not say, and some specify a size of the group, such as half of Bowman's space. The World Health Organization's definition is two layers or more of cells that partially or completely fill Bowman's space. On any definition, crescents

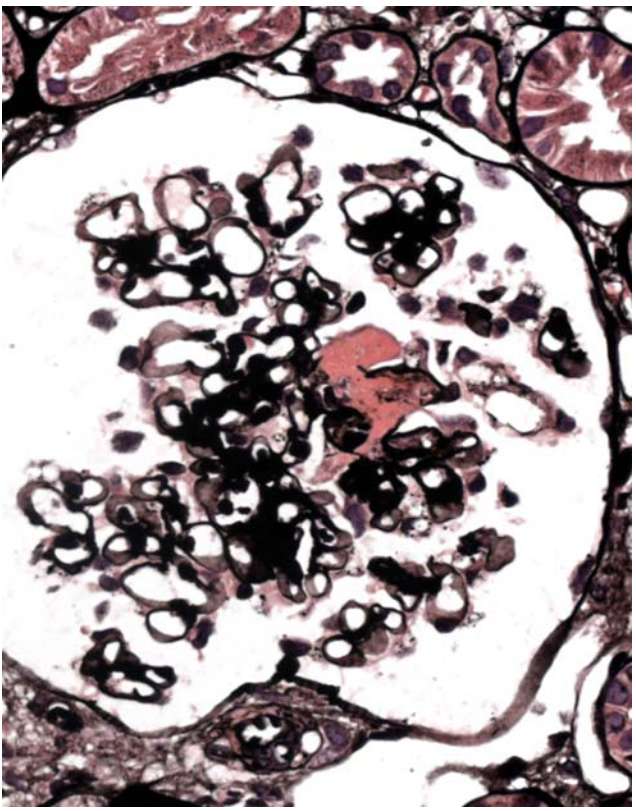

**Fig. 7.13** Glomerulus in a renal biopsy specimen from a woman of 73 with a purpuric rash, hematuria, proteinuria, and acute renal failure. There is a small segmental area of thrombosis and disruption of capillary loops, shown by periodic acid-methenamine silver staining. This is the earliest recognisable stage of vasculitic glomerulonephritis

are not a constant feature of vasculitic glomerulonephritis. Crescents can also be found in acute postinfective glomerulonephritis, subendothelial membranoproliferative glomerulonephritis, and other conditions. There is a similar problem with precision of terminology about crescentic glomerulonephritis, which means different things to different people. Some pathologists apply this when at least half of all glomeruli contain what can be considered to be crescents.

Vasculitic abnormalities not only change with time. Different stages can be present at the same time in a biopsy specimen (Figs 7.15–7.17), and even in the same glomerulus (Fig. 7.18). In some people, renal vasculitis seems to be due to a single event, and in others to a prolonged process. There may be relapses at various intervals after the original acute changes have healed.

The pathologist can often see glomerular changes of vasculitis at low power on microscopy. The glomerular count should include the total number and the number of globally sclerosed glomeruli, as usual, and the number of glomeruli with

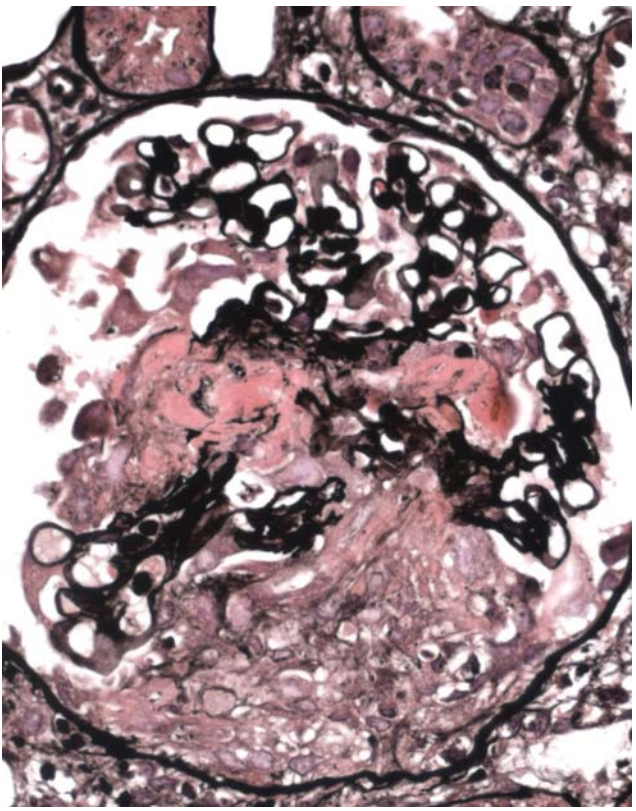

**Fig. 7.14** Another glomerulus in the renal biopsy specimen from the woman of 73 illustrated in **Fig. 7.13**. This shows a larger lesion, with thrombosis, disruption of capillary loops, and cells in Bowman's space

vasculitic abnormalities, which needs high power microscopy. These abnormalities can be divided into stages, such as **acute** or **active** if thrombosis or tuft disruption or cells in Bowman's space are seen, **healing** if fibres appear amongst the cells, and **healed** if there are fibrosed areas in glomeruli.

The glomerular tuft away from segmental changes is normal in typical vasculitic glomerulonephritis, with no deposition of immunoproteins away from vasculitic abnormalities on immunohistologic study. This explains the term pauci immune glomerulonephritis, in which the first syllable in pauci, which comes from the Latin word for few, is pronounced either as in lawn or as in harm.

Glomeruli are not the only abnormal structures in renal vasculitis.

1. **Tubules**: In acute renal failure, there is acute tubular damage. If the disease has been present for a few weeks or more, there may be areas of tubular atrophy, more extensive than expected for the age of the person biopsied. Occasionally, a

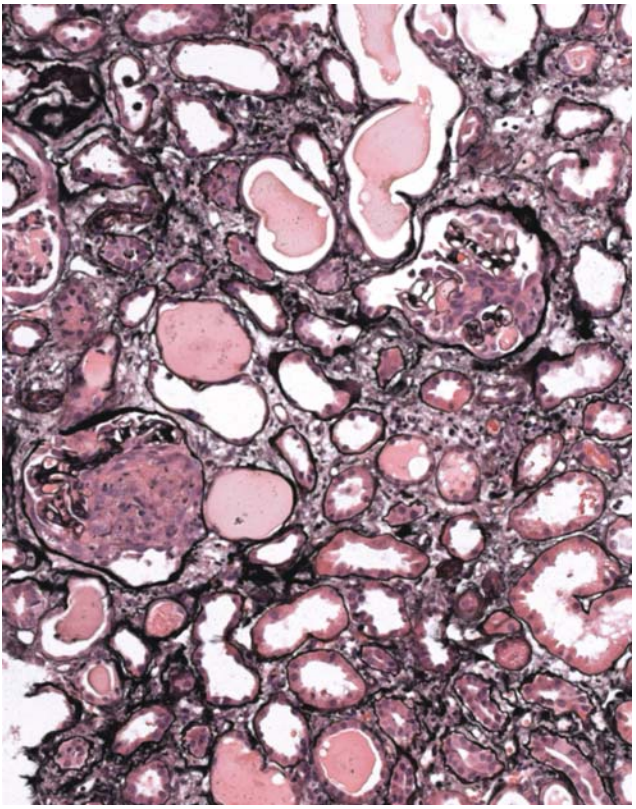

**Fig. 7.15** Cortex in a renal biopsy specimen from a woman of 67 with nose bleeds, mouth ulcers, infiltrates in the lungs on radiography, arthralgia, a strongly positive antineutrophil cytoplasmic antibody of cANCA type, hematuria, proteinuria, and acute renal failure. Two glomeruli have segmental areas of tuft disruption, with cells in Bowman's space. This is an active stage of vasculitic glomerulonephritis. The clinical diagnosis was Wegener's granulomatosis. A common pronunciation of the eponym is *vayg-a-ner*. At a meeting in 1936, reported in 1937, Wegener described autopsy findings in three people with what he thought was an infective condition. They had granulomatous inflammation in the nose, generalised arteritis, and glomerulonephritis (Wegener F. On generalised septic vessel diseases. Translated in *Thorax* 1987; **42:** 918–919). Friedrich Wegener (1907–1990) qualified in medicine in Germany, and became a pathologist in Kiel, and later elsewhere. His first autopsy was said to be on one of the people he described in 1936. The name Wegener's granulomatosis seems to have been used first in 1947

renal biopsy is taken in a suspected vasculitic condition in which renal function is normal. In these circumstances, the tubules may be normal (Fig. 7.12).

Most specimens with active vasculitic glomerulonephritis have **blood in tubules**, with a distinctive appearance. Blood in tubules may be seen in any condition, but has a different appearance. This is due to the trauma of the biopsy procedure, and the blood appears fresh, with identifiable and separate red cells, usually in tubules at the edges of the specimen (Fig. 7.19). Tubules in vasculitic glomerulonephritis

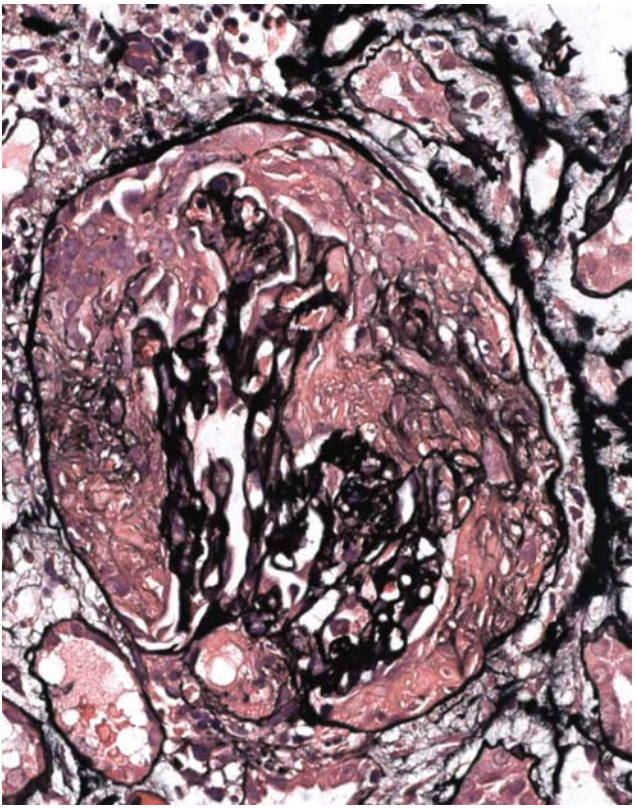

**Fig. 7.16** Glomerulus in the renal biopsy specimen from the woman of 67 that is illustrated in **Fig. 7.15**. Bowman's space is filled with cells. Fibres are beginning to appear among the cells, shown by periodic acid-methenamine silver staining. This is early healing of vasculitic glomerulonephritis

often contain blood that seems solid or discolored, with disruption of cells and release of hemoglobin, which is called laking. Tubules in the centre of the specimen are just as likely to be affected as those at the edges (Fig. 7.20). If there is this type of blood on initial sections, but glomeruli appear normal, the pathologist should request extra sections, because there is a chance that at least one glomerulus has vasculitic changes.

2. **Interstitial tissues**: Interstitial tissues often have an infiltrate of mixed inflammatory cells in vasculitis, sometimes with striking numbers of eosinophils. This is part of the vasculitic disorder, and should not be given an additional diagnosis of acute interstitial nephritis. There may also be interstitial hemorrhage (Fig. 7.21).
3. **Blood vessels**: Arteritis or arteriolitis may be seen in a renal biopsy specimen, almost always associated with vasculitic glomerulonephritis. The affected vessels may not even be in the cortex or medulla (Figs 4.6 and 7.22). These changes are often patchy. The muscular layer of the vessel may be replaced

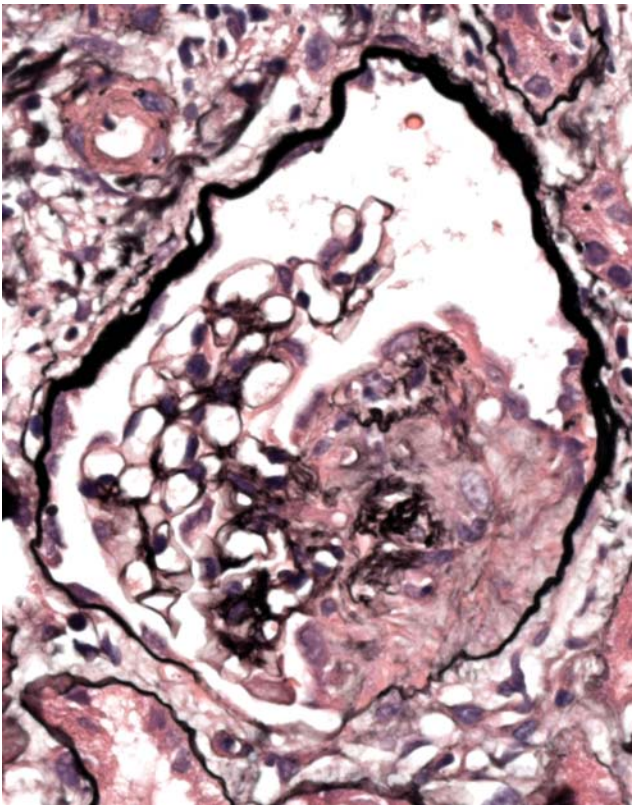

**Fig. 7.17** Glomerulus in the renal biopsy specimen from the woman of 67 that is illustrated in **Figs** 7.15 and **7.16**. On a section stained by periodic acid-methenamine silver, there is a sharply defined, fibrous, segmental lesion, which includes a disrupted area in the tuft and adjacent Bowman's space, and is adherent to Bowman's capsule. This is healed vasculitic glomerulonephritis

by eosinophilic material, a change called **fibrinoid necrosis**. There may be a thrombus in the lumen, with an infiltrate of various types of inflammatory cells in the wall. This is sometimes called leukocytoclastic vasculitis, if disrupted neutrophils are a prominent feature.

The combined effect of these changes in glomeruli, tubules, interstitial tissues, and vessels makes a specimen with active vasculitis other than the mildest look strikingly abnormal at low power on microscopy (Fig. 7.23).

## Clinical Conditions with Renal Vasculitis

Classification of vasculitic disorders is artificial, because there are overlaps between them. Nevertheless, many people with vasculitis can be given a satisfactory clinical diagnosis, even though the findings in a renal biopsy specimen may be the same in several different disorders.

**Fig. 7.18** Glomerulus in a renal biopsy specimen from a man of 42 with asthma, neuropathy, arthropathy, hematuria, proteinuria, and normal renal function. On a section stained by periodic acid-methenamine silver, part of the glomerulus has a sharply defined, fibrous segmental lesion, which includes an old disrupted area in the tuft and adjacent Bowman's space with adhesion to Bowman's capsule. The rest of the glomerulus has active disruption of capillary loops with cells on the surface. This is active and healed vasculitic glomerulonephritis in the same glomerulus. The clinical diagnosis was Churg–Strauss syndrome, in which the names are commonly pronounced *tchurg* and *strowss*. This was described by Jacob Churg, known as Jack (born 1910), and Lotte Strauss (1913–1985), at the Mount Sinai Hospital in New York, where both were pathologists (Churg J, Strauss L. Allergic granulomatosis, allergic angiitis and periarteritis nodosa. *American Journal of Pathology* 1951; **27:** 277–294). The term Churg–Strauss syndrome was in use by 1961

Renal vasculitis, with otherwise normal glomeruli and no significant deposition of immunoproteins, can be seen in several clinical conditions. **The pathologist is not able to differentiate these on renal biopsy appearances**. Common vasculitic disorders that affect the kidney are Wegener's granulomatosis and microscopic polyangiitis, also called microscopic polyarteritis. Others are Churg–Strauss syndrome and the vasculitis associated with infective endocarditis. On current definitions, polyarteritis nodosa cannot be diagnosed if there is vasculitic

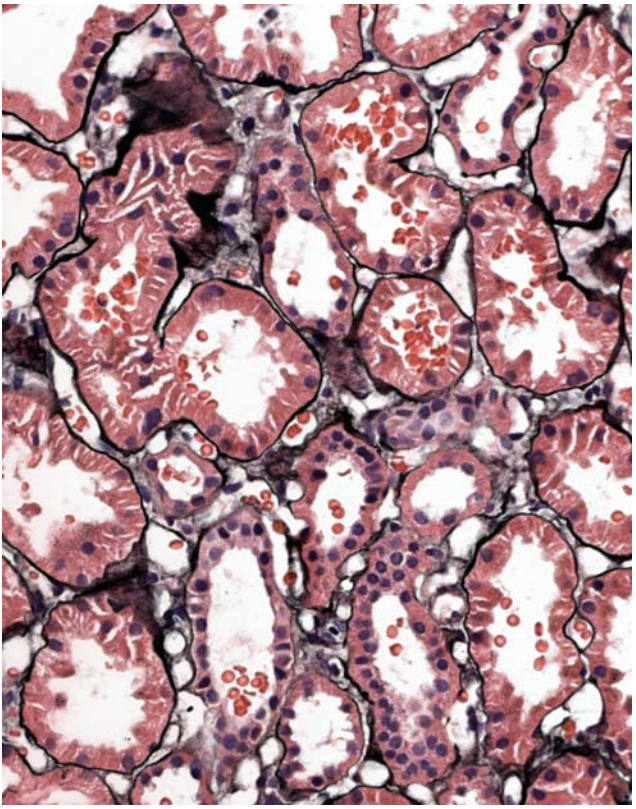

**Fig. 7.19** Cortex in a renal biopsy specimen from a man of 37 with proteinuria, but no hematuria. There are red blood cells in the lumen of several tubules, which is a consequence of trauma from the biopsy procedure. This appearance is unlike that of bleeding into tubules before the biopsy, illustrated in **Fig. 7.20**

glomerulonephritis. The antithyroid drug, propylthiouracil, and the antihypertensive drug, hydralazine, are rare causes of renal vasculitis.

Despite the name of the condition, granulomas are not seen in the kidney in **Wegener's granulomatosis** (Figs 7.15–7.17). The strict pathologic definition of a granuloma is a localised microscopic collection of macrophages, with or without other cells, as seen in tuberculosis or sarcoid. What Wegener called granulomas were glomeruli with global destruction by vasculitis.

Wegener's granulomatosis is a condition in which there is active chronic inflammation, sometimes with true granulomas and arteritis, affecting the nose, nasal sinuses, middle ear, and other parts of the respiratory tract, sometimes with renal vasculitis, which may include arteritis of vessels up to the size of the main renal artery. There are usually antibodies in the serum against the cytoplasm of neutrophils. These antibodies are detected throughout the cytoplasm in some tests, and are called cytoplasmic antineutrophil cytoplasmic antibodies or cANCA. The

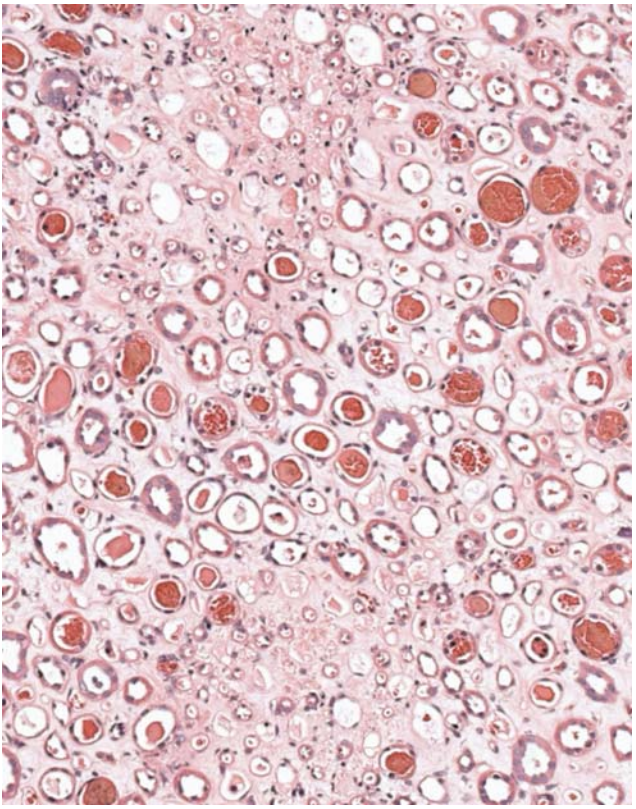

**Fig. 7.20** Medulla in a renal biopsy specimen from a man of 52 with a multisystem illness, a weakly positive antineutrophil cytoplasmic antibody, hematuria, proteinuria, and acute renal failure. Many tubules contain blood, which is more solid than in the tubules illustrated in **Fig. 7.19**. This finding suggests that there is likely to be vasculitic glomerulonephritis. Cortex in this man's specimen is illustrated in **Figs 7.21** and **7.23**

antigen recognised by most cANCA is proteinase three. The pathologist should not be influenced by reported presence or absence of these antibodies in determination of whether a biopsy specimen shows vasculitis, because cANCA are not specific for Wegener's granulomatosis, and the condition may occur without them. This illustrates a problem with the term ANCA-associated glomerulonephritis.

**Microscopic polyangiitis** is the condition in which there is vasculitis of small vessels in at least one organ, usually the kidney, sometimes with vasculitis of arteries including those the size of the main renal artery, but without the features of Wegener's granulomatosis in the respiratory tract. If the disorder is only in the kidney, this may be called renal-limited microscopic polyangiitis, or renal-limited vasculitis. There are often antibodies in serum against the cytoplasm of neutrophils, with a characteristic perinuclear distribution in some tests, called perinuclear antineutrophil cytoplasmic antibodies or pANCA. The antigen recognised by

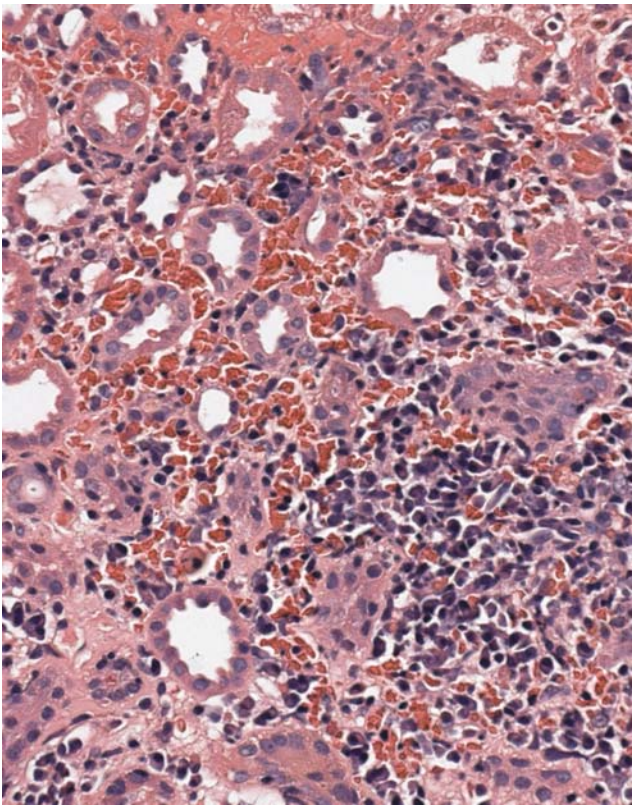

**Fig. 7.21** Cortex in the renal biopsy specimen from the man of 52, the medulla in which is illustrated in **Fig.** 7.20. There is a heavy, patchy infiltrate of inflammatory cells in interstitial tissues, which also contain hemorrhage. These are features associated with vasculitic glomerulonephritis, which is illustrated in this man's specimen in **Fig.** 7.23

pANCA is myeloperoxidase. These antibodies are not specific for microscopic polyangiitis.

Although infiltrates of eosinophils in various organs may be seen in **Churg–Strauss syndrome**, an acute eosinophilic interstitial infiltrate in the kidney can occur in all vasculitic disorders, and is not by itself evidence of Churg–Strauss syndrome. Asthma and eosinophilia in the blood are clinical features of this condition, and often there are antineutrophil cytoplasmic antibodies, either cANCA or pANCA (Fig. 7.18).

**Polyarteritis nodosa** is now uncommon. Arteries are affected by vasculitis in this condition. If there is vasculitic glomerulonephritis, the clinical diagnosis may have to be amended to one of the other vasculitic disorders. Hepatitis B virus infection is occasionally found in polyarteritis nodosa. There may be giant cell arteritis in any of the vasculitic disorders, but this is uncommon (Fig. 7.24).

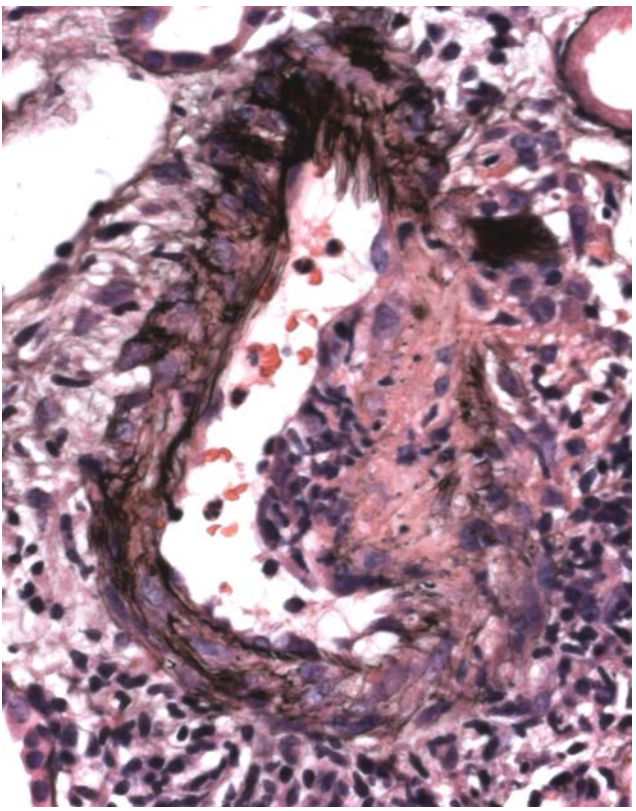

**Fig. 7.22** Cortex in a renal biopsy specimen from a woman of 58 with nasal ulceration, mononeuritis multiplex, a positive antineutrophil cytoplasmic antibody of cANCA type, and hematuria. An interlobular artery has fibrinoid necrosis of part of its wall, and an infiltrate of inflammatory cells

**Infective endocarditis** can affect the kidney in several ways. One of the commonest is by production of vasculitis. The vasculitic glomerulonephritis in infective endocarditis used to be called focal embolic nephritis and embolic nonsuppurative focal nephritis. Infective endocarditis can also affect the kidney by causing acute postinfective glomerulonephritis, subendothelial membranoproliferative glomerulonephritis, infarcts due to embolism, renal cortical necrosis due to severe hypotension, and pure acute tubular damage due to hypotension or sepsis. Antibiotics used to treat infective endocarditis may cause acute tubular damage or acute interstitial nephritis. Combinations of any of these conditions may occur. Usually, the pathologist is told on the request form that there is infective endocarditis, and this helps interpretation of the specimen.

Vasculitic glomerulonephritis is probably a consequence of glomerular endothelial damage. This follows interaction with neutrophils activated by antineutrophil cytoplasmic antibodies bound to proteinase three or myeloperoxidase, expressed on the cell membrane of neutrophils primed by inflammatory mediators.

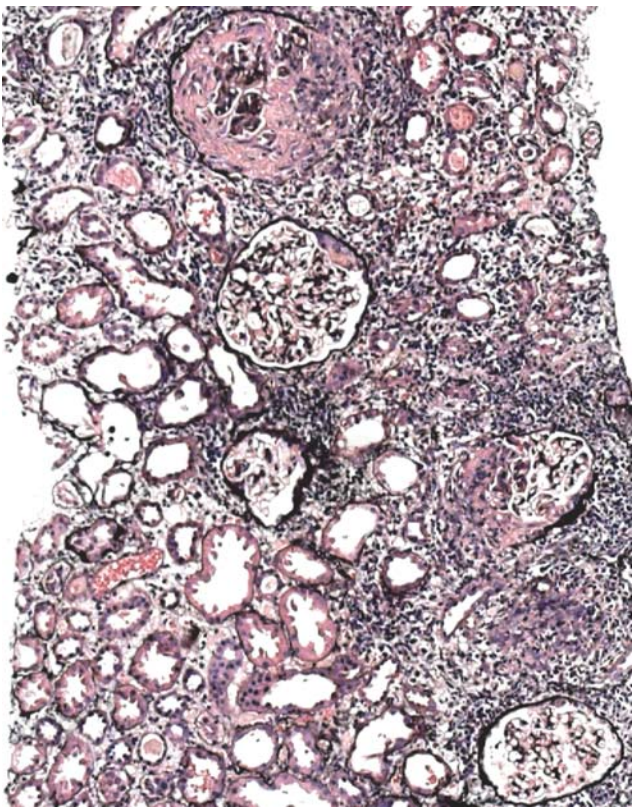

**Fig. 7.23** Cortex in the renal biopsy specimen from the man of 52, the medulla in which is illustrated in **Fig. 7.20**, and cortex in **Fig. 7.21**. On microscopy at low magnification, there are several abnormalities, which include acute tubular damage, blood in tubules, an interstitial inflammatory infiltrate, acute segmental glomerular lesions, and an acute global glomerular lesion. Some glomeruli have disruption of Bowman's capsule. These are all features of renal vasculitis

Vasculitic glomerulonephritis may respond well to aggressive treatment with immunosuppression, provided that most of the renal damage is acute rather than chronic. The response also depends upon the severity of vasculitis outside the kidney, and the general state of the person affected.

## *If There is Renal Vasculitis, Are There Clues to Recognisable Conditions?*

Four other disorders can give vasculitic changes in the kidney, with features that allow the pathologist to recognise them, mainly because they have deposits of immunoproteins in glomeruli. The diagnosis of vasculitic glomerulonephritis or pauci immune vasculitic glomerulonephritis in a report implies that there is not

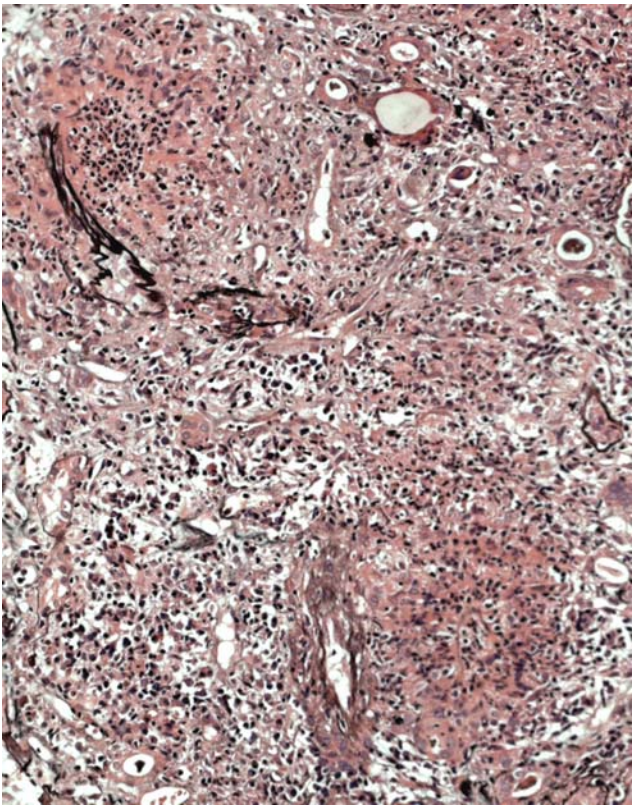

**Fig. 7.24** Cortex in a renal biopsy specimen from a man of 69 with a long history of dermatomyositis and pulmonary fibrosis, and recent development of acute renal failure, hematuria, and proteinuria. There is a severe acute granulomatous arteritis. This responded to immunosuppressive treatment

one of these four conditions, which should be named in the diagnosis. These are Henoch–Schönlein nephritis, lupus nephritis, Goodpasture's disease, and cryoglobulinemic glomerulonephritis.

## Conditions That Can be Differentiated from Pauci Immune Vasculitic Glomerulonephritis: 1 Henoch–Schönlein Nephritis

This is a condition in which vasculitic changes occur in glomeruli, but the glomerular tuft away from these changes appears abnormal, with mesangial expansion, sometimes even with a few doubled basement membranes next to the mesangium. On immunohistologic study, there is mesangial deposition of IgA, which indicates Henoch–Schönlein nephritis. This can also be called vasculitic IgA nephropathy, or similar terms (Figs 7.25–7.27). The condition can be regarded as part of IgA

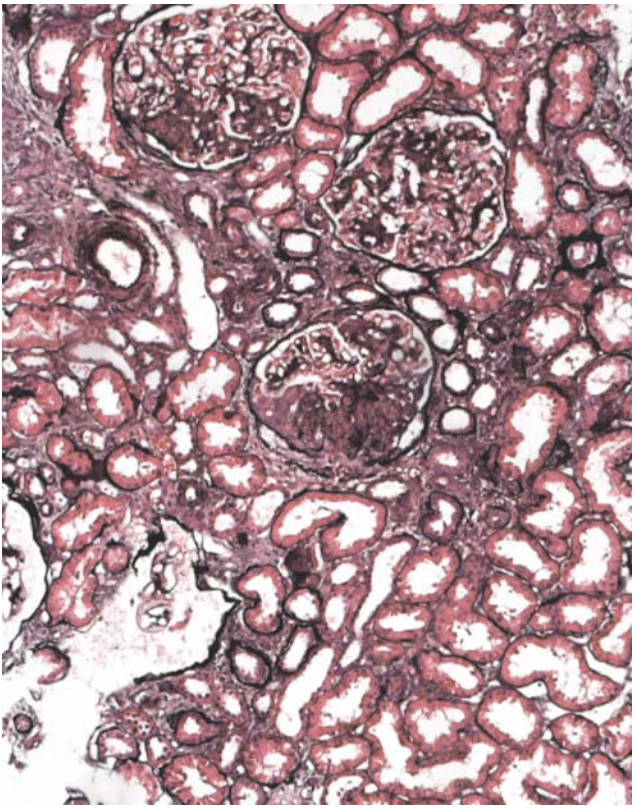

**Fig. 7.25** Cortex in a renal biopsy specimen from a woman of 33 with mild acute renal impairment, hematuria, proteinuria, and a history of a rash and arthralgia 2 years before the biopsy. Tubules have a little atrophy and a little acute damage. There are segmental lesions of vasculitic type in glomeruli. Immunohistologic study showed mesangial deposition of IgA, and gave the diagnosis of Henoch–Schönlein nephritis. Glomerular changes are illustrated at higher magnification in **Fig. 7.26**. The names are often pronounced *hee-nock* and *shern-line*. What is now usually called Henoch–Schönlein purpura was first given the name Schönlein–Henoch syndrome in 1948. Sometimes, in English, Schönlein is spelled Schoenlein to avoid use of the umlaut symbol. He preceded Henoch, but now follows him in the name of this disease. Eduard Heinrich Henoch (1820–1910) was born in Berlin, and was a pupil of Schönlein, as was Virchow (**Fig. 4.5**). In 1868, Henoch, who was what would now be called a pediatrician, described children with attacks of purpura, joint pains, intestinal colic, and intestinal hemorrhage. He later added the association with renal disease. Johann Lukas Schönlein (1793–1864) was Professor of Pathology and Therapy in Würzburg, and then Professor of Medicine in Zurich and Berlin. His accounts of an illness with joint pains and a rash were given in various editions of a textbook written by students based on his lectures. In the 1834 edition, Schönlein mentioned oliguria as a finding in the condition. The first report of the finding of IgA in glomeruli in Henoch–Schönlein nephritis seems to have been in 1968, although the significance of this was overlooked by the authors.There is a strong chance that the composer W A Mozart (1756–1791) had Henoch–Schönlein purpura as a boy, and died of renal failure when he was 35

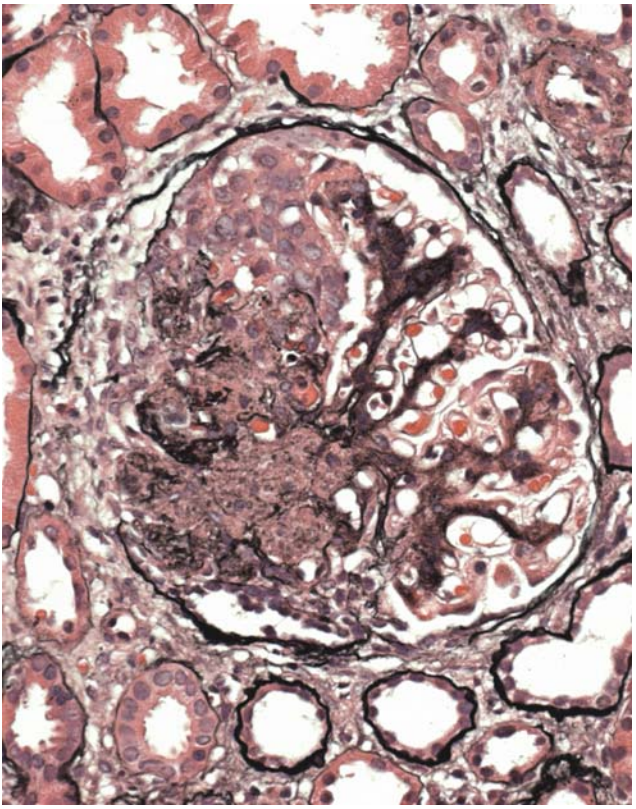

**Fig. 7.26** Glomerulus in the renal biopsy specimen from the woman of 33 with Henoch–Schönlein nephritis, the cortex in which is illustrated in **Fig.** 7.25. There is an acute segmental lesion with tuft disruption and cells in Bowman's space, but this is not so sharply defined as the lesions in other types of vasculitis, such as in **Figs** 7.12, **7.15**, and **7.17**. The rest of the tuft is not normal, and has mesangial increase, with IgA deposition on immunohistologic study

nephropathy in its widest sense, rather than as a separate condition. In Henoch–Schönlein nephritis, the intensity of immunostaining for IgA may appear less than in most examples of IgA nephropathy without vasculitic lesions, possibly because the deposits are overshadowed by the acute glomerular changes.

Often, Henoch–Schönlein nephritis appears to have characteristic vasculitic changes in glomeruli, but sometimes these seem atypically vasculitic or not fully characteristic, particularly in that they are not so well outlined as usual vasculitic changes (Fig. 7.26). On the initial sections stained by hematoxylin and eosin, the combination of glomerular changes that are vasculitic, either definitely or nearly, and abnormal mesangium suggests a strong likelihood of Henoch–Schönlein nephritis. The diagnosis is made certain by the finding of IgA deposition.

Generally, Henoch–Schönlein nephritis has vasculitic lesions in only a few glomeruli, and these are often of different ages, some active and some healed. If

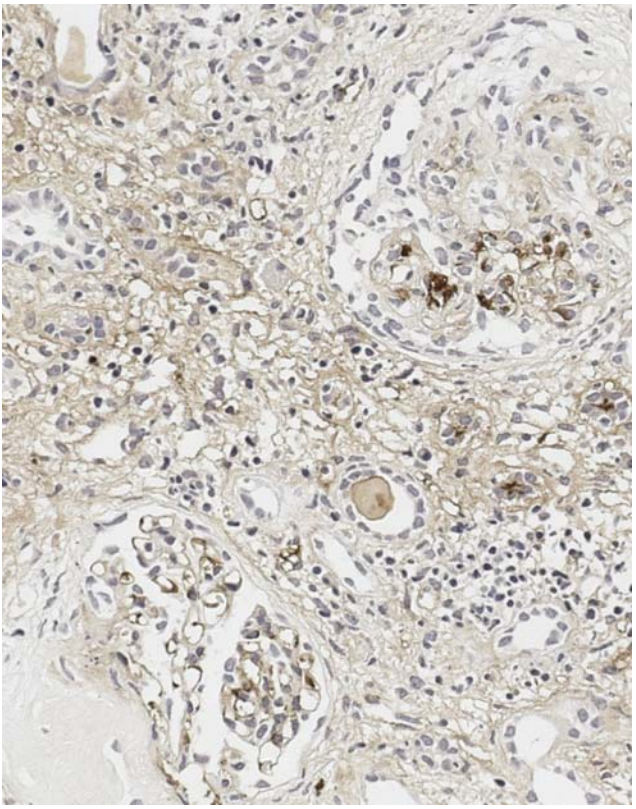

**Fig. 7.27** Cortex in a renal biopsy specimen stained by an immunoperoxidase method to detect IgA from a woman of 34 with acute renal failure, hematuria, and proteinuria. A glomerulus resembles the one in **Fig. 7.26**, and shows IgA deposition in mesangium away from the vasculitic lesion, with light mesangial deposition of IgA in the other glomerulus. This indicates Henoch–Schönlein nephritis

there is a severe vasculitic glomerulonephritis with lesions all at the same stage, the finding of IgA in glomeruli is more likely to indicate the coincidence of IgA nephropathy and vasculitic glomerulonephritis, in a condition such as Wegener's granulomatosis, rather than Henoch–Schönlein nephritis (Fig. 7.28). This is an example of the rule that **there may be more than one condition in a renal biopsy specimen**. Clinical and serologic findings, such as pulmonary vasculitis and a high titre of cANCA, help to differentiate coincidental IgA nephropathy and Wegener's granulomatosis, for example, from Henoch–Schönlein nephritis.

Henoch–Schönlein nephritis is not the same thing as **Henoch–Schönlein purpura**, also called anaphylactoid purpura, which is a systemic disorder with various combinations of arthralgia, rash, abdominal pain, melena, hematuria, proteinuria, and acute renal failure. In children, in whom the disorder is recognised most often, renal biopsy is not usually done, at least at the height of the clinical illness, because the disorder generally resolves. If there is a biopsy, the specimen usually shows

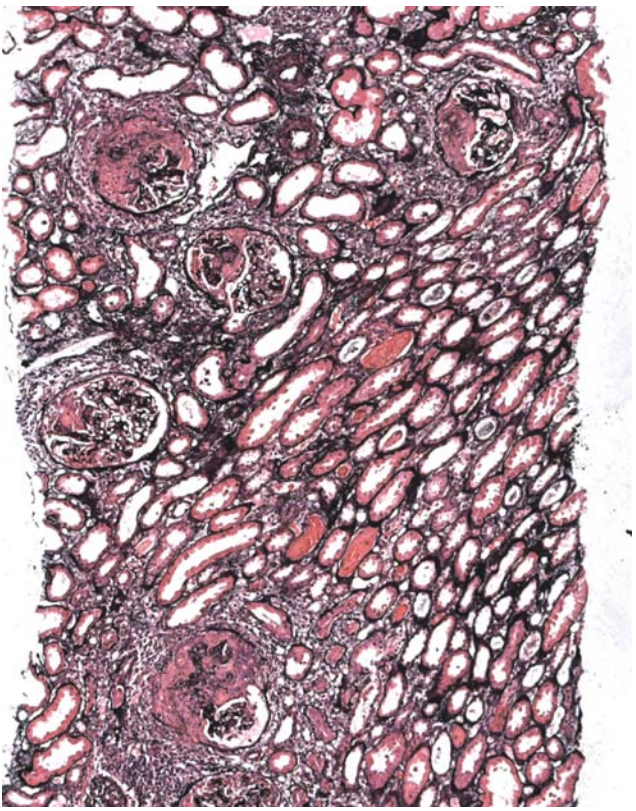

**Fig. 7.28** Cortex in a renal biopsy specimen from a man of 52 with a multisystem illness, which included upper respiratory tract problems, a strongly positive antineutrophil cytoplasmic antibody of cANCA type, acute renal failure, hematuria, and proteinuria. There are acute vasculitic lesions in glomeruli. On immunohistologic study, there is mesangial deposition of IgA. Even so, the diagnosis was considered to be vasculitic glomerulonephritis, consistent with Wegener's granulomatosis, with coincidental IgA nephropathy, rather than Henoch–Schönlein nephritis. This was because the vasculitic lesions were more widespread and more sharply defined than usually seen in Henoch–Schönlein nephritis, the overall effect on the kidney was more severe, and the lesions were all at the same stage. Clinical and serologic findings supported this interpretation

Henoch–Schönlein nephritis, but may show IgA nephropathy without vasculitic changes.

A diagnosis of Henoch–Schönlein purpura is less common in adults, and if there is a biopsy, about half have Henoch–Schönlein nephritis, and the other half have IgA nephropathy without vasculitic changes. Henoch–Schönlein nephritis is just as often seen in adults who do not have obvious clinical features of Henoch–Schönlein purpura outside the kidney, as in those with a vasculitic rash or other systemic features at the time of biopsy (Figs 7.25–7.27). About one in ten of people with IgA nephropathy, in its widest sense, in a renal biopsy specimen, but no systemic features of Henoch–Schönlein purpura, have Henoch–Schönlein nephritis.

## Conditions That Can be Differentiated from Pauci Immune Vasculitic Glomerulonephritis: 2 Lupus Nephritis

The next condition that can have vasculitic changes is **lupus nephritis**. Almost always, the clinical diagnosis of systemic lupus erythematosus has been made before the biopsy, usually in a young woman. There are often combinations of changes in glomeruli in lupus nephritis, and the finding of such combinations is a clue to the diagnosis (Figs 6.54–6.57). Deposition of all immunoproteins on immunohistologic study confirms the diagnosis (Fig. 6.62).

## Conditions That Can be Differentiated from Pauci Immune Vasculitic Glomerulonephritis: 3 Goodpasture's Disease

Changes of severe acute vasculitic glomerulonephritis in initial sections of a biopsy specimen, with diffuse global abnormalities all at the same stage, should make the pathologist suggest the possibility of **Goodpasture's disease** (Fig. 7.29). This is the disorder associated with antibodies to glomerular basement membranes. The diagnosis is given by the finding of linear deposition of IgG and complement in glomerular basement membranes on immunohistologic study (Fig. 7.30).

Goodpasture's disease can be a difficult diagnosis to confirm by immunohistology when virtually all the glomerular basement membranes are destroyed. The disease is rare, can occur at any age, and presents with acute renal failure, with hematuria and proteinuria. There may be hemoptysis, which indicates pulmonary hemorrhage. Not every example of renal vasculitis that either has diffuse and global glomerulonephritis, or is associated with hemoptysis, is due to Goodpasture's disease. The terms Goodpasture's syndrome, or pulmonary/renal vasculitic syndrome, can be used if there is renal vasculitis with pulmonary hemorrhage, but no antibodies against glomerular basement membranes.

Occasionally, both antibodies to glomerular basement membranes and antibodies to neutrophil cytoplasmic antigens, or ANCA, are found. Arteriolitis and arteritis are more likely in the kidney and other organs if both antibodies occur, than if there are only antibodies to basement membranes.

Goodpasture's disease has strong associations with some DR alleles of HLA, which is the abbreviation for human leukocyte antigens, or human lymphocyte antigens, or histocompatibility linked antigens. These alleles determine the ability of antigen presenting cells to bind peptides derived from either the noncollagenous domain of the alpha three chain of collagen type four, or similar microbial antigens. This leads to the generation of antibodies to collagen type four, which is found in glomerular basement membranes.

Goodpasture's disease is more difficult to treat than other types of vasculitis, and is more likely to progress rapidly to irreversible renal failure.

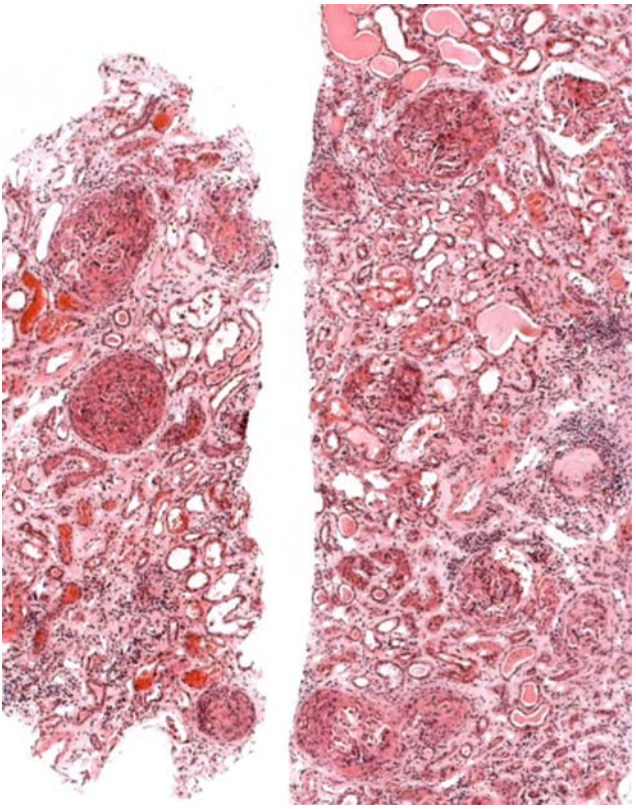

**Fig. 7.29** Cortex in a renal biopsy specimen from a man of 69 with acute renal failure, hematuria, proteinuria, and no other systemic features. Nearly every glomerulus has global vasculitic changes at the same early stage. Immunoperoxidase study, shown in **Fig. 7.30**, confirmed antiglomerular basement membrane antibody disease or Goodpasture's disease. Good and pasture in the eponym are pronounced in the usual way. Ernest William Goodpasture (1886–1960) was a pathologist in the United States Naval Hospital in Chelsea, Massachusetts, when he did autopsies on two young men who caught influenza at the height of the pandemic in September 1918, but he was in Harvard Medical School when he described them (Goodpasture EW. The significance of certain pulmonary lesions in relation to the etiology of influenza. *American Journal of the Medical Sciences* 1919; **158:** 863–870). Only one of the two men had disease outside the lungs. He was 18 and had pulmonary hemorrhage, vasculitis in the spleen and small intestine, and a glomerular disorder with a fibrinous exudate in Bowman's space and proliferation in tufts. In 1958, M C Stanton and J D Tange suggested the name Goodpasture's syndrome for the combination of pulmonary hemorrhage and glomerulonephritis, and they took no notice of the vasculitis in the spleen and intestine in the man reported by Goodpasture. Later, the term Goodpasture's disease began to be applied when Goodpasture's syndrome was associated with antiglomerular basement membrane antibodies, after linear deposition of IgG in glomerular basement membranes was reported in 1964. The man with renal disease reported by Goodpasture had Goodpasture's syndrome, but may not have had antibodies to glomerular basement membranes, now considered essential for the diagnosis of Goodpasture's disease

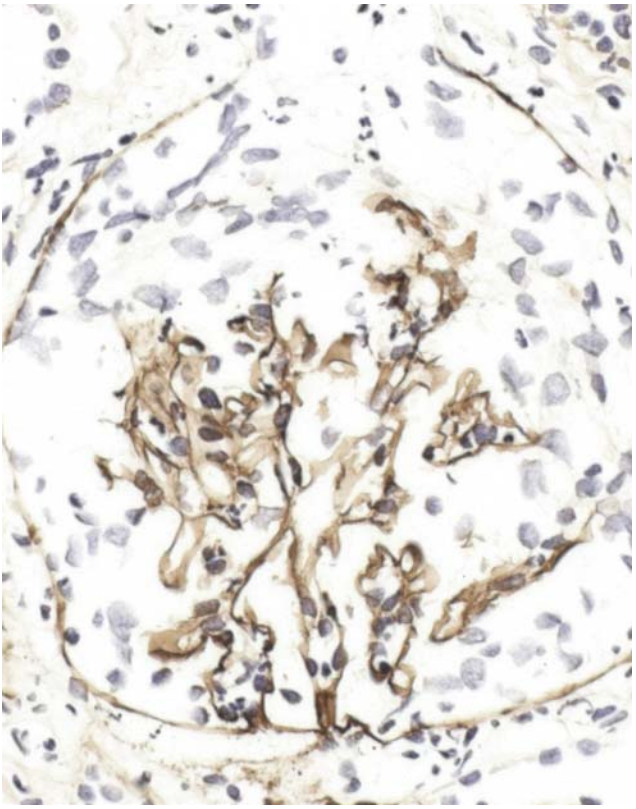

**Fig. 7.30** Glomerulus in the renal biopsy specimen of the man of 69 shown in **Fig. 7.29**. An immunoperoxidase method to detect C9 shows linear deposition in the remains of the glomerular basement membrane, which is disrupted in places, with cells throughout Bowman's space. The distribution of IgG is similar. These features indicate antiglomerular basement membrane antibody disease or Goodpasture's disease

## Conditions That Can be Differentiated from Pauci Immune Vasculitic Glomerulonephritis: 4 Cryoglobulinemic Glomerulonephritis

In **cryoglobulinemic glomerulonephritis**, there may rarely be vasculitic changes in glomeruli that have other abnormalities, particularly expansion of mesangial areas, and doubled basement membranes with the appearance of subendothelial membranoproliferative glomerulonephritis. There is also deposition of acellular material in capillary loops, which suggests the diagnosis (Figs 7.31 and 7.32). This material consists of aggregated immunoglobulins, and on immunohistologic study contains IgM and often IgG (Fig. 7.33). Arteritis and arteriolitis are more commonly seen than vasculitic glomerulonephritis.

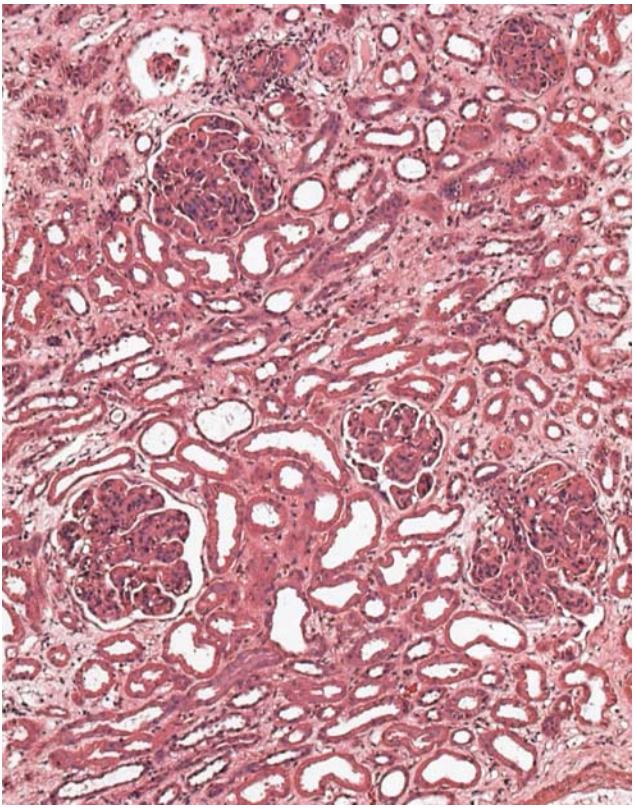

**Fig. 7.31** Cortex in a renal biopsy specimen from a man of 53 with acute renal failure, hematuria, and proteinuria. Glomeruli appear solid and hypercellular. Further investigations, illustrated in **Figs 7.32** and **7.33**, gave the diagnosis of cryoglobulinemic glomerulonephritis. This was due to precipitation of a monoclonal IgM paraprotein with polyclonal IgG

Cryoglobulins are immunoglobulins that clinical immunologists detect by cooling serum to see if there is a precipitate. Cryo comes from the Greek word for frost. The pathologist should not be concerned if immunologists cannot find cryoglobulins in blood, although the pathologist's diagnosis is more readily believed if they do. The abnormal immunoglobulins that precipitate in glomeruli when plasma proteins are suddenly concentrated, as water is filtered, may not precipitate when serum is cooled. Complement components C4 and C3 are usually in low concentration in serum in cryoglobulinemia.

Cryoglobulins are divided into a few types. The pathologist cannot differentiate these easily, but clinical immunologists are usually able to determine the type from findings in the serum. The first type is a monoclonal IgM paraprotein, which precipitates by itself, and there is often Waldenström's macroglobulinemia, due to a non-Hodgkin's lymphoma. Sometimes, a renal biopsy specimen in this condition just shows the glomerular deposits, with little else. In the second type of cryoglobulins,

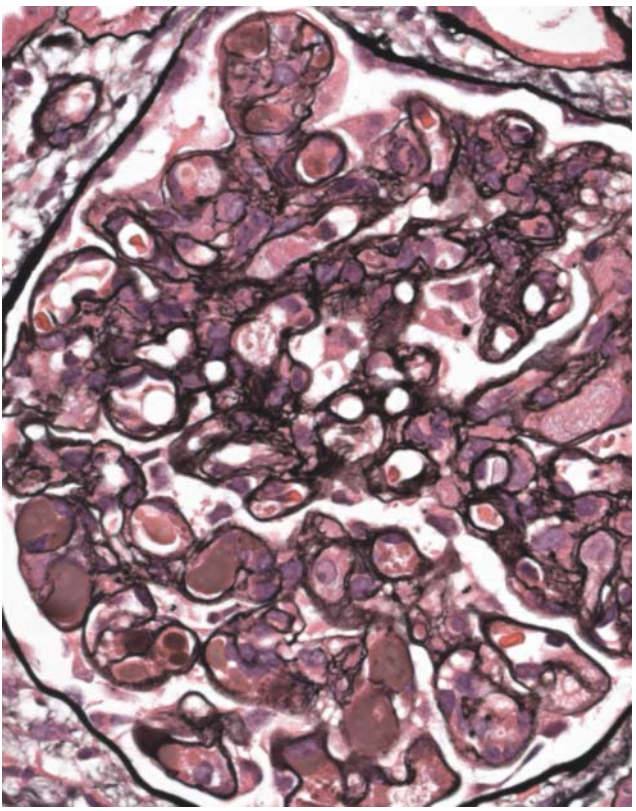

**Fig. 7.32** Glomerulus in the renal biopsy specimen from the man of 53 with cryoglobulinemic glomerulonephritis, the cortex in which is illustrated in **Fig. 7.31**. Staining with periodic acid-methenamine silver shows deposits of material in several capillary loops, with double basement membranes in several loops, to give the appearance of subendothelial membranoproliferative glomerulonephritis. Immunohistologic findings are illustrated in **Fig. 7.33**

the precipitates are mixtures of a monoclonal IgM paraprotein and polyclonal IgG, which means that the paraprotein has rheumatoid factor activity, acting as an antibody to IgG. Many of the people with this type have chronic infection with hepatitis C virus, and a few have Waldenström's macroglobulinemia. In the third type of cryoglobulins, which are rarely associated with the glomerular disorder, the precipitates are mixtures of polyclonal IgM with rheumatoid factor activity, and polyclonal IgG. Rheumatoid arthritis and related diseases are the usual underlying explanations of this type.

In the past, the term essential mixed cryoglobulinemia was sometimes used when there were IgM and IgG cryoglobulins, usually of the second type, without a lymphoma, although now most are recognised to be due to hepatitis C virus infection. The prognosis of cryoglobulinemic glomerulonephritis is that of the underlying disease.

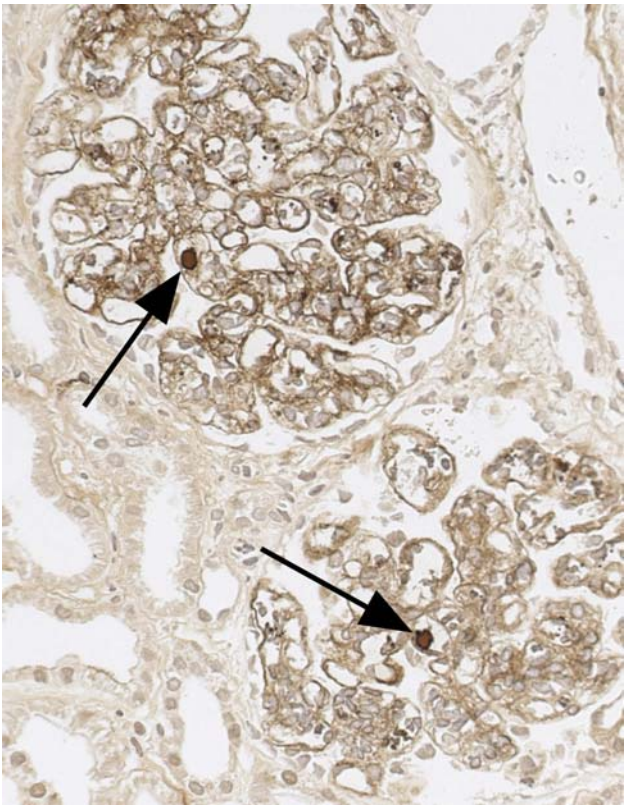

**Fig. 7.33** Glomeruli in the renal biopsy specimen from the man of 53 with cryoglobulinemic glomerulonephritis that is illustrated in **Figs 7.31** and **7.32**. An immunoperoxidase method to detect IgM shows solid aggregates of IgM in a few capillary loops (arrowed)

### *Are Glomeruli Abnormal but There Is No Evidence of Vasculitis?*

In acute renal failure, if glomeruli are abnormal, but do not have features of vasculitic disorders, the most likely condition is **acute postinfective glomerulonephritis**.

## Diagnosis of Acute Postinfective Glomerulonephritis

Clues to this diagnosis are that every glomerulus is affected equally, and the whole of each glomerulus is affected. Glomeruli appear large, solid, and filled with cells, a mixture of neutrophils, monocytes, and swollen cells inside basement membranes (Fig. 6.79). These endocapillary cells are mesangial and endothelial, which are not easily differentiated. Glomerular tufts may be so large that they prolapse into the origin of the proximal tubule (Fig. 6.20). Unusually, there may be cells in Bowman's

space forming structures that can be called crescents, but if the features are otherwise typical of acute postinfective glomerulonephritis, the prognosis should still be good.

Confirmation of acute postinfective glomerulonephritis requires sections stained by periodic acid-methenamine silver and by an immunohistologic method. Silver staining shows that glomerular basement membranes are single. If membranes appear double, the diagnosis is **subendothelial membranoproliferative glomerulonephritis** (Fig. 6.80). Immunohistologic staining in acute postinfective glomerulonephritis shows granular deposits, of various sizes, of IgG and complement in mesangium, and on the outside of glomerular basement membranes (Fig. 6.81). These differ from the large deposits seen in subendothelial membranoproliferative glomerulonephritis (Fig. 6.82). Complement persists longer than IgG and may be the only type of immunoprotein detected in acute postinfective glomerulonephritis. Electron microscopy will also help to differentiate these two conditions (Figs 6.83 and 6.84).

IgA is not found in pure acute postinfective glomerulonephritis, and its presence suggests either the coincidence of IgA nephropathy and acute postinfective glomerulonephritis, or lupus nephritis, most easily differentiated by serologic studies.

## Diagnosis of Subendothelial Membranoproliferative Glomerulonephritis

**Subendothelial membranoproliferative glomerulonephritis** is sometimes called type one membranoproliferative or mesangiocapillary glomerulonephritis, to distinguish it from a condition that in practice has little resemblance to it, better called **dense deposit disease** than type two membranoproliferative or mesangiocapillary glomerulonephritis. The use of these type numbers is unfortunate and misleading, suggesting a connection between unrelated conditions.

Subendothelial membranoproliferative glomerulonephritis resembles acute postinfective glomerulonephritis in several ways. Every glomerulus is affected, and the whole of each is affected. Glomeruli appear larger, more solid, and more cellular than normal (Fig. 6.80). There may be cells in Bowman's space forming structures which can be called crescents.

The differences from acute postinfective glomerulonephritis are that many or all glomerular basement membranes appear double on silver staining, and there is heavy deposition of immunoproteins in glomeruli, in a different distribution from that in acute postinfective glomerulonephritis. There are coarse deposits of IgG, IgM, and complement, mainly on the inside of glomerular capillary loops, and sometimes in mesangium (Fig. 6.82). Lupus nephritis can give the appearance of subendothelial membranoproliferative glomerulonephritis, but immunohistologic and serologic findings should indicate lupus (Figs 6.55 and 6.56).

Dense deposit disease has distinctive appearances on orthodox microscopy, immunohistology, and electron microscopy (Figs 6.16–6.18).

Membranoproliferative glomerulonephritis is an overused diagnosis. Three conditions that may be given this name are acute postinfective glomerulonephritis, membranous nephropathy, and nodular light chain glomerulopathy, but there are others. Satisfactory silver staining and immunohistology should settle the diagnosis, plus electron microscopy, if necessary.

Membranoproliferative glomerulonephritis has been the subject of classifications based on subtle and often subjective distinctions. The disorder sometimes called membranoproliferative or mesangiocapillary glomerulonephritis type three is the combination of subendothelial membranoproliferative glomerulonephritis and membranous nephropathy. Type three is also sometimes applied to rare examples of subendothelial membranoproliferative glomerulonephritis with prominent intramembranous deposits that are not so dense, uniform, and well defined as those in dense deposit disease. These are examples of the difficulties associated with classifications that use numbers rather than descriptions.

## Impression of Glomerulonephritis Given by Ischemic Glomeruli

If there is no glomerulonephritis, glomeruli in acute renal failure usually appear shrunken and smaller than normal in proportion to Bowman's capsule. This is because they are perfused at less than their usual pressure. Such ischemic shrinkage makes glomeruli appear more solid than normal, and basement membranes appear thick, because they are wrinkled (Fig. 5.9). These features can give an impression of glomerulonephritis, but there are no segmental changes of vasculitis, there is not the tuft enlargement of acute postinfective glomerulonephritis, and silver staining shows the wrinkling of basement membranes.

### *Has a Glomerular Disorder Been Excluded in Acute Renal Failure?*

If there is no glomerulonephritis, the explanation of acute renal failure may be seen in interstitial tissues, tubules, or blood vessels.

### *Has a Glomerular Disorder Been Excluded? Is There a Clue in Interstitial Tissues to the Cause of Acute Renal Failure?*

**Interstitial tissues** are usually abnormal even in pure acute tubular damage, and show edema, with separation of tubules by loose tissue which contains few cells (Fig. 7.3).

An interstitial infiltrate of inflammatory cells is common in acute renal failure associated with glomerular disorders such as vasculitic glomerulonephritis, lupus nephritis, and acute postinfective glomerulonephritis (Figs 6.57, 7.21, and 7.23). The term acute interstitial nephritis should not be used in these conditions, but only in the absence of glomerulonephritis.

## Diagnosis of Acute Interstitial Nephritis

In **acute interstitial nephritis**, also called acute tubulo-interstitial nephritis, there is acute tubular damage with interstitial edema and an interstitial infiltrate of inflammatory cells. There are lymphocytes, plasma cells, macrophages, and eosinophils, in various proportions (Fig. 7.34). Often there are inflammatory cells inside tubular epithelial cells, and cells and cellular debris in the lumen of tubules, although these features are not essential for the diagnosis (Fig. 7.35).

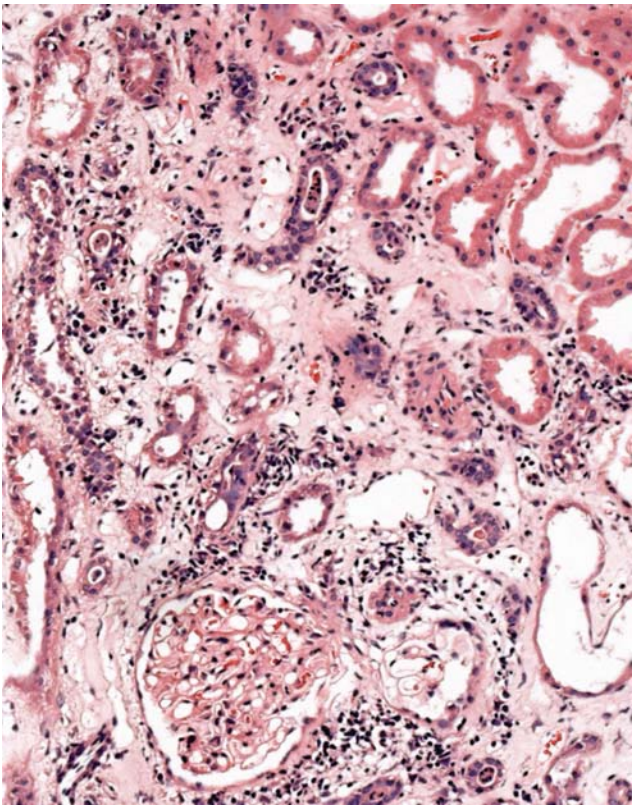

**Fig. 7.34** Cortex in a renal biopsy specimen from a man of 60 with acute renal failure. There is an interstitial infiltrate of inflammatory cells, mostly lymphocytes. A few cells enter the epithelium of tubules. **Fig. 7.35** illustrates other tubules in this specimen. The diagnosis was acute interstitial nephritis, attributed to a response to antibiotics used to treat salmonella enteritis

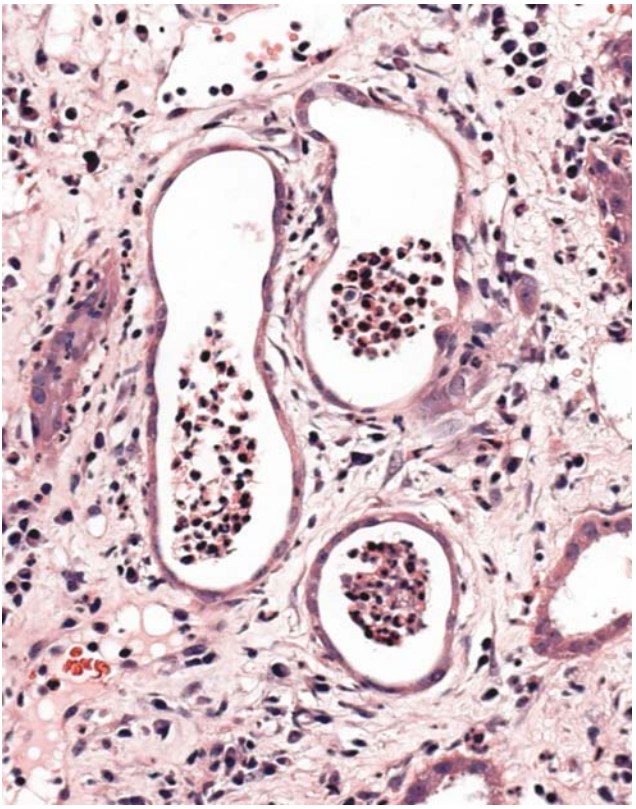

**Fig. 7.35** Cortex in the renal biopsy specimen from the man of 60 with acute interstitial nephritis, which is also illustrated in **Fig. 7.34**. A few tubules contain cells, at least some apparently polymorphs. Differentiation may be impossible between cellular debris produced by infiltration of tubules as part of acute interstitial nephritis, illustrated in **Fig. 7.34**, and pus as a sign of coincidental ascending infection, illustrated in **Fig. 7.36**

Neutrophil polymorphs may be present, but if they are the dominant cell line, or if there are groups of neutrophils forming pus inside tubules, the pathologist should consider whether the changes are likely to be those of ascending infection of the kidney, giving **acute pyelonephritis** (Fig. 7.36). This is usually in radial streaks through the cortex, compared with a more even distribution of acute interstitial nephritis, and may have detectable bacteria or fungi in tubules. Abscesses from infection carried to the kidney in the blood are also filled with neutrophils, and may contain detectable microorganisms, but are randomly scattered in the kidney. Both acute interstitial nephritis and ascending or blood-borne infection can occur in the same renal biopsy specimen, and features of purulent infection can be seen in any specimen. This is an example of the general rule that **there may be more than one condition in a renal biopsy specimen**. The pathologist should tell nephrologists

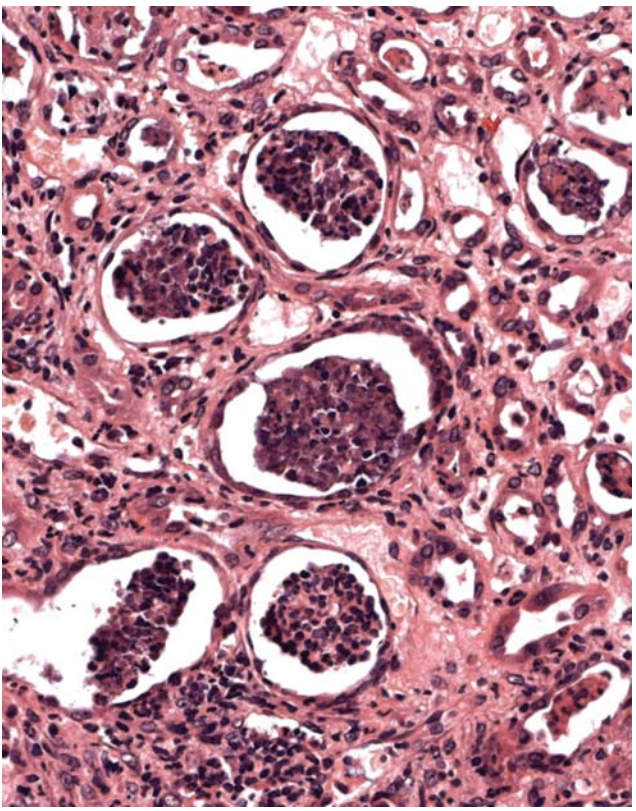

**Fig. 7.36** Cortex in a biopsy specimen of kidney, taken 6 months after transplantation into a man of 44. There are groups of tubules distended by pus. A Gram stain showed Gram-positive cocci in these tubules. *Staphylococcus aureus* was found in the urine. This is acute pyelonephritis

whenever ascending or other infection seems a possibility. Urinary infection may not be easy to investigate in people without urine output, and untreated infection could have severe effects if immunosuppression were to be used.

Eosinophils are not always present, but are helpful to the pathologist, because they usually indicate significant acute interstitial nephritis. If eosinophils are easily seen or are the main cell type, the term **acute eosinophilic interstitial nephritis** can be used.

Occasionally, in acute interstitial nephritis, there are groups of macrophages, sometimes with a few giant cells, generally forming small, poorly defined collections, when the condition can be called **acute granulomatous interstitial nephritis** (Fig. 7.37). Granulomas that are large, or well defined, or contain many giant cells are unlikely in an acute disorder, and are more likely in a biopsy specimen taken in investigation of chronic renal failure (Fig. 7.38).

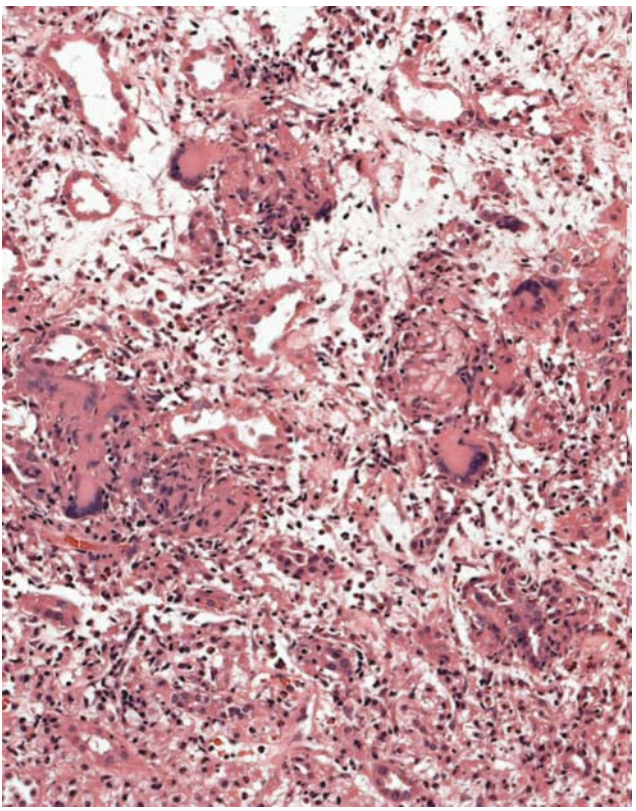

**Fig. 7.37** Cortex in a renal biopsy specimen from a man of 65 with acute renal failure. There is severe acute interstitial nephritis with several granulomas, which include giant cells. The diagnosis is acute granulomatous interstitial nephritis, attributed to a response to antibiotics used to treat a liver abscess. When this appearance is seen, exclusion of tuberculosis may be impossible, but is approached by a combination of the clinical features, lack of acid-fast bacilli on Ziehl–Neelsen staining, and knowledge that there is almost always chronic renal damage in granulomatous conditions such as tuberculosis and sarcoid, illustrated in **Fig. 7.38**

## Causes and Associations of Acute Interstitial Nephritis

Acute interstitial nephritis, including eosinophilic and granulomatous variants, can have several causes or associations. The pathologist is not usually able to determine the underlying explanation.

Common causes and associations are these.

1. Allergic responses to drugs, such as nonsteroidal anti-inflammatory drugs and antibiotics, particularly penicillin derivatives, although almost every drug that has ever been used has been said to cause acute interstitial nephritis, usually on inadequate evidence.

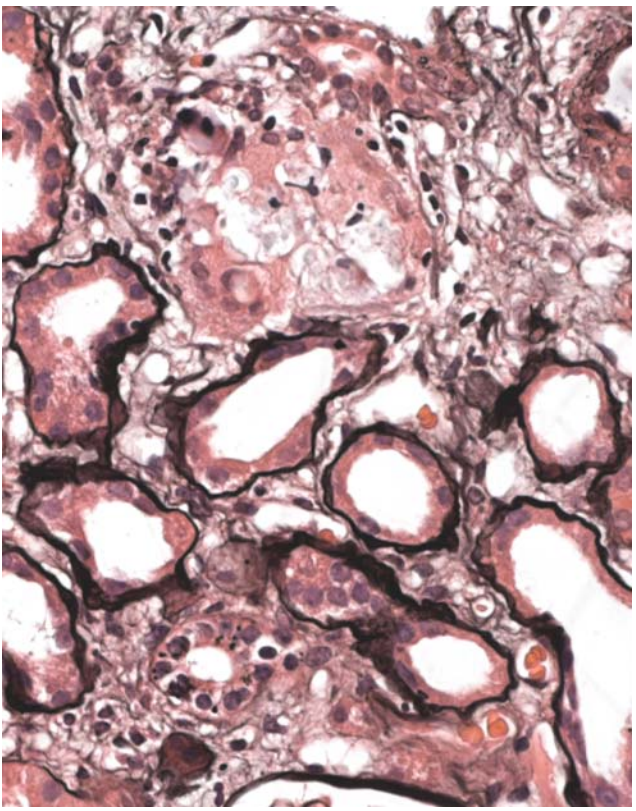

**Fig. 7.38** Cortex in a renal biopsy specimen from a woman of 37 with chronic renal failure and systemic features suggestive of sarcoid. There is chronic damage with a small granuloma, which contains giant cells. Appearances are consistent with sarcoid in the kidney

2. Infections, such as leptospirosis and hantavirus diseases.
3. The condition called tubulo-interstitial nephritis with uveitis, abbreviated to TINU. This condition is almost always in young women, and the renal problem may be detected at the same time as the eye problem, or may be before or after it.

Sjögren's syndrome, which is the combination of dry eyes and mucous membranes with arthritis, can be associated with acute interstitial nephritis, but there is often late damage at presentation. This is almost always with chronic renal failure, rather than acute renal failure, although there may also be disordered function of some segments of the nephron (Fig. 7.39). Acute granulomatous interstitial nephritis may occur in immunodeficiency disorders, such as inherited or acquired hypogammaglobulinemia.

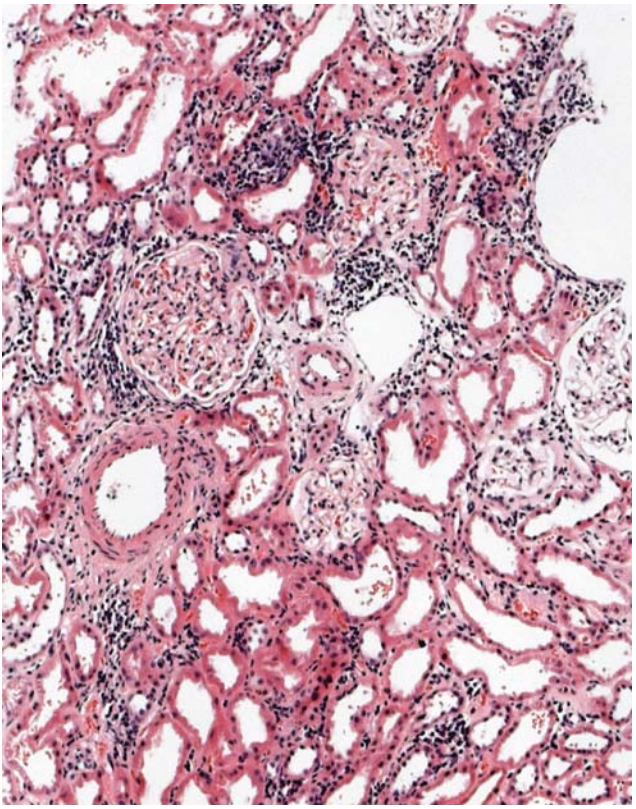

**Fig. 7.39** Cortex in a renal biopsy specimen from a woman of 31, with Sjögren's syndrome, proteinuria, hypokalemia, and renal tubular acidosis. There is a patchy lymphocytic infiltrate, mainly around collecting ducts. The disorder is named after Henrik Samuel Conrad Sjögren (1899–1989), a Swedish ophthalmologist. The name is often pronounced *shyo-gren*

## *Has a Glomerular Disorder Been Excluded? Is There a Clue in Tubules to the Cause of Acute Renal Failure?*

In acute renal failure, if the renal biopsy specimen shows no signs of glomerulonephritis, nor of acute interstitial nephritis, the pathologist should examine **tubules** for evidence of a disorder other than pure acute damage, or of a clue to the cause of acute damage.

**Only if there is no indication of a cause, either in the tubules themselves or in other parts of the kidney, should the diagnosis be given as acute tubular damage**, or acute tubular necrosis, because such damage is expected to be found in every specimen in acute renal failure. For example, there is no need to give the diagnosis as acute interstitial nephritis with acute tubular damage, because acute interstitial nephritis implies that there is acute tubular damage.

If acute tubular damage is the only finding, the appearances are similar in acute renal failure caused by **tubular toxins**, which include drugs such as gentamicin, and **ischemia**, as in hypovolemia, hypotension, and sepsis, which is one cause of the systemic inflammatory response syndrome, in which there are many mechanisms leading to underperfusion of the kidney. These include increased vascular permeability in many organs, with reduced blood volume, vasoconstriction in the kidney, and myocardial damage, causing hypotension.

The clinical term **hepatorenal syndrome** is sometimes used when there is acute renal failure in liver failure. Renal biopsy is rarely done in liver failure because there is a risk of bleeding, but may be necessary to exclude conditions such as vasculitis. If there is no recognisable condition, a specimen will show acute tubular damage, with casts stained by bile. The renal failure is due to ischemia from severe vasoconstriction in the kidney.

## Findings in Tubules: Myeloma Kidney

In particular, the pathologist should think about the possibility of effects of myeloma on tubules, especially in old people. A renal biopsy specimen sometimes gives the diagnosis of myeloma before other investigations can be done. The shorthand term myeloma kidney means the condition in which an abnormal immunoglobulin is filtered by glomeruli and damages tubules, although myeloma can affect the kidney in other ways. Other names for this include immunoglobulin light chain cast nephropathy and myeloma cast nephropathy.

The clue to the diagnosis of myeloma kidney is the presence in tubules of solid material that differs from the cast material commonly seen. In myeloma, the casts appear dry, palely stained, brittle, and cracked, unlike the more usual casts that appear wet, shiny, and deeply stained. In myeloma, the casts are surrounded by giant cells within tubules, and sometimes by polymorphs (Fig. 7.40). The giant cells are fused macrophages. Occasionally, there are needle-shaped casts. There may be an interstitial infiltrate of various types of inflammatory cells. On periodic acid Schiff staining, myeloma casts are virtually unstained, while the usual or ordinary casts found in almost all conditions, including in some tubules in myeloma kidney, are strongly stained (Fig. 7.41).

When these changes are well developed, the diagnosis can be given on sections stained by hematoxylin and eosin, and the pathologist should not be dissuaded by failure of the nephrologists to make the diagnosis clinically before biopsy. Clinical immunologic investigation of serum and urine should confirm the diagnosis.

If the changes are slight, immunohistologic study of the specimen is necessary to confirm the diagnosis. This should show disproportionate amounts of either kappa or lambda light chains in casts and in tubular epithelial cells (Figs 7.42 and 7.43). The casts sometimes stain with Congo red, and may give anomalous colours when the section stained with Congo red is examined between crossed polariser and analyser (Fig. 6.68). This does not mean there is amyloid in the kidney.

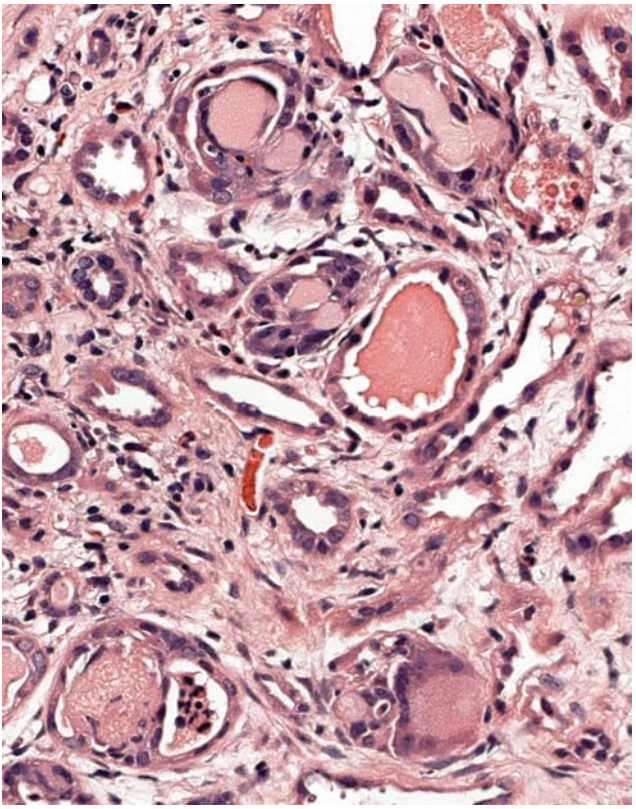

**Fig. 7.40** Cortex in a renal biopsy specimen from a woman of 65 with acute renal failure. Some tubules are atrophic, which suggests that the renal failure is acute on chronic. There are casts in several tubules, several surrounded by giant cells. These gave the diagnosis of myeloma kidney. After the biopsy, a lambda light chain paraprotein was found in the woman's serum

Renal failure from myeloma kidney rarely improves.

There are several other ways in which myeloma and related paraproteinemias can affect the kidney, although just as people with diabetes mellitus can have renal disease that is not due to diabetic glomerulopathy, people with a paraprotein can have renal disease that is unrelated to their paraprotein. Paraproteinemia is a common finding in old people, and even if the pathologist is told on the request form about a paraprotein, this may be irrelevant to the findings in a renal biopsy specimen.

The main ways, other than myeloma kidney, in which paraproteinemia can affect the kidney include **amyloidosis** of AL type (Figs 6.65–6.67 and 6.74–6.76), **nodular light chain glomerulopathy** (Figs 6.45–6.48), and **cryoglobulinemic glomerulonephritis** (Figs 7.31–7.33). An interesting observation is that these are not often seen in combination, either with each other or with myeloma kidney. Rarely, the neoplastic cells in myeloma or another lymphoma may be seen in or around the kidney (Figs 4.2 and 7.11).

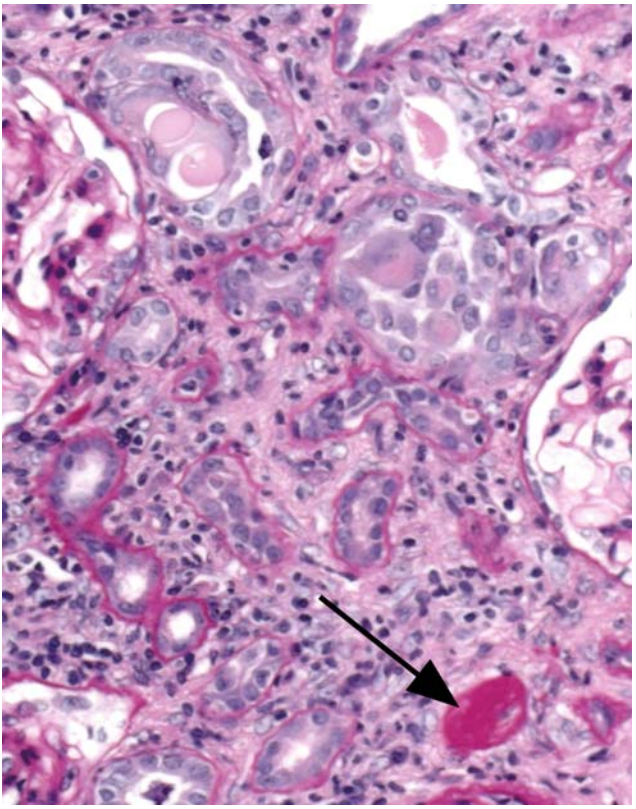

**Fig. 7.41** A renal biopsy specimen from a woman of 58 with acute renal failure and myeloma. Periodic acid Schiff staining shows the difference between myeloma casts, which are palely stained and surrounded by giant cells, and the common or ordinary type of cast found in many conditions, including myeloma. The ordinary cast is deeply stained, and has no cellular reaction around it (arrowed)

## Findings in Tubules: Myoglobinuria or Crystals

Tubules may contain things other than myeloma casts that give the diagnosis. They may have casts that appear orange or brown on sections stained by hematoxylin and eosin, which suggest **myoglobinuria** (Fig. 7.44). This is confirmed by immunohistologic staining for myoglobin (Fig. 7.45). The request form may give a history of injury to skeletal muscles, or myositis, for instance in viral infections, or exposure to drugs known to cause rhabdomyolysis, such as statins, which are used to lower lipid concentrations in the blood, or cocaine. **Hemoglobin** may be seen in tubules, if there is severe hemolysis, for instance, following a mismatched blood transfusion.

The finding of many oxalate crystals in acutely damaged tubules suggests **poisoning**, particularly by ethylene glycol which is used as antifreeze, although a few crystals may be seen in any specimen with acute or chronic tubular damage. Many

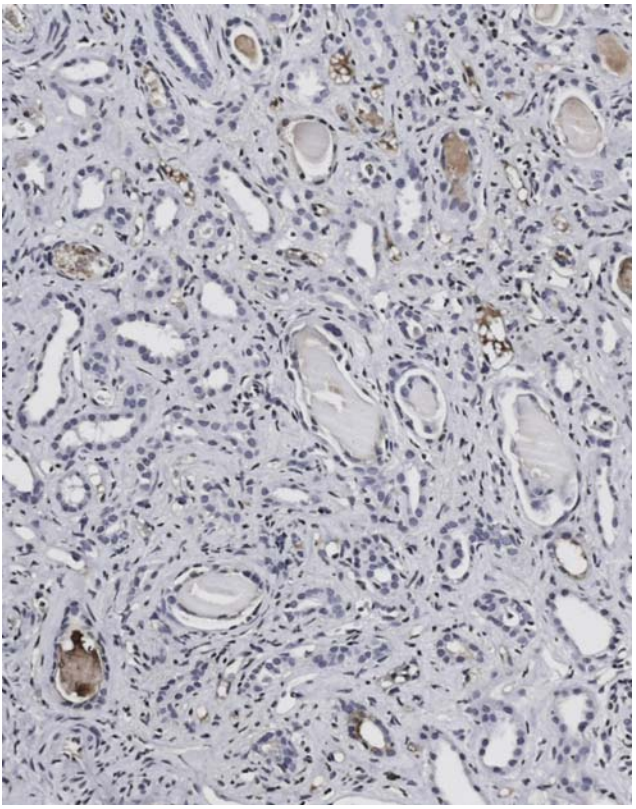

**Fig. 7.42** Medulla in a renal biopsy specimen from a man of 71 with acute renal failure and hypercalcemia. Immunoperoxidase staining to detect lambda light chains shows no staining in most casts. An adjacent section stained for kappa light chains is shown in **Fig. 7.43**

oxalate crystals may also be seen if there is tubular damage, generally chronic rather than acute, associated with either **genetic hyperoxaluria**, or chronic intestinal or pancreatic disorders with malabsorption of fat. Excess fatty acids in the bowel bind calcium, which cannot combine with oxalic acid, and this allows increased absorption of oxalates. This is called **enteric hyperoxalosis**.

Oxalate crystals may be seen within tubules on orthodox microscopy, even though they are transparent and do not stain with routine methods. Oxalates are more easily detected when the section is examined between crossed polariser and analyser, because the crystals are birefringent and appear bright (Figs 7.46 and 7.47).

Extensive deposition of calcified material, other than oxalates, within tubular epithelium or basement membranes and elsewhere, may be seen in severe hypercalcemia, which may cause acute renal failure. These deposits are not birefringent but stain with hematoxylin, and can be detected on sections stained with hematoxylin and eosin, and even better on sections stained by Congo red or van

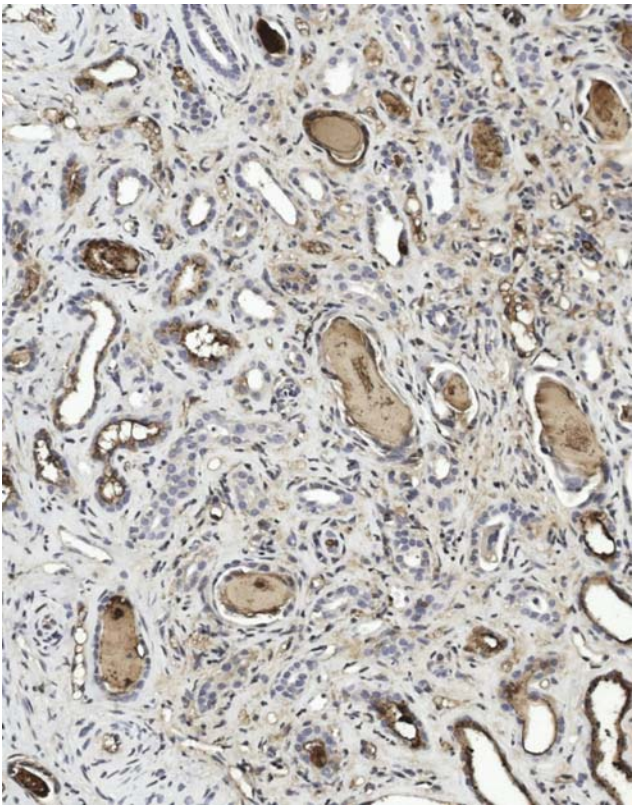

**Fig. 7.43** An adjacent section to that in **Fig. 7.42**. Immunoperoxidase staining to detect kappa light chains shows staining in casts, and in tubular epithelial cells. The renal biopsy specimen showed myeloma kidney and gave the diagnosis of paraproteinemia, which was confirmed later by detection of an IgA kappa serum paraprotein, with a kappa Bence Jones protein, and other evidence of myeloma

Gieson, with hematoxylin counterstain. If necessary, von Kossa stain will confirm calcification, or rather the presence of insoluble phosphate and carbonate, which are assumed to be calcium salts. Calcium oxalate does not react with von Kossa stain.

## *Has a Glomerular Disorder Been Excluded? Is There a Clue in Blood Vessels to the Cause of Acute Renal Failure?*

In acute renal failure, if there is no sign of glomerulonephritis, acute interstitial nephritis, myeloma kidney, or another identifiable tubular disorder, a clue to the cause may be in **blood vessels**.

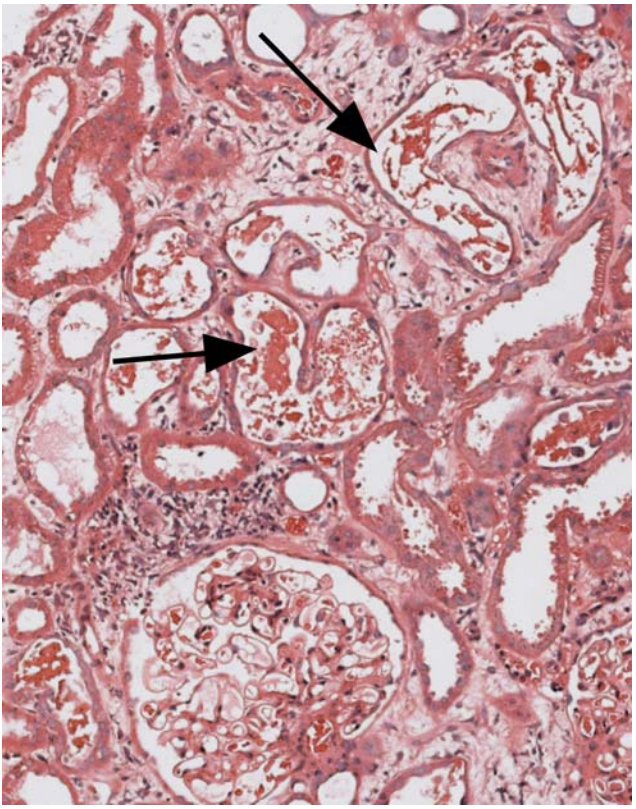

**Fig. 7.44** Cortex in a renal biopsy specimen from a man of 85 with acute renal failure. There is acute tubular damage, with several casts containing flakes or granules that appear red/orange on hematoxylin and eosin staining (arrowed). This finding suggests myoglobinuria, which is confirmed by immunohistologic study, illustrated in **Fig. 7.45**. The man was found to have high concentrations of muscle enzymes in the serum, attributed to alcoholic myopathy

## Changes in Blood Vessels: Vasculitis or Embolism

Arteritis and arteriolitis are rarely the only evidence of **vasculitis** in a biopsy specimen, and vasculitic glomerulonephritis is almost always found if they occur (Figs 4.6, 7.22, and 7.24).

Evidence of atherosclerotic or thrombotic **embolism** may be seen in arteries in acute renal failure, but almost always in old people with more extensive chronic damage than expected for their age, as a reflection of severe chronic ischemia of the kidney (Fig. 7.10). The renal failure is usually an acute worsening of chronic renal failure, rather than acute impairment of previously normal function. **Only one artery with embolic material in it has to be found to give the diagnosis**, because the implication is that the biopsy is highly unlikely to have hit the only embolus, and that there is widespread embolism in the kidney. Embolism may

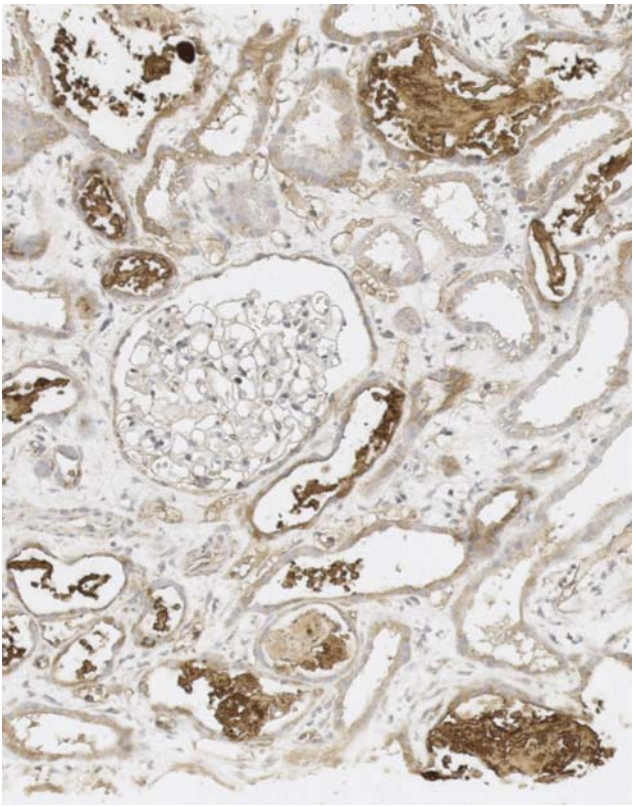

**Fig. 7.45** Cortex in the renal biopsy specimen from the man of 85 with myoglobinuria, which is illustrated in **Fig.** 7.44, stained by an immunoperoxidase method to detect myoglobin. Tubules contain myoglobin, and the diagnosis is confirmed

be found in association with any other renal disorder in old people, an example of the rule that **more than one condition may be found in a renal biopsy specimen**.

## Acute Renal Ischemia

The finding of extensive acute tubular damage or early tubular atrophy, especially if these are uniform and most glomeruli survive, but without clues to a glomerular, tubular or interstitial disorder that would explain the acute changes, suggests that a likely cause is **severe ischemia of recent onset** (Fig. 7.48).

This could be due to multiple atherosclerotic emboli in the kidney, but the biopsy specimen has not included any to allow the diagnosis to be made. Another possibility is that there is stenosis of the main renal artery, which is usually due to

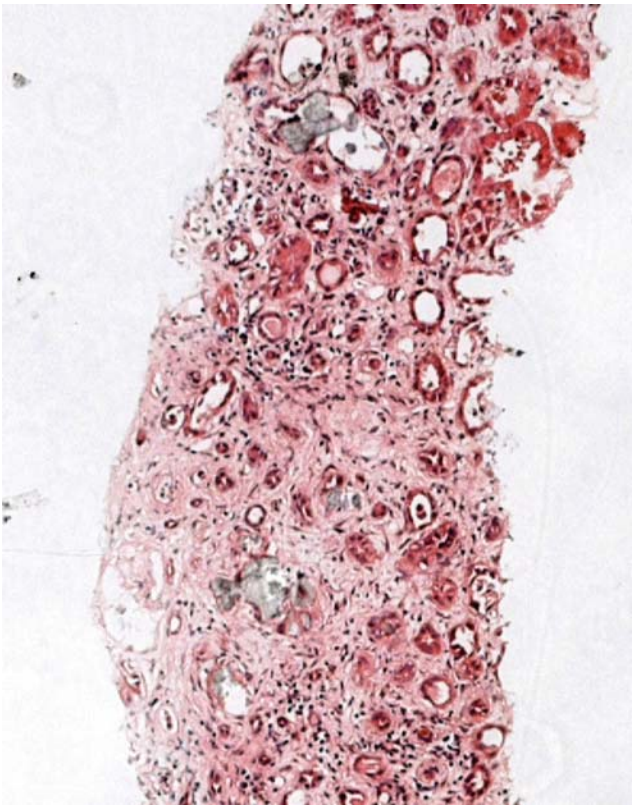

**Fig. 7.46** Cortex in a renal biopsy specimen from a man of 70 with acute renal failure. There is a mixture of acute and chronic tubular damage, but most appears acute. Examination of this section stained by hematoxylin and eosin between crossed polariser and analyser is illustrated in **Fig** 7.47, and suggests the diagnosis

atherosclerosis, and the person has been treated with an angiotensin converting enzyme inhibitor. Such treatment may cause a sudden and severe worsening of renal function, by reduction of glomerular filtration. As in atherosclerotic embolism, there is likely to be a background of marked chronic damage. Another possibility is reduced perfusion of the kidney because there is hypotension, perhaps due to a myocardial infarct. Renal biopsy is not often used to investigate acute renal failure in this circumstance.

Renal vein thrombosis causes acute tubular damage from ischemia. This is almost always in the nephrotic syndrome, and thrombus is hardly ever seen in the small veins included in a renal biopsy specimen (Figs 6.1 and 6.2).

The most common explanation of acute renal ischemia is usually suggested by findings in small blood vessels in the specimen. This is a small vessel vasculopathy, also called thrombotic microangiopathy.

**Fig. 7.47** The section illustrated in **Fig. 7.46**, examined between crossed polariser and analyser. There are crystals in several tubules. These are oxalates. The man had malabsorption from chronic pancreatitis. The diagnosis was predominantly acute tubular damage as a complication of enteric hyperoxalosis

## Diagnosis of Small Vessel Vasculopathy, also Called Thrombotic Microangiopathy

In a **small vessel vasculopathy**, also called **thrombotic microangiopathy**, small arteries in the renal cortex have concentric intimal thickening, which differs from changes seen with age or with nonaccelerated hypertension, sometimes called essential or benign hypertension, although benign is not an appropriate term for a potentially fatal condition. The intimal thickening appears loose, mucoid, and poorly stained by routine methods, and is sometimes called onion skin change (Fig. 7.8).

Arterioles have another abnormality, and show replacement of parts of their wall by material that has few cells, stains deeply with eosin, and is called fibrinoid necrosis. The lumen of affected arterioles may be blocked by thrombus (Fig. 7.9). There may be hemorrhage into the walls of small arteries or arterioles (Fig. 7.49). The fibrinoid necrosis and the thrombosis may extend into glomerular tufts.

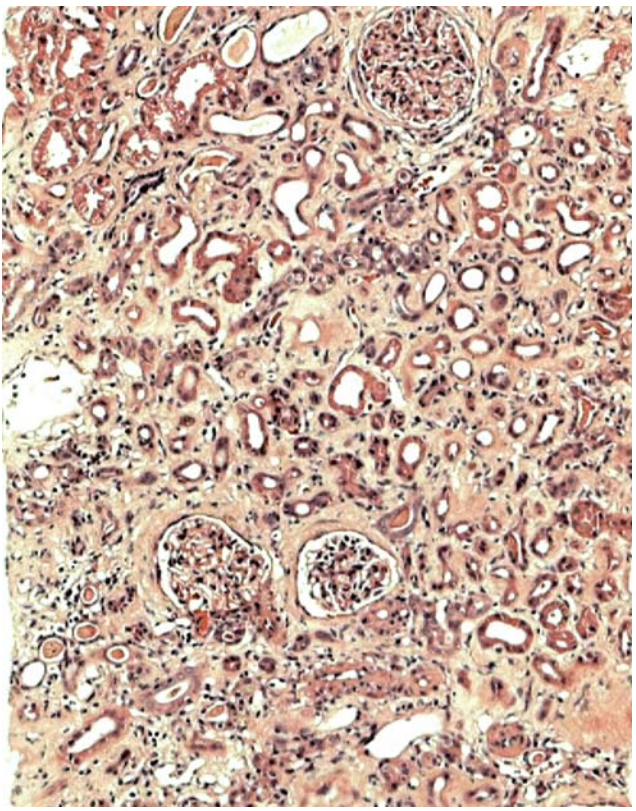

**Fig. 7.48** Cortex in a renal biopsy specimen from a man of 58 with acute renal failure and severe ischemic heart disease, for which he was under consideration for heart transplantation. There is severe tubular damage, which mostly appears early atrophy, and affects the cortex uniformly. Glomeruli appear close to normal. These findings suggest severe recent ischemia of the kidney

Glomeruli often show only severe shrinkage from ischemia, but they may have loose material on the inside of capillary loops between the endothelium and the basement membrane. This can be followed by the appearance of double basement membranes, resembling subendothelial membranoproliferative glomerulonephritis, but there are few or no deposits of immunoproteins. Also, the mesangium may disappear, by the process of mesangiolysis. The vascular changes may be so severe that infarction of cortex may be seen. A lack of inflammatory cells in the walls of affected vessels, the concentric changes, and the lack of fibrinoid necrosis in arteries help to differentiate small vessel vasculopathy, also called thrombotic microangiopathy, from vasculitis.

On immunohistologic study, there is deposition of IgM and complement in small arteries and arterioles, in the intima and sometimes in the media (Fig. 7.50).

Sometimes, only the arterial changes or the arteriolar changes occur. With time, the arterial intimal thickening becomes more fibrous, and the arteriolar necrosis

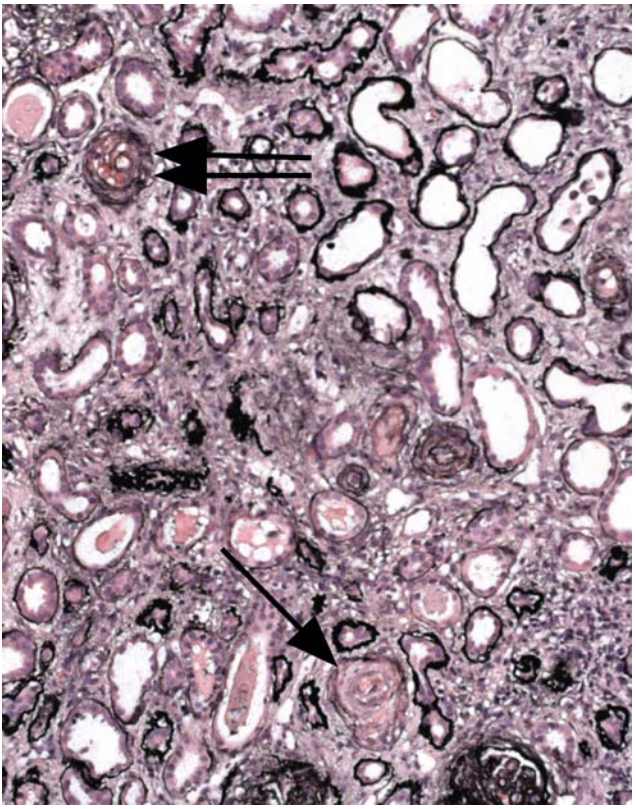

**Fig. 7.49** Cortex in the renal biopsy specimen, also illustrated in **Fig. 7.1**, from the man of 30 with acute renal failure. There is a small vessel vasculopathy, also called thrombotic microangiopathy, with loose intimal thickening in one interlobular artery (single arrow), and intimal hemorrhage in another (double arrow). These changes are consistent with effects of accelerated hypertension

resembles severe hyalinosis (Fig. 7.51). The pathologist can usually still see hints that there is this type of vasculopathy, no longer in its acute or most active stage.

Renal failure from a small vessel vasculopathy, also called thrombotic microangiopathy, may recover, depending on the underlying condition, but often does not.

## Disorders Associated with Small Vessel Vasculopathy

This type of vasculopathy can be seen in **accelerated hypertension**, some examples of **hemolytic uremic syndrome** and related disorders, and a group of conditions that include **systemic lupus erythematosus**, the **antiphospholipid syndrome**, and the one called either **scleroderma** or **systemic sclerosis**.

These disorders cannot usually be differentiated by a pathologist, unless there are other features, such as a glomerular disorder, which suggests lupus nephritis. Nephrologists may also be unsure what clinical diagnosis to give to a person with

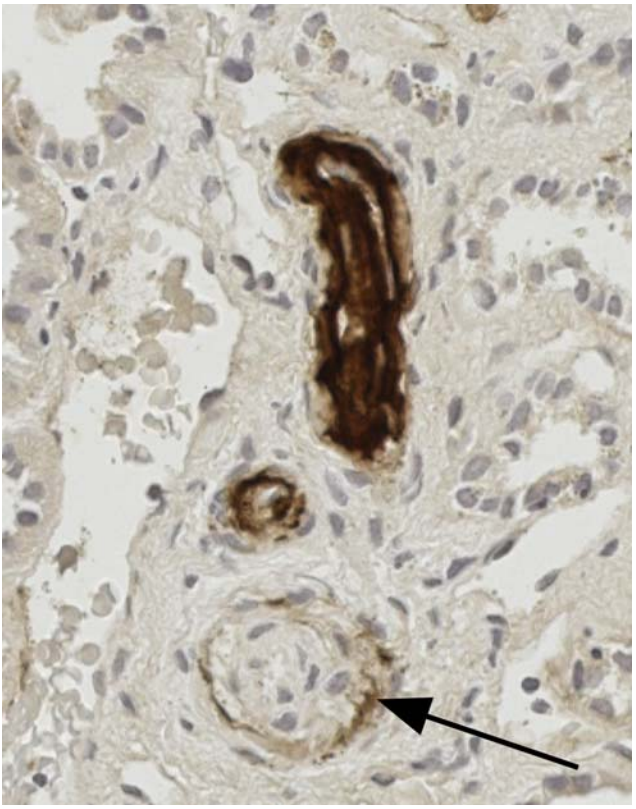

**Fig. 7.50** Cortex in a renal biopsy specimen from a woman of 70 with acute renal failure and clinical features of early scleroderma. An immunoperoxidase method to detect IgM shows heavy deposition in the wall of an arteriole with fibrinoid necrosis, and lighter deposition in the intima of a small artery (arrowed). The diagnosis is small vessel vasculopathy, also called thrombotic microangiopathy

acute renal failure and small vessel vasculopathy, also called thrombotic microangiopathy. For example, scleroderma or systemic sclerosis may have no characteristic clinical features at the time of presentation with acute renal failure (Fig. 7.8).

**Accelerated hypertension** is sometimes called malignant hypertension. Hypertension with clinical features of the accelerated phase may not be accompanied by pathologic features of small vessel vasculopathy, also called thrombotic microangiopathy, and the vasculopathy may occur without clinically accelerated hypertension.

The vasculopathy due to accelerated hypertension may be the only change in a biopsy specimen, or there may be evidence of a renal disorder, which accounts for the hypertension. The commonest glomerular disorder to be found associated with the vasculopathy is IgA nephropathy, diagnosed on immunohistologic appearances (Fig. 7.1). Two possible explanations of a sudden deterioration of renal function

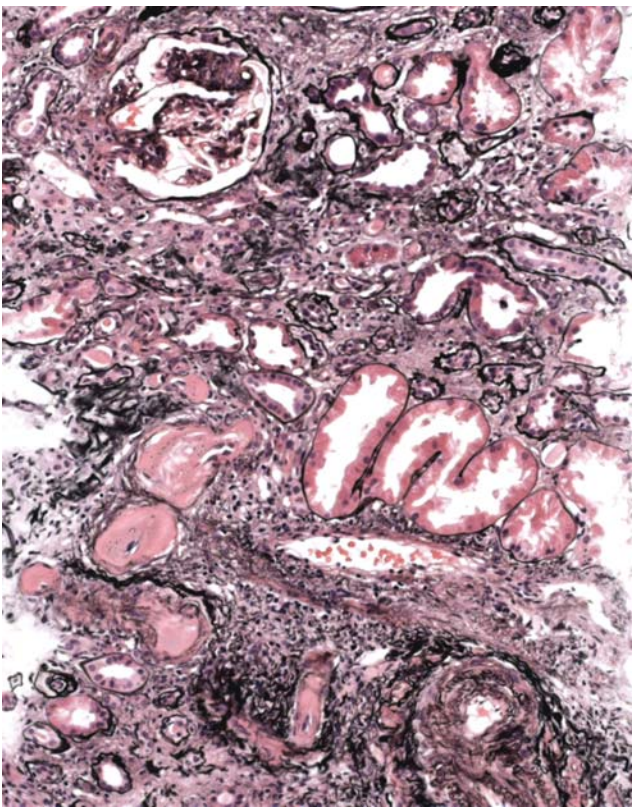

**Fig. 7.51** Cortex in a renal biopsy specimen from a man of 67 with chronic renal failure and severe hypertension. Arterioles have marked hyalinosis, suggestive of resolved fibrinoid necrosis, and a small artery has chronic intimal thickening. These findings are consistent with a late small vessel vasculopathy, also called thrombotic microangiopathy, in previously accelerated hypertension. A glomerulus has a segmental area of sclerosis

in someone known to have IgA nephropathy are the development of accelerated hypertension and the development of Henoch–Schönlein nephritis (Figs 7.25–7.27).

A problem for the pathologist, when there is a small vessel vasculopathy, also called thrombotic microangiopathy, is the finding of segmental sclerosing abnormalities in glomeruli, without significant deposition of immunoproteins (Figs 7.51 and 7.52). These segmental glomerular lesions may be a result of accelerated hypertensive effects, by mechanisms such as extension of arteriolar necrosis or thrombosis into the tuft, or hyperfiltration effects following global sclerosis of other glomeruli due to ischemia. Alternatively, the segmental lesions may indicate an underlying, pre-existing glomerular disorder, which explains the accelerated hypertension. Whether the glomerular abnormalities are the result or the cause of accelerated hypertension may be difficult to determine, and the pathologist may only be able to report that there is a small vessel vasculopathy, also called thrombotic microangiopathy, associated with segmental sclerosing glomerular lesions.

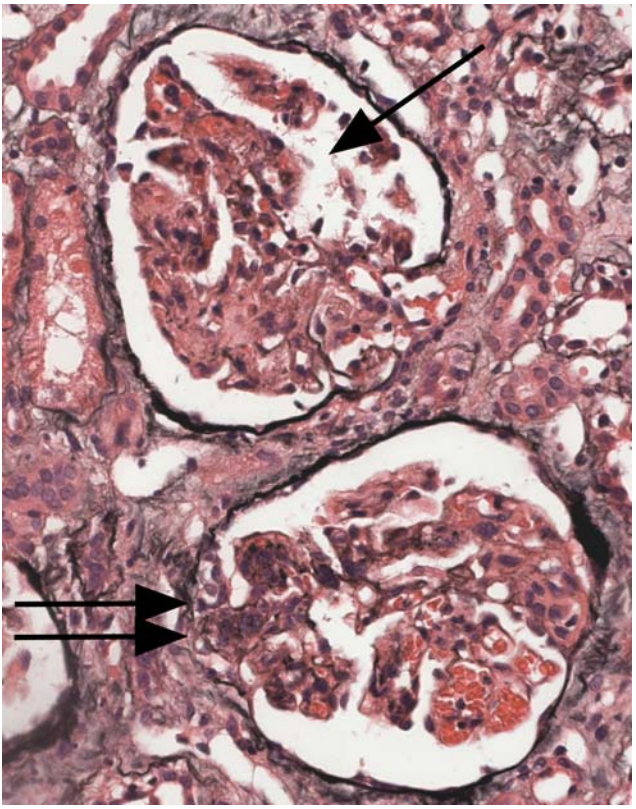

**Fig. 7.52** Cortex in a renal biopsy specimen from a woman of 44 with acute renal failure and clinically accelerated hypertension. There is early tubular atrophy, with ischemic shrinkage of one glomerulus (single arrow). The other glomerulus has an area of sclerosis, with adhesion to Bowman's capsule (double arrow)

**Hemolytic uremic syndrome** can give the changes of the vasculopathy. These are the usual appearances in adults, although renal biopsy is not often done at the height of the illness, because there is a risk of bleeding. The disorder called **thrombotic thrombocytopenic purpura** overlaps clinically with hemolytic uremic syndrome, but typically has neurological signs, and is less likely to give acute renal failure.

Both are conditions in which platelets are activated, but coagulation is usually normal. In hemolytic uremic syndrome, endothelial damage from various causes leads to platelet adhesion. In thrombotic thrombocytopenic purpura, there is a deficiency of an enzyme, ADAMTS 13, which stands for a disintegrin-like and metalloproteinase with thrombospondin type one motif. Deficiency, either genetic or due to an acquired antibody, means that multimers of von Willebrand factor circulate in the blood, and cause platelet aggregation. Thromboses in glomeruli and elsewhere in the kidney may be seen (Fig. 7.7). There is evidence of a microangiopathic

hemolytic anemia, with red cell fragments, reduced haptoglobin concentration, and other features in the blood.

Biopsy is rare in children with hemolytic uremic syndrome associated with diarrhea due to infection with *Escherichia coli* type O157, because a confident diagnosis can usually be made clinically. The condition is due to a verocytotoxin, or Shiga-like toxin, from the bacteria. There is thrombosis in glomeruli, which sometimes extends into afferent arterioles or arteries. Acute renal failure in this type of hemolytic uremic syndrome generally recovers.

Children and adults with clinically atypical hemolytic uremic syndrome, not associated with diarrhea due to infection with *Escherichia coli* type O157, have glomerular changes resembling subendothelial membranoproliferative glomerulonephritis, with mesangial increase and doubled basement membranes, but few or no immune deposits. Combinations of glomerular and vascular changes can be seen in a renal biopsy specimen in this type of hemolytic uremic syndrome, in which acute renal failure generally does not recover (Fig. 7.53).

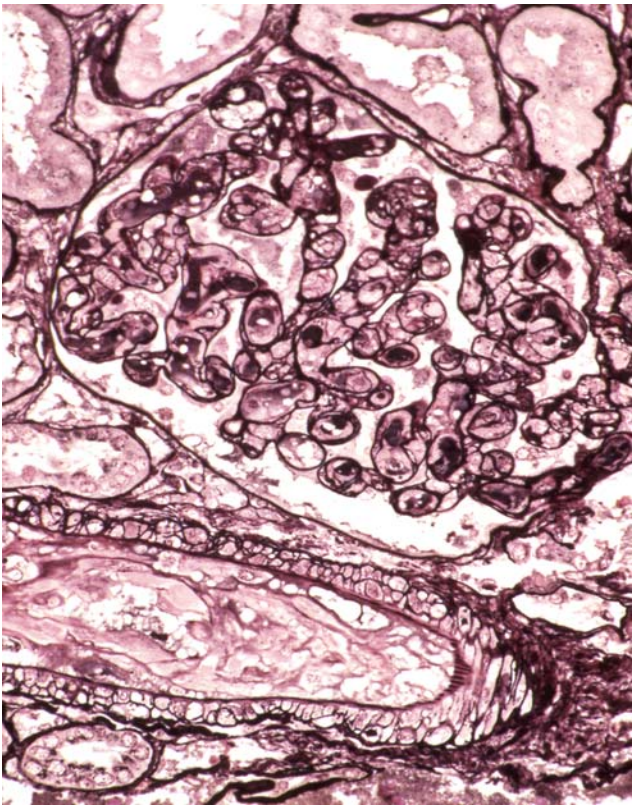

**Fig. 7.53** Cortex in a renal biopsy specimen from a boy of 8 with acute renal failure and clinically atypical hemolytic uremic syndrome, not associated with diarrhea. A small artery has loose intimal thickening. A glomerulus has mesangial and endothelial swelling with doubling of basement membranes, which gives the appearance of subendothelial membranoproliferative glomerulonephritis

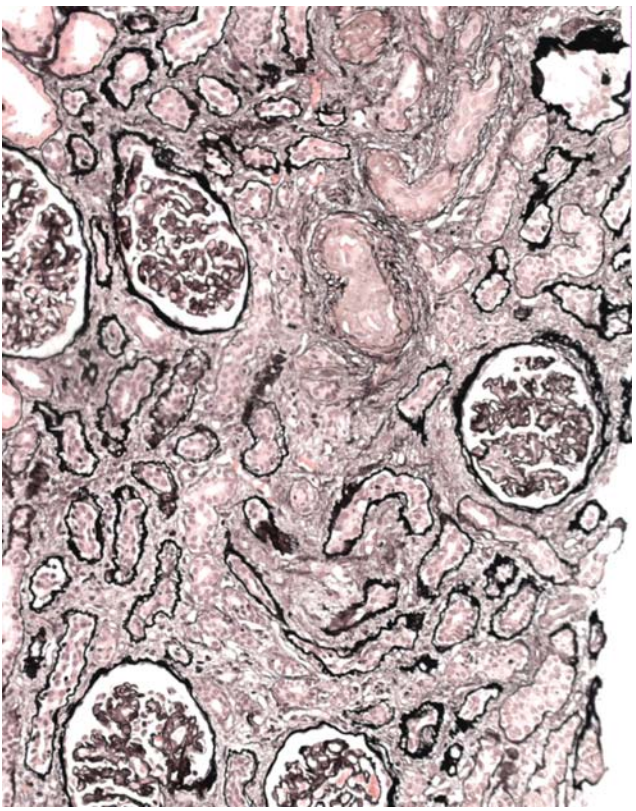

**Fig. 7.54** Cortex in a renal biopsy specimen from a woman of 30 with chronic renal failure, systemic lupus erythematosus, a history of repeated spontaneous abortion, and anticardiolipin antibodies in the serum. There is late renal damage with features of a small vessel vasculopathy, also called thrombotic microangiopathy, consistent with the antiphospholipid syndrome

There are several causes of clinically atypical hemolytic uremic syndrome. These include familial disorders, such as hypocomplementemia associated with persistent activation of complement, due to deficiency of regulators of the alternate pathway of complement activation, particularly factor H and factor I, which are both found in normal serum, and membrane cofactor protein or CD46, found on the surface of normal cells. Other causes of the hemolytic uremic syndrome are effects of drugs, such as calcineurin inhibitors and the cytotoxin mitomycin, infections, such as with HIV or the pneumococcus, irradiation, bone marrow transplantation, and some cancers.

In the **antiphospholipid syndrome**, or antiphospholipid antibody syndrome, there are antibodies in the serum to various phospholipids. The antibodies are also called anticardiolipin antibodies, reagin antibodies, or lupus anticoagulant, depending upon the method of detection. Many people with these antibodies have systemic lupus erythematosus, but some have either incomplete features of lupus or no evidence of it. Women with these antibodies have a high risk of repeated abortion. Other features include venous and arterial thrombosis, which may be seen

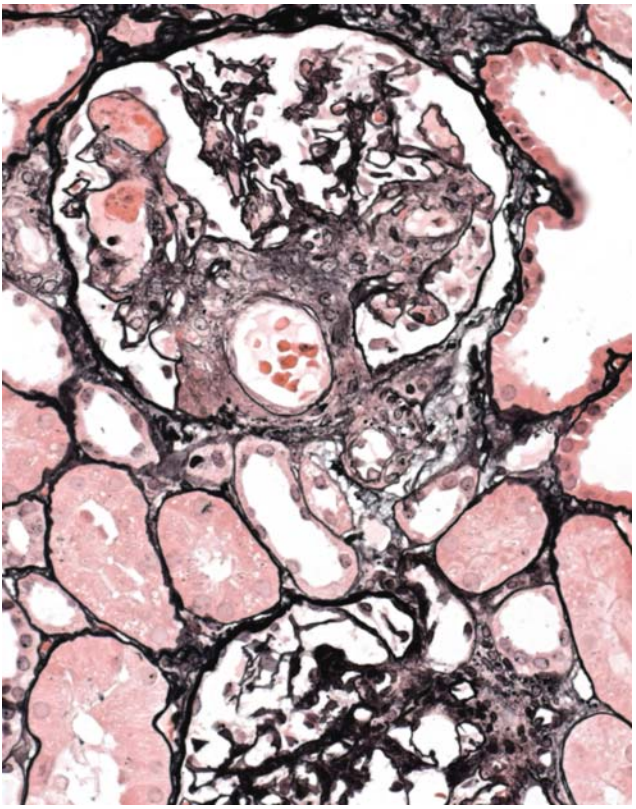

**Fig. 7.55** Cortex in a renal biopsy specimen from a woman of 27 with acute renal failure, systemic lupus erythematosus, disseminated intravascular coagulation, and anticardiolipin antibodies. A glomerulus contains thrombosed capillary loops, consistent with the antiphospholipid syndrome

in the kidney. The antiphospholipid syndrome is usually diagnosed when there is late renal damage, and there may be features of a small vessel vasculopathy, also called thrombotic microangiopathy, or late intimal thickening in arteries (Fig. 7.54). Occasionally acute changes are seen, such as thrombosis in glomeruli (Fig. 7.55).

**Disseminated intravascular coagulation** is due to stimulation of both the coagulation cascade and platelets, often by septicemia, and sometimes by other factors, such as hemorrhagic problems related to pregnancy. Renal biopsy is hardly ever done, but the specimen shows thrombosis in glomeruli or arterioles.

## Summary: Acute Renal Failure

Most people with acute renal failure do not have a renal biopsy.

Acute renal failure is associated with acute abnormalities in tubules. Provided acutely abnormal tubules are not in an infarcted area of cortex, they may recover to normal.

The most likely finding in renal biopsy specimens from adults with acute renal failure is vasculitis. This almost always takes the form of vasculitic glomerulonephritis.

Other common findings in acute renal failure are various glomerular disorders, acute interstitial nephritis, tubular disorders such as myeloma kidney, and a small vessel vasculopathy, also called thrombotic microangiopathy.

Only if none of these identifiable conditions is found should the diagnosis be given as acute tubular damage not explained by anything in the biopsy specimen.

## Further Reading: Acute Renal Failure

D'Agati VD, Jennette JC, Silva FG. Non-Neoplastic kidney diseases. Atlas of Nontumor Pathology, first series, fascicle 4. Washington, DC: American Registry of Pathology and Armed Forces Institute of Pathology, 2005. Chapters 10–16, 18–22.

Jennette JC, Olson JL, Schwartz MM, Silva FG. Heptinstall's Pathology of the Kidney. Sixth ed. Philadelphia:Lippincott Williams and Wilkins, 2007. Chapters 7, 8, 10, 12–16, 19, 21, 23, 24.

# Chapter 8
# Indication for Biopsy: Chronic Renal Failure

## Introduction to Chronic Renal Failure

This is permanently reduced renal excretory function, meaning a reduced glomerular filtration rate, due to a reduced number of nephrons. This contrasts with acute renal failure, in which the number of nephrons may be normal, and renal function may recover. Chronic renal failure, at least in adults, usually appears to have been present for months or years, rather than days or weeks, unlike acute renal failure. **Chronic renal impairment** can be used with the same meaning.

For many decades, the term Bright's disease was used as a diagnosis in clinical disorders of the kidney, particularly in chronic renal failure (Figs 6.34 and 6.50).

The separation from acute renal failure is not always straightforward. Renal failure that clinically appears chronic may have acute changes in a biopsy specimen, and vice versa. There may also be acute disease superimposed on chronic disease. There may be hematuria, proteinuria that may be heavy enough to produce the nephrotic syndrome, and hypertension, which clinically may be in the accelerated phase. If the nephrotic syndrome is present, the biopsy specimen should be assessed in the way suggested in Chapter 6.

People with chronic renal failure come to medical attention in many ways, and may have no symptoms or only nonspecific symptoms, such as lassitude, nausea, and anorexia. Symptoms related to urination, such as pain on passing urine or difficulty of urination usually indicate a disorder of the lower urinary tract, not of the kidneys. Renal function is assessed by chemical tests, and chronic renal failure is often detected almost as an incidental finding.

After an amount of chronic damage that is different for each person, chronic renal failure becomes relentlessly progressive, even if the original cause is no longer active, and even if hypertension is controlled. One reason is that loss of some nephrons leads to increased functional activity and structural enlargement in remaining nephrons, which lead to irreversible damage in some of these, which in turn imposes an increased work load on surviving nephrons, and so on. This progresses to **end-stage renal failure**, when renal function is not enough to support life. Renal replacement therapy is then required, which means hemodialysis or peritoneal dialysis or renal transplantation.

A. J. Howie, *Handbook of Renal Biopsy Pathology.*

**Not every person with chronic renal failure is investigated by renal biopsy**. Several causes can be diagnosed clinically or radiologically, without the need for biopsy. In some centres, biopsy is rarely used to establish the diagnosis in chronic renal failure, if there are small kidneys with no clues to the cause, while in others, biopsy is used commonly.

Because the kidneys are often small in chronic renal failure, percutaneous needle biopsy is more difficult than in conditions with kidneys of normal size, and the specimen may not contain cortex. Provided that the specimen is suitable for analysis, there are always abnormalities in chronic renal failure. The pathologist should almost always be able to give information of help to nephrologists, and can often suggest the diagnosis.

## Assessment of Chronic Renal Failure

Nephrologists usually rely on measurement of **serum creatinine concentration** as an indicator of renal excretory function. This is crude and has a nonlinear relation with glomerular filtration rate, but is much cheaper and simpler than accurate measures of glomerular filtration rate. There may be a reduction of glomerular filtration rate to half the normal value while the serum creatinine concentration is in the normal range. In practice, the pathologist can understand a high serum creatinine concentration to be a sign of definite renal impairment, while a concentration in the normal range may still occur in the presence of a surprising amount of renal damage in a renal biopsy specimen (Fig. 5.5).

Accurate determination of glomerular filtration rate requires measurement of **clearance**, the amount of plasma that is cleared of a substance by excretion in the urine in an interval of time. The ideal substance for clearance measurements is completely filtered by glomeruli, and neither reabsorbed nor secreted by tubules. The pathologist should be aware that measurement of **creatinine clearance** can be unreliable as an indication of glomerular filtration rate, partly because creatinine is secreted by tubules, but mainly because this investigation requires collection of urine in a timed period. The collection is often incomplete, and this is the largest reason for error in calculations, giving an underestimate of creatinine excretion. The unreliability of reported creatinine clearances explains why a pathologist may see virtually normal kidney in a specimen from someone said to have renal impairment based on this investigation, although if the serum creatinine concentration is high, or if accurate tests of glomerular filtration rate show renal impairment, there will always be structural changes in the kidney. Glomerular filtration rate is often estimated rather than measured, using various formulas based on serum creatinine concentration and other factors such as age and body size.

## Stages of Chronic Kidney Disease

Because chronic renal failure is not all or none, meaning that the definition is arbitrary, **chronic kidney disease** is divided into stages to help clinical management. This classification is not so helpful to pathologists, but is given here to explain

the meaning of stages if numbers are written on request forms. These stages are based on measurements or estimates of the glomerular filtration rate, standardised to a body surface area of 1.73 $m^2$. Body surface area is calculated from a formula based on height and weight, and the reference area of 1.73 $m^2$ was derived from supposedly average adult height and weight. Standardisation allows the stages to be applied irrespective of age or body size, including in children.

1. **Stage one of chronic kidney disease** means a normal glomerular filtration rate, defined as over 90 ml/min/1.73 $m^2$, but with at least one of these features of renal disease: persistent proteinuria, persistent hematuria after exclusion of other causes, structural abnormality of the kidney shown by ultrasound examination, or a glomerular disorder shown by biopsy. Stage one is not renal failure, as conventionally defined.
2. **Stage two** is mild renal impairment, defined as a glomerular filtration rate of 60–90 ml/min/1.73 $m^2$, with at least one of the other features of renal disease.
3. **Stage three** is moderate renal impairment, with a glomerular filtration rate of 30–59 ml/min/1.73 $m^2$.
4. **Stage four** is severe impairment, with a glomerular filtration rate of 15–29 ml/min/1.73 $m^2$.
5. **Stage five** is established renal failure, meaning either the glomerular filtration rate is under 15 ml/min/1.73 $m^2$ or the person is on dialysis.

## Causes of Chronic Renal Failure

There are many causes of chronic renal failure, and these are different between the sexes, at different ages, and in different parts of the world. More males than females have chronic renal failure.

In **children**, the main causes are **developmental abnormalities** of the kidney, with malformation of the urinary tract. Abnormalities include renal agenesis, which means complete failure of development of a kidney, hypoplasia, which means that a kidney is small but otherwise normally formed, and dysplasia, which means abnormal, incomplete differentiation of part or all of a kidney. Dysplasia is almost always associated with other disorders of the urinary tract, such as duplex ureters, prenatal vesicoureteric reflux, and obstruction of the urinary tract, particularly by posterior urethral valves in boys. Among other causes of chronic renal failure in children are glomerular disorders, reflux nephropathy, metabolic conditions such as cystinosis and hyperoxaluria, and cystic disorders, particularly juvenile nephronophthisis, which is pronounced *nefro-no-ff-thigh-siss* or *nefro-no-thigh-siss*, and is a group of disorders similar to medullary cystic disease. Phthisis comes from a Greek word meaning wasting away or decay.

In **adults**, the commonest cause is **diabetes mellitus**. Hypertensive renal damage or hypertensive nephrosclerosis is often used as a diagnosis in a person with hypertension, small symmetrical kidneys, chronic renal failure, and no other obvious cause. Many other conditions can cause chronic renal failure, such as nondiabetic

glomerular disorders, reflux nephropathy, autosomal dominant polycystic kidney disease, ischemia from atherosclerosis of the aorta and renal arteries, collectively called renovascular disease, and obstruction of the urinary tract. In some countries, analgesic nephropathy and tuberculosis of the urinary tract are common, and there are parts of the world where there are characteristic disorders associated with chronic renal failure, such as the endemic nephropathy of the Balkans.

## Value of a Renal Biopsy in Chronic Renal Failure

The loss of nephrons is irreversible, and in theory every person with chronic renal failure, if they live long enough, will eventually need renal replacement therapy. There is no treatment at present that will regenerate nephrons after atrophy, although there are ways to slow down the rate of progression of chronic renal failure, such as by control of hypertension. Accordingly, some nephrologists think that a biopsy will give little or no information of any use, and that this does not justify the difficulties associated with the procedure.

Renal biopsy may be justified in chronic renal failure for these reasons:

1. The specimen may show a reversible and treatable condition, with predominantly acute tubular damage, rather than tubular atrophy. A combination of acute and chronic changes may also be seen, which means that there could be an improvement in renal function.
2. Even though the specimen usually confirms established chronic damage in the kidney, knowledge of the diagnosis may help in clinical decisions, such as need for further investigations, study of relatives, and selection of renal replacement therapy. Some conditions commonly recur in renal allografts, and the knowledge that there is such a condition may influence management.
3. The specimen may allow the pathologist to give an indication of the prognosis, meaning how long the kidney will function without the need for replacement therapy. This is because there is a statistical relation between the amount of chronic damage at biopsy and the length of survival of renal function.

## Findings in Renal Biopsy Specimens in Chronic Renal Failure

Although there are many explanations of chronic renal failure, only a few conditions are seen commonly in biopsy specimens.

In **adults**, many specimens show evidence of chronic renal damage due to something other than a glomerular disorder. Most of the rest have IgA nephropathy, various segmental sclerosing glomerular conditions, or diabetic glomerulopathy.

In biopsy specimens in **children**, many have evidence of a nonglomerular disorder, often familial.

## Assessment of Renal Biopsy Specimens in Chronic Renal Failure

Chronic renal failure is more likely than other indications for renal biopsy to have more than one disease process or type of abnormality in the kidney.

The general rule is that **renal function is more closely correlated with structural changes in tubules than with any other changes. Chronic renal failure is associated with chronic abnormalities in tubules.**

The pathologist should first determine that most or all of the tubular damage is chronic, which means that the clinical problem is indeed chronic renal failure, rather than acute. This is important because chronic damage will not get better, and its associated renal impairment will not reverse to give normal function, but acute damage and acute renal impairment may recover to normal.

Chronic damage is detected as various combinations of reduced number of tubules, shrunken tubules, thickening of tubular basement membranes, thyroidization, which means more marked dilatation of tubules and more marked flattening of tubular epithelium than seen in acute tubular damage, and cysts, although the distinction between dilated tubules and cysts is arbitrary. These tubular changes may be accompanied by interstitial fibrosis, an interstitial infiltrate of chronic inflammatory cells, global sclerosis of glomeruli, and chronic intimal thickening in small arteries. Surviving tubules may be larger than normal, and may have acute damage if there is an acute deterioration of renal function in someone with chronic renal failure (Figs 5.2, 5.3, 5.12, and 5.14).

If the number of tubules without atrophy appears appropriate for the age of the person biopsied, the problem is acute rather than chronic, and the specimen should be analysed in the way suggested in Chapter 7.

The next stage of assessment is to see if there is evidence of a glomerular disorder. This is unlikely if there is no proteinuria and no hematuria. Proteinuria below the nephrotic range and hematuria may occur in disorders that are not primarily of glomeruli, but proteinuria in the nephrotic range almost always indicates a glomerular disorder that is the explanation of the chronic renal failure.

### *Is There a Glomerular Disorder?*

Two common glomerular disorders in chronic renal failure are straightforward to diagnose. These are IgA nephropathy and diabetic glomerulopathy.

**IgA nephropathy** has mesangial increase that may differ in extent between glomeruli (Fig. 8.1). There is IgA deposition on immunohistologic study, and IgA may still be seen in glomeruli with global sclerosis (Fig. 8.2).

**Diabetic glomerulopathy** has a history of diabetes mellitus given on the request form, and several features such as mesangial increase with Kimmelstiel-Wilson nodules and thickened glomerular basement membranes (Figs 6.34–6.44).

**Segmental sclerosing glomerular conditions** are usually easy to see in renal biopsy specimens in chronic renal failure, but interpretation of their significance

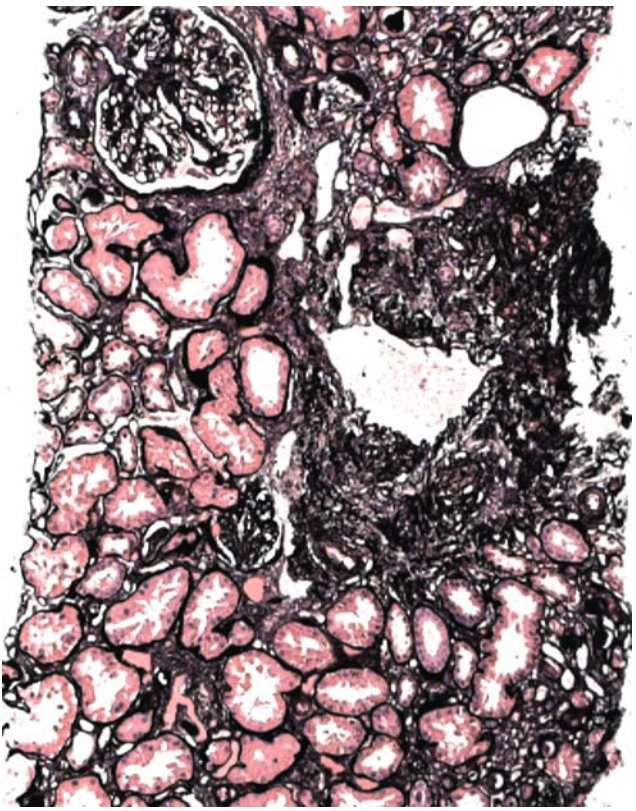

**Fig. 8.1** Cortex in a renal biopsy specimen from a man of 62 with chronic renal failure, hematuria, proteinuria, and hypertension. There is patchy tubular atrophy. A glomerulus has mesangial increase. Immunohistologic study shows mesangial deposition of IgA, and gives the diagnosis of IgA nephropathy

is difficult. These are often considered to be one condition called focal segmental glomerulosclerosis, but this is not helpful to nephrologists because the term is applied to several different disorders. The pathologist may be able to give a more precise diagnosis of more use in prognosis and management.

Late stages of nearly every glomerular disorder and nonglomerular disorder may be complicated by the development of segmental areas of sclerosis in glomeruli. If the glomerular disorder can be recognised, **this should be given as the diagnosis**. Some texts say that focal segmental glomerulosclerosis can occur in IgA nephropathy, membranous nephropathy, diabetic glomerulopathy, and so on. This is an example of the lack of precision of the term focal segmental glomerulosclerosis. A better approach is to give the diagnosis as late IgA nephropathy or late membranous nephropathy, or a late stage of whatever other condition can be recognised.

Segmental abnormalities are often automatically considered focal and segmental, although they may not be focal but diffuse, which means present in every

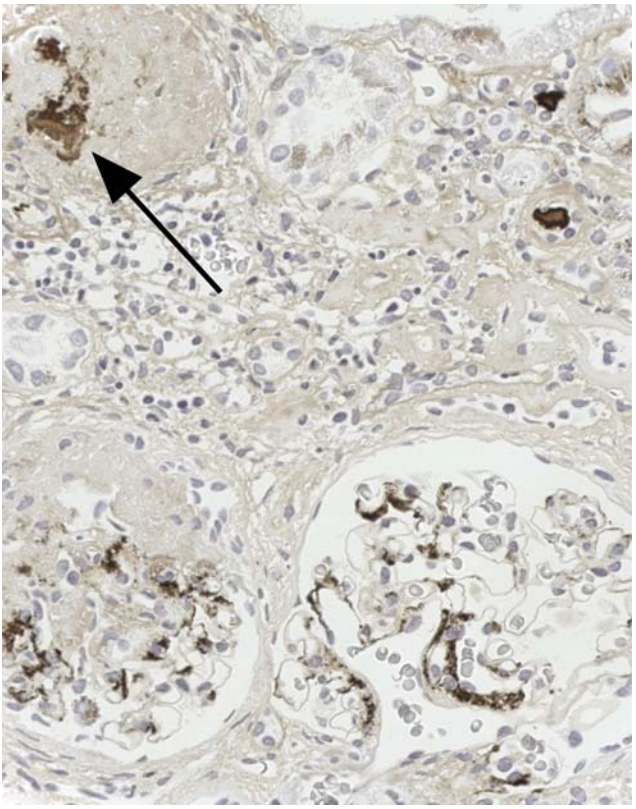

**Fig. 8.2** Cortex in a renal biopsy specimen from a man of 49 with chronic renal failure, hematuria, proteinuria, and hypertension. An immunoperoxidase method to detect IgA shows deposition of IgA in the mesangium of surviving glomeruli, and also in a glomerulus with global sclerosis (arrowed). The diagnosis is IgA nephropathy

glomerulus, even though this may not be apparent on a single section or on a few random sections. A value of serial sections is that they help the pathologist to find segmental lesions, because just one lesion in a specimen may make a significant difference to the diagnosis, and because the proportion of glomeruli that contain segmental lesions may also influence the diagnosis.

## Differentiation of Types of Segmental Sclerosing Glomerular Disorders

In a biopsy specimen in chronic renal failure, a segmental sclerosing glomerular condition may be either a consequence of reduced number of glomeruli or a marker of an underlying glomerular disorder. Differentiation between these possibilities may be difficult, but should be attempted.

**Reduced number of glomeruli** is an equivalent term to reduced renal mass or reduced nephron number. Reduced renal mass can be understood to mean that the number of nephrons is ultimately inadequate to maintain a glomerular filtration rate appropriate for the size of the body, although there may be increases in size and function of surviving nephrons to compensate for a time.

The reduction could be congenital, in which too few nephrons were formed in the fetal kidney, or acquired, following any cause of loss of nephrons. A congenitally small kidney with compensatory enlargement of glomeruli is sometimes said to show **oligomeganephronia**, or oligomeganephronic hypoplasia, in which the components oligo, mega, hypo, and plasia come from Greek words meaning few, big, under, and forming or moulding. Only the most marked examples of this are likely to be recognised, and lesser degrees of inadequate formation of nephrons are usually too subtle to be detected. **Severe obesity** can be considered a cause of relatively reduced renal mass, which is disproportionately small compared with the body mass.

Effects of reduced renal mass are called glomerular overload, or hyperfiltration, or hyperperfusion. Surviving glomeruli enlarge, which may stretch and damage visceral epithelial cells. This may lead to proteinuria, loss of visceral epithelial cells, adhesion of the glomerular tuft to Bowman's capsule, development of areas of segmental sclerosis, and eventual global sclerosis of glomeruli with atrophy of their tubules.

There are clues that a segmental sclerosing condition may be explained by reduced glomerular number. There may be more extensive global sclerosis of glomeruli and tubular atrophy than expected for the age of the person biopsied, usually with ischemic shrinkage of the tuft and wrinkled basement membranes in some surviving glomeruli, the worst affected of which have thickening of the inner aspect of Bowman's capsule. Other glomeruli appear large (Fig. 5.11). Surviving tubules are also enlarged. The sclerosed areas in glomeruli are often at the hilum of glomeruli, although why they usually have this distribution is unclear (Figs 5.13 and 8.3). Sometimes, the pathologist can suggest that there are overload effects even when there are no segmental lesions, but the other features are well marked.

Usually, the segmental sclerosis in **overload changes** is **genuinely or truly focal**, meaning that not every glomerulus is affected. This is stressed, because some conditions called focal segmental glomerulosclerosis are actually **diffuse** disorders, affecting every glomerulus.

Segmental lesions at the hilum correspond with the perihilar variant of focal segmental glomerulosclerosis in the Columbia classification.

If the pathologist suspects that there are changes consistent with reduced glomerular number, there may be clinical evidence of reduced renal mass, possibly even a single kidney or relatively reduced renal mass in obesity. As well as chronic renal failure, there should be proteinuria, which occasionally is in the nephrotic range, although without the other features of the nephrotic syndrome. Glomerular overload effects are not considered an adequate explanation of the nephrotic syndrome, and if this is found, there should be another diagnosis, most likely a late stage of classic segmental sclerosing glomerulonephritis (Figs 6.27 and 6.28).

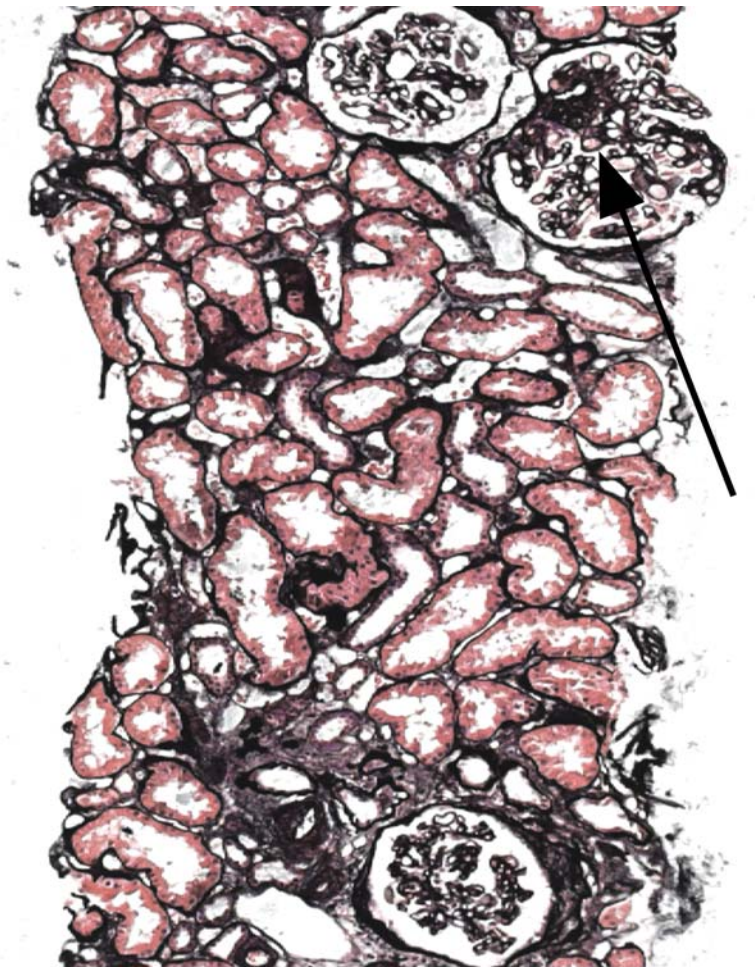

**Fig. 8.3** Cortex in a renal biopsy specimen from a man of 38 with chronic renal failure, proteinuria, and asymmetrical kidneys. There had been denervation of the bladder in a road traffic collision, several years before the biopsy. This specimen from the larger kidney shows patchy tubular atrophy, glomeruli with ischemic shrinkage, enlargement of tubules and another glomerulus, and an area of sclerosis at the hilum of the large glomerulus (arrowed). These changes are interpreted to be effects of reduced glomerular numbers, following chronic damage from drainage problems, which particularly affected the other kidney

Even if there are apparently two kidneys of normal size on clinical investigation, the finding of the typical changes of overload effects should be reported as consistent with reduced nephron number. Many examples of segmental sclerosing glomerular lesions in so-called hypertensive nephrosclerosis are probably explained by reduced renal mass (Fig. 8.4).

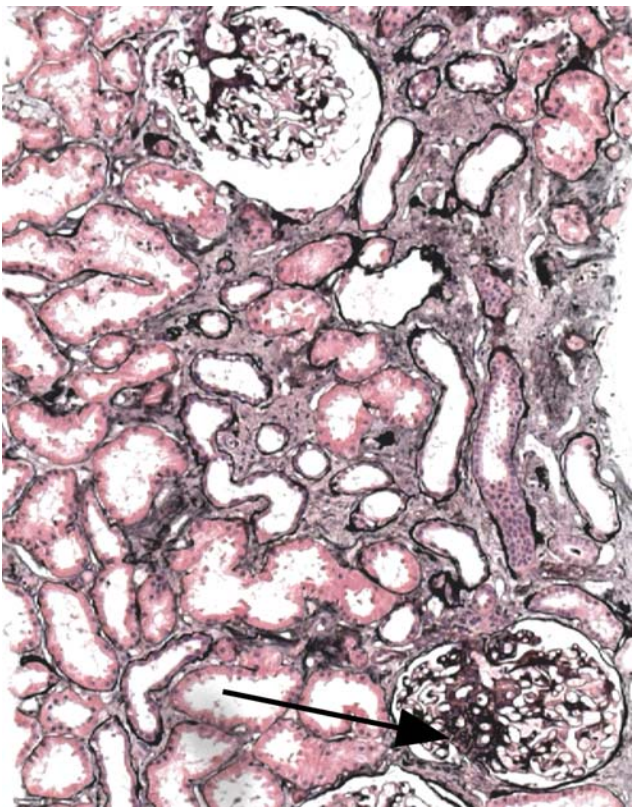

**Fig. 8.4** Cortex in a renal biopsy specimen from a woman of 67 with apparently normal renal function, proteinuria, and hypertension. There are early atrophic changes in tubules, which suggest there is renal impairment. One glomerulus has an area of sclerosis (arrowed). The diagnosis could be given as a truly focal segmental sclerosing disorder, possibly even hypertensive nephrosclerosis, but glomeruli and tubules appear large, and there is a likelihood that this is due to reduced renal mass

A practical problem is the finding of a segmental sclerosing lesion that is not at the glomerular hilum, in a biopsy specimen in which there is no identifiable glomerular disorder such as IgA nephropathy, glomeruli are not markedly enlarged, and there is little evidence of chronic damage in the form of global sclerosis of glomeruli and tubular atrophy. The separation of this type of abnormality from overload changes is arbitrary, and probably many if not all examples of this are early or mild forms of overload changes.

This condition may be called a **truly** or **genuinely focal segmental sclerosing disorder** to avoid the ambiguity of the term focal segmental glomerulosclerosis (Figs 8.4 and 8.5). This is a condition in which only one segmental lesion has to be found to suggest the diagnosis. Proteinuria below the nephrotic range is usually a feature of a truly focal segmental sclerosing disorder.

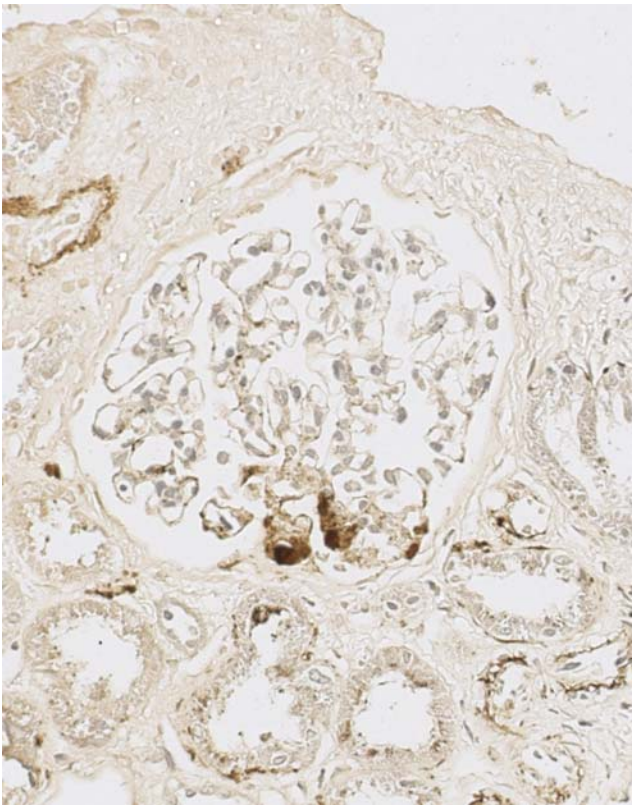

**Fig. 8.5** Glomerulus in a renal biopsy specimen from a woman of 37 with proteinuria. An immunoperoxidase method to detect C9 shows deposition in a segmental lesion. This glomerulus and the rest appear slightly large, but otherwise normal. The diagnosis can be given as a truly focal segmental sclerosing disorder

If every glomerulus or nearly every glomerulus has segmental sclerosis, the condition is not focal but diffuse. In such circumstances there is likely to be a story of the nephrotic syndrome at some time, and the diagnosis can be given as a **late classic segmental sclerosing condition** (Figs 6.27 and 6.28). This is important to recognise because this type of disorder may recur in a renal allograft, although the segmental sclerosing disorder associated with reduced glomerular number does not recur, nor do truly focal segmental sclerosing disorders.

Occasionally, there is evidence of a segmental sclerosing condition, but the specimen is so small or the changes are so late that the pathologist can only report a segmental sclerosing glomerular condition of undetermined significance. Even this is more helpful to nephrologists than the vague term focal segmental glomerulosclerosis.

## Differential Diagnosis of Overload Changes in Glomeruli

Strikingly large glomeruli are rarely seen except when there is reduced glomerular number. One condition that can be associated with uniformly large glomeruli is **chronic hypoxia**. The pathologist is given the information on the request form that the person biopsied has a congenital heart disorder with cyanosis due to a right to left shunt, or a chronic lung disease with hypoxia, or sleep apnea (Fig. 8.6). There is also mesangial expansion that is most marked at the glomerular hilum. The uniformity of the enlargement and relatively little tubular atrophy support the diagnosis of hypoxic changes in glomeruli, and are against a diagnosis of overload effects.

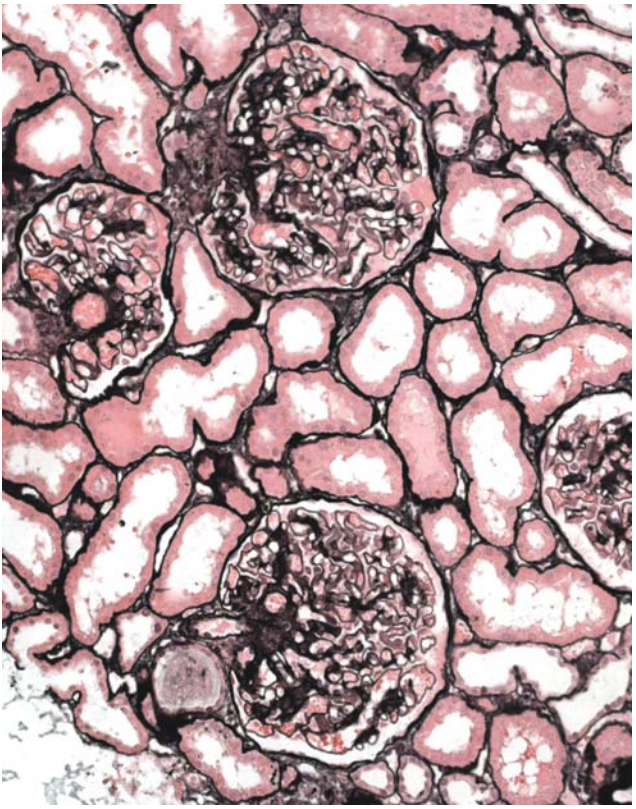

**Fig. 8.6** Cortex in a renal biopsy specimen from a man of 34 with chronic renal failure, proteinuria, and sleep apnea. All glomeruli appear large with expanded mesangium, particularly at the hilum. These are hypoxic changes in glomeruli

## *Is There Evidence of a Glomerular Disorder Other than IgA Nephropathy, Diabetic Glomerulopathy, or a Segmental Sclerosing Condition?*

Renal biopsy specimens in chronic renal failure may have evidence of late stages of glomerular abnormalities, such as vasculitic glomerulonephritis (Figs 7.15 and 7.16), amyloid (Fig. 6.49), subendothelial membranoproliferative glomerulonephritis (Fig. 6.80), membranous nephropathy (Fig. 6.2), or lupus nephritis (Figs 6.52 and 6.57).

Interpretation is made simpler if there was an earlier biopsy specimen from the same person that had established the diagnosis. A later specimen may show another disease, or a coincidental disorder, or a complication of treatment, rather than just a later stage of the initial condition.

If there is no previous specimen, the pathologist should examine glomeruli without global sclerosis and without much segmental sclerosis to see if there are any features of identifiable disorders.

**Irradiation** damages the kidney and leads to chronic renal failure. There are glomerular abnormalities that resemble subendothelial membranoproliferative glomerulonephritis with doubled basement membranes, although the mesangium may show disruption that is called mesangiolysis, rather than expansion, and few or no immune deposits are found on immunohistologic study (Fig. 8.7). Generally, tubules have severe atrophy. Blood vessels have chronic changes, and they may also show a small vessel vasculopathy, also called thrombotic microangiopathy.

A few rare inherited disorders may give chronic renal failure, and some have characteristic changes in glomeruli. An example is **Fabry's disease**, in which there is lack of a lysosomal enzyme alpha galactosidase A. This has distinctive features in the kidney (Fig. 8.8). **Lecithin cholesterol acyl transferase deficiency** is a condition in which lipid deposits accumulate in glomerular basement membranes to give an irregularly vacuolated appearance. Another inherited disorder is **hereditary nephropathy of Alport type**, which requires electron microscopy to make the diagnosis. This is considered in Chapter 9, because the typical presentation is with hematuria.

## *Is There No Evidence of a Glomerular Disorder?*

If glomeruli appear normal or have only ischemic changes, there is likely to be a nonglomerular disorder, or a combination of such disorders, to explain chronic renal failure. These types of disorder should also underlie glomerular changes ascribed to effects of reduced glomerular number.

Such disorders include these:

1. Chronic ischemic damage, including effects of hypertension.
2. Problems with urinary drainage, meaning obstruction of the urinary tract and reflux of urine into the kidney.

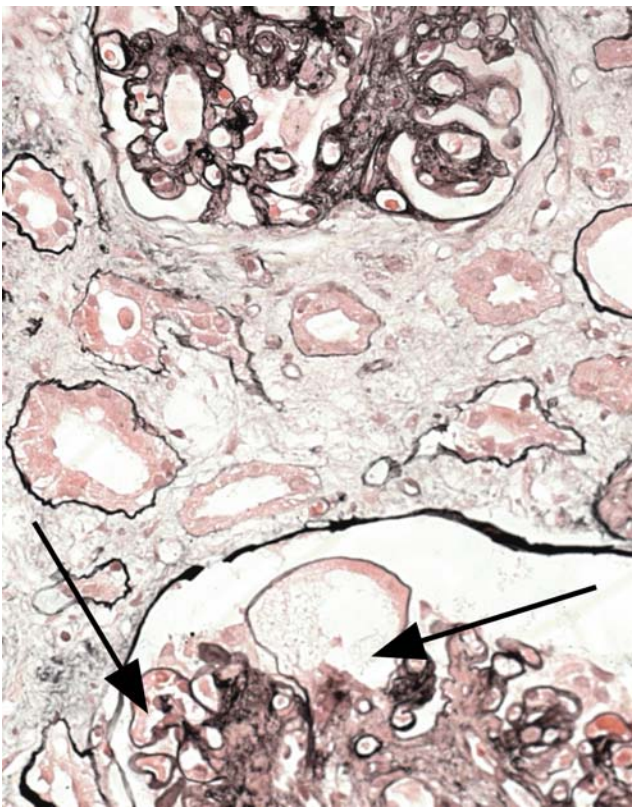

**Fig. 8.7** Glomeruli in a renal biopsy specimen from a man of 42 with chronic renal failure, hematuria, proteinuria, and hypertension, and a history of abdominal irradiation for Hodgkin's disease, 17 years before the renal biopsy. In one glomerulus, basement membranes are doubled, and in the other, the mesangium appears to have shrunk or disappeared in several areas (arrowed). These are features of irradiation nephropathy

3. Problems in the renal medulla, such as gout, papillary necrosis, and the inherited disorders juvenile nephronophthisis and medullary cystic disease. These can be regarded as intrarenal causes of drainage problems.
4. Other cystic diseases.
5. Tubular disorders, such as damage from toxins, paraproteins, or crystals.
6. Late stages of interstitial nephritis, including granulomatous disorders.

Few specimens have features characteristic of only one condition, but many have features suggestive of either a likely explanation of chronic renal failure, or a likely combination of explanations.

Frequently, all late renal damage is labelled chronic tubulo-interstitial nephritis or chronic interstitial nephritis. These names are not helpful because nearly all diseases lead eventually to similar appearances in the kidney. This was recognised by Ellis in 1942: "Chronic interstitial nephritis is merely the end stage of various forms of

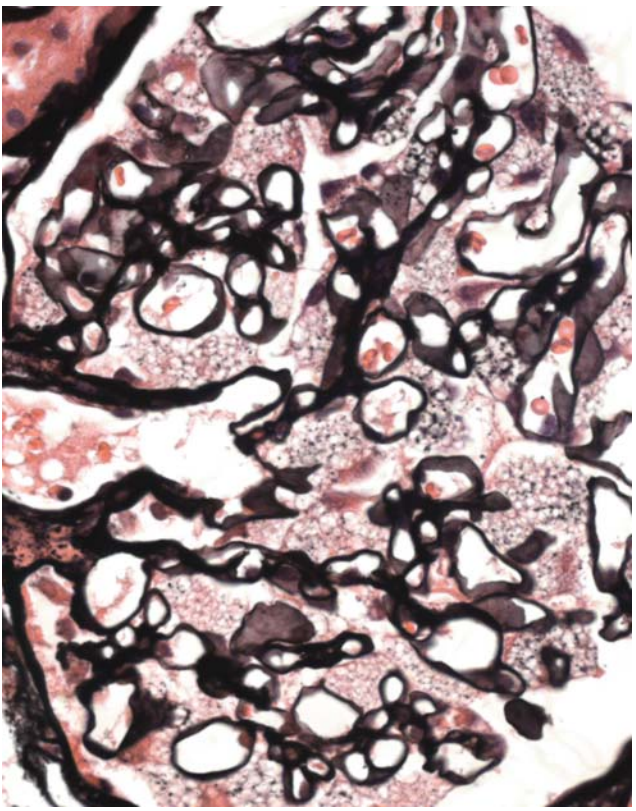

**Fig. 8.8** Glomerulus in a renal biopsy specimen from a man of 28 with chronic renal failure, hematuria, and proteinuria. His mother was on hemodialysis. Visceral epithelial cells have finely vacuolated cytoplasm characteristic of Fabry's disease. Johannes Fabry (1860–1930), pronounced *fah-bree*, was a German dermatologist who described the skin changes of this condition in 1898. Sometimes, the name Anderson Fabry disease is used. William Anderson (1842–1900), pronounced in the usual way, independently described the skin changes also in 1898, when he was a dermatologist in London, United Kingdom

renal disorder, and for a proper understanding of Bright's disease this term should be discarded" (Fig. 6.34).

If possible, the pathologist should try to find clues to the explanation of late damage. Sometimes, the diagnosis can only be given as late nonglomerulonephritic renal damage, but even that is helpful to nephrologists (Fig. 8.9). The various possible explanations of such damage may be considered in turn.

## *Is There Evidence of Chronic Ischemic Damage?*

**Chronic ischemic damage**, including hypertensive damage, as the explanation of chronic renal failure, is suggested by changes in glomeruli, tubules, and blood

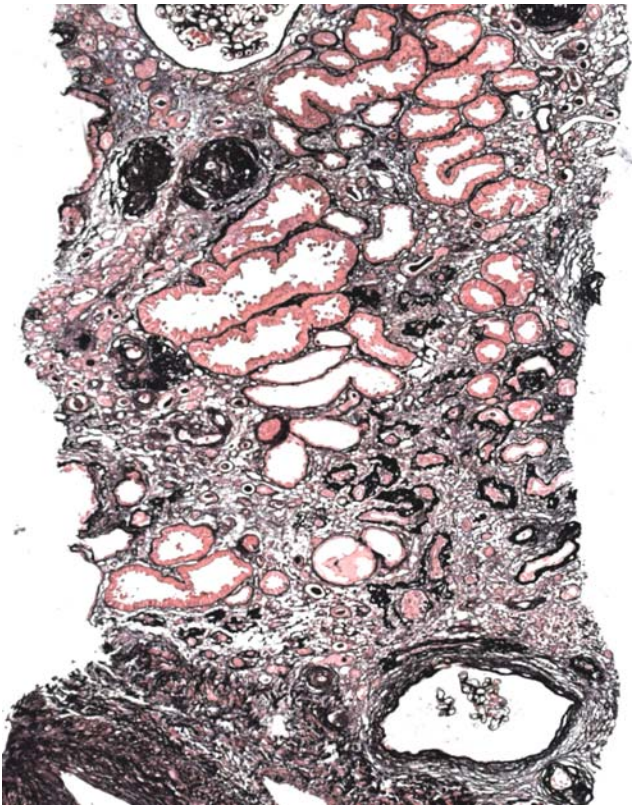

**Fig. 8.9** Cortex in a renal biopsy specimen from a woman of 37 with chronic renal failure, small symmetrical kidneys, hypertension for a few years, and recent urinary tract infection. There is severe chronic damage, without evidence of a glomerulonephritic disorder. Otherwise, no clue to the cause is seen

vessels, and by a lack of other identifiable abnormalities. Almost all renal biopsy specimens from middle aged and old people have evidence of chronic ischemic damage, and this may not be the only explanation of chronic renal failure. Clinical clues that there may be more extensive chronic ischemic damage than expected from the age of the person biopsied include evidence of hypertension, renal artery stenosis, asymmetrical kidneys, ischemia of the legs called peripheral vascular disease, and other features of atherosclerosis, such as myocardial infarction or stroke.

Glomeruli show either ischemic changes only, or features consistent with effects of reduced glomerular number, including segmentally sclerosed areas (Figs 5.9, 5.12, and 8.4). Tubules show atrophy with fibrosis and a light infiltrate of lymphocytes (Figs 5.5, 7.1, and 7.48). Blood vessels may show only the changes likely to be seen in most specimens in chronic renal failure with intimal fibroelastic thickening in arteries and hyaline arteriolosclerosis (Figs 5.14 and 5.15).

These changes are seen in so-called hypertensive nephrosclerosis. Problems with this diagnosis are discussed in Chapter 5, and are summarised here. Undoubtedly, hypertension causes ischemia of the kidney, and produces chronic ischemic changes. What is unclear is the cause of essential hypertension, and whether such hypertension damages a previously normal kidney, or develops as a consequence of an underlying renal disorder, such as a congenitally reduced number of nephrons. Almost all conditions that affect the kidney produce hypertension, and hypertension causes chronic renal damage, which perpetuates the hypertension. This is a mechanism that contributes to the progression of chronic renal failure.

Other changes seen in blood vessels may be loose, concentric, mucoid intimal thickening in small arteries and fibrinoid necrosis of arterioles with the appearance of a small vessel vasculopathy, also called thrombotic microangiopathy (Figs 7.49 and 7.51). There may be evidence of atherosclerotic or thrombotic embolism in arteries with cholesterol clefts in vessels, where fat has been removed during processing of the specimen (Fig. 7.10).

These features can be associated with signs of other things. Changes of small vessel vasculopathy, also called thrombotic microangiopathy, consistent with accelerated hypertension, may occur in IgA nephropathy. Identical vascular changes are found in scleroderma and related conditions, and in some examples of hemolytic uremic syndrome. Atherosclerotic embolism is common in association with diabetic glomerulopathy.

## *Is There Evidence of a Disorder of Urinary Drainage?*

**Problems with urinary drainage** can be impossible to diagnose on a biopsy specimen, but there may be clues.

Pus in tubules seen as clusters of living and dead neutrophil polymorphs in the lumen, often with similar cells in tubular epithelium and around tubules, is a strong sign of ascending infection, also called **acute pyelonephritis** (Fig. 7.36). This sign may be seen in any renal condition, and the pathologist should suggest that there is ascending infection as well as the other condition.

Sometimes, clusters of various inflammatory cells are found within tubules when there is an interstitial inflammatory infiltrate, as in acute interstitial nephritis (Figs 7.34 and 7.35). If the pathologist cannot be sure if these clusters are pus or not, a sensible course is to suggest the possibility of ascending infection. Renal biopsy is not usually done if there is clinical evidence of ascending infection, but sometimes this may be impossible to exclude, for instance if there is no urine output.

**Reflux nephropathy**, also called **chronic pyelonephritis**, is suggested by coarse areas of chronic damage to the kidney, with a dense infiltrate of lymphocytes, thyroidization of tubules, sometimes the presence of lymphoid polyps in tubules, and signs of ascending infection (Figs 5.3 and 8.10). Not all these features may be present, and there may not be enough evidence of them to allow the pathologist to make a confident diagnosis. Granulomas containing giant cells in a specimen with these other features suggest tuberculous pyelonephritis (Fig. 8.11).

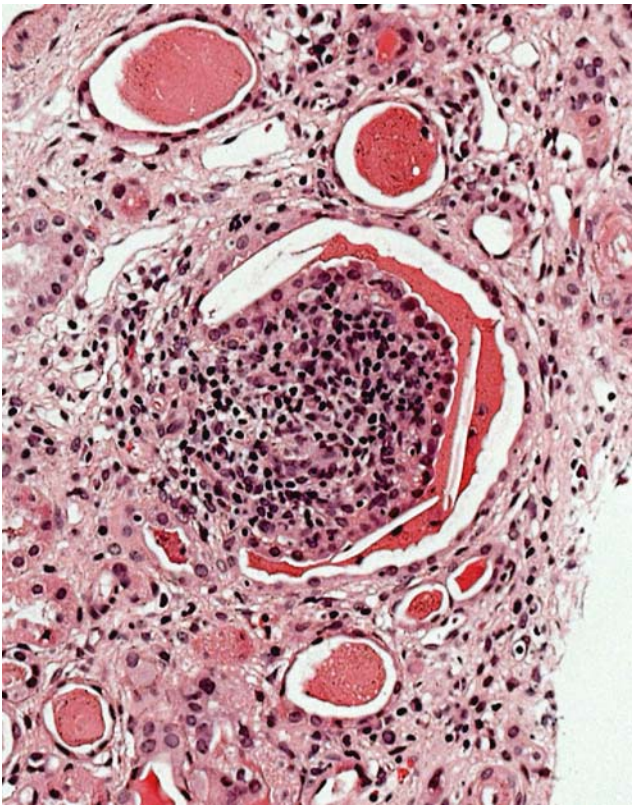

**Fig. 8.10** Cortex in a renal biopsy specimen from a man of 31 with chronic renal failure, proteinuria, and HIV infection. A tubule contains a lymphoid polyp consistent with reflux nephropathy

**Obstruction of drainage** of the kidney will produce **hydronephrosis** if present for long enough. Obstruction is usually diagnosed by methods other than biopsy, and may be difficult to diagnose with certainty on a biopsy specimen unless the biopsy specimen includes medulla showing thinning (Figs 5.2 and 8.12).

## *Is There Evidence of a Medullary Disorder?*

Hundreds of nephrons drain into only a few terminal collecting ducts. This means that the medulla is a funnel into which the cortex drains. A small amount of damage in the medulla can have extensive effects in the cortex.

Features of late nonglomerulonephritic damage in the cortex may be due to a **medullary** lesion (Fig. 8.13). This is rarely confirmed or excluded by a biopsy specimen, but by chance a specimen may contain evidence of a medullary lesion.

**Urate deposition** is seen as spaces from which crystals have been removed, surrounded by chronic inflammatory cells (Fig. 4.7). Urate deposition could be a sign of gouty nephropathy, but is more likely to be coincidental in another condition.

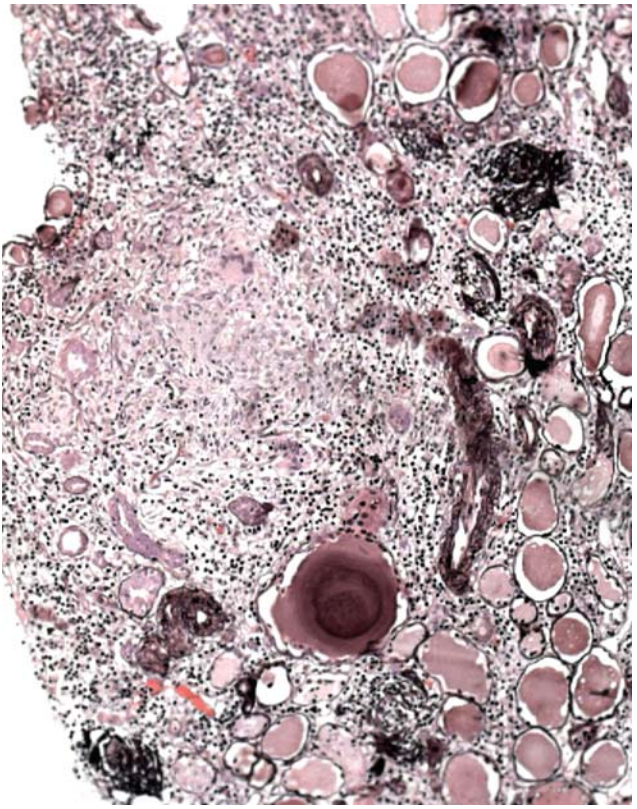

**Fig. 8.11** Cortex in a renal biopsy specimen from a man of 41 with chronic renal failure, hematuria, proteinuria, and hypertension. There is chronic damage with extensive thyroidization of tubules. In the chronic inflammatory infiltrate, there are granulomas that contain giant cells. These features suggest tuberculous pyelonephritis

**Papillary necrosis** is seen as ghostly areas that are poorly stained, often with a rim of inflammatory cells at the junction with viable tissues (Fig. 8.14). Papillary necrosis is a powerful feature because it gives the diagnosis. One cause is use of analgesic drugs when the condition is called analgesic nephropathy. Other causes are sickle cell disease, arteritis, and severe acute pyelonephritis, especially if there is diabetes mellitus.

Changes apart from papillary necrosis in **sickle cell disease** include the pattern of subendothelial membranoproliferative glomerulonephritis without immune deposits, segmental sclerosing glomerular lesions, which may be due to reduced nephron numbers, tubular atrophy, and iron deposition in tubules as a result of hemolysis (Fig. 8.15). Sickle cell trait can give similar but milder changes.

**Cysts** may be seen at the corticomedullary junction and in the medulla, and could indicate juvenile nephronophthisis or medullary cystic disease (Fig. 8.16). These are

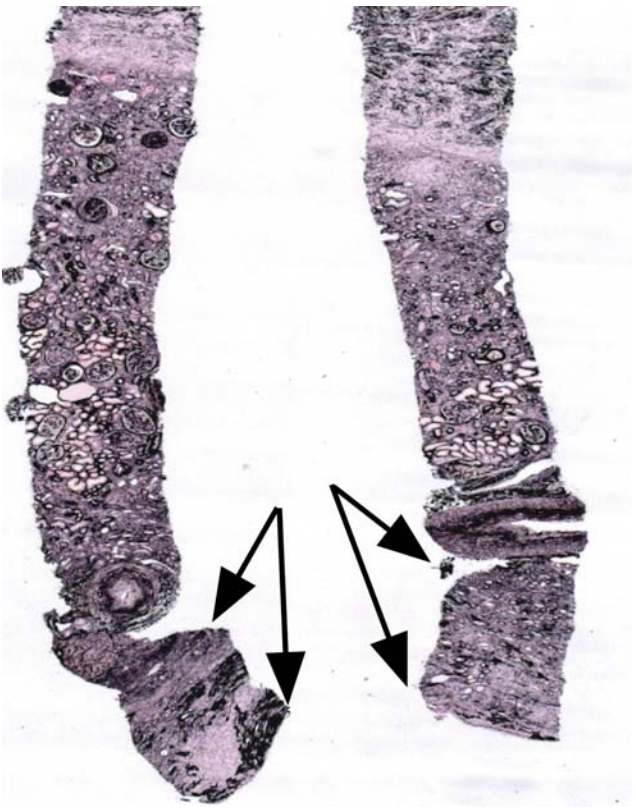

**Fig. 8.12** A renal biopsy specimen from a woman of 66 with chronic renal failure, progressive fibrosis around the aorta, and fibrosis in the pleura, peritoneum, and elsewhere. The other kidney was known to have blockage of the ureter, but the biopsied kidney appeared nearly normal on imaging. The two pieces include perirenal tissues and full thickness of the cortex and medulla. There is retroperitoneal fibrosis with thinned cortex, which has areas of chronic damage. The medulla, between both sets of arrows, is severely thinned. This shows there is hydronephrosis, presumed to be due to ureteric obstruction from retroperitoneal fibrosis

inherited disorders with similar structural findings, but with several different genetic abnormalities.

**Nephronophthisis** is a group of autosomal recessive disorders of nephrocystin proteins, and the renal disease is often associated with abnormalities of other organs. Although nephronophthisis is traditionally considered a cystic disorder, there may be few or no cysts. Tubular basement membrane abnormalities are described in nephronophthisis, including thickening, thinning, and splitting to give a laminated appearance, but similar changes may be seen in areas of tubular atrophy in many other conditions.

**Medullary cystic disease** has autosomal dominant inheritance, and presents later in life than nephronophthisis, usually in young adults. One form of this condition may be the same as familial juvenile hyperuricemic nephropathy, which is

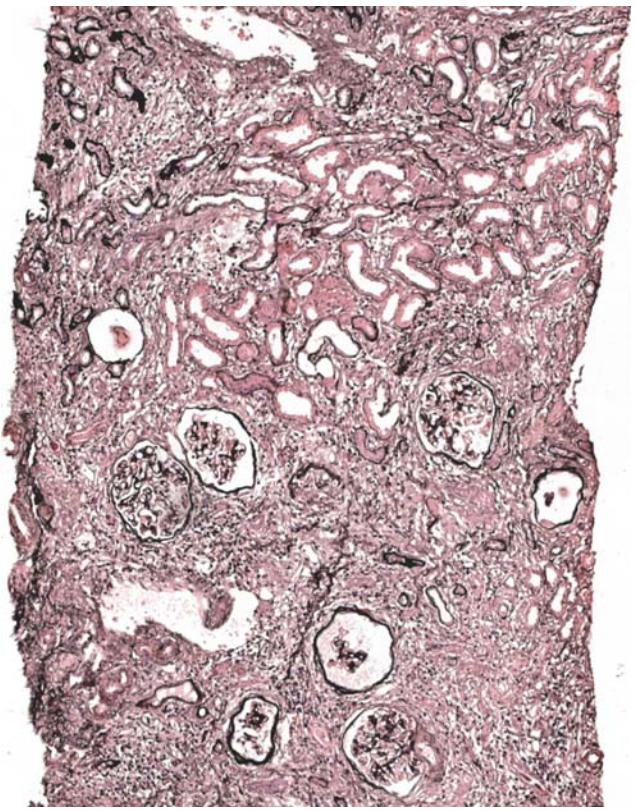

**Fig. 8.13** Cortex in a renal biopsy specimen from a woman of 64 with chronic renal failure. There is severe chronic damage without evidence of a glomerular disorder, but otherwise without clues to the cause. There was no medulla in this specimen. A renal biopsy specimen taken in another country a few months before this specimen was reviewed. This contained medulla, which showed acute papillary necrosis, later attributed to nonsteroidal anti-inflammatory drugs. The cortical damage seen in this figure is a late consequence of papillary necrosis

associated with mutations in the gene for Tamm-Horsfall protein, also called uromodulin in this context. Medullary cystic disease is not the same as **medullary sponge kidney**, in which there are dilated collecting ducts towards the tip of papillae. If there are no complications of these dilated ducts, which predispose to formation of stones, the kidney should be otherwise normal in medullary sponge kidney.

## *Is There Evidence of a Cystic Disorder in the Cortex?*

**Cysts** may be seen in the cortex (Fig. 8.17). Their significance is often difficult to determine. Any late renal disease may have cysts, sometimes called simple, although their pathogenesis is likely to be complicated rather than simple.

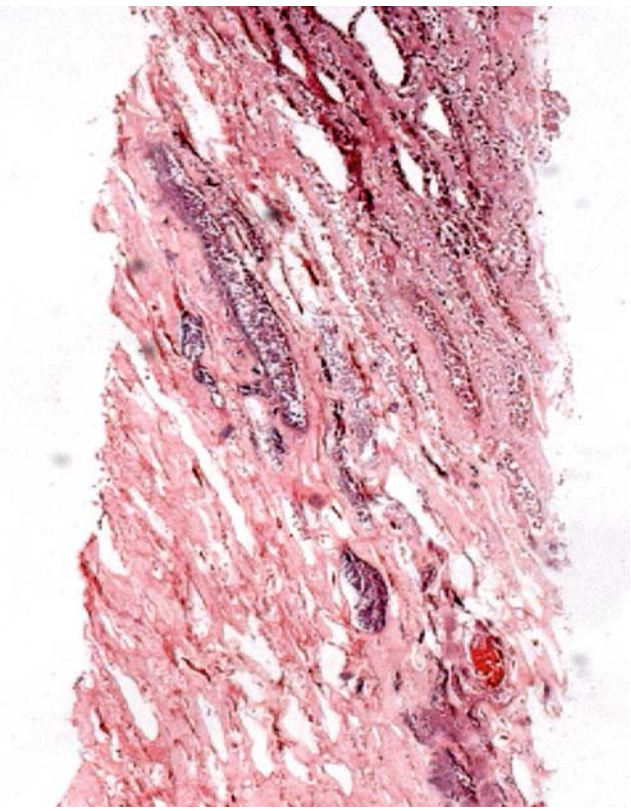

**Fig. 8.14** Medulla in a renal biopsy specimen from a man of 68 with chronic renal failure that rapidly worsened over a short time, insulin resistant or type two diabetes mellitus for 20 years, and recent urinary tract infection. There is acute papillary necrosis

**Autosomal dominant polycystic kidney disease** rarely requires a renal biopsy to be diagnosed, because the disease is usually apparent on other investigations, but biopsy may be done in a young person before the diagnosis is made in other ways. This condition shows cysts of various sizes in all parts of the nephron, including glomeruli. Disorders of more than one gene give similar clinical features, and a polycystin protein is abnormal in each.

**Autosomal recessive infantile polycystic kidney disease** may be seen in a biopsy specimen as dilated collecting ducts that appear tubular, rather than rounded and truly cystic. The abnormal protein is fibrocystin. This, like polycystins and several other proteins that are abnormal in inherited cystic diseases of the kidney, is important in the structure and function of the centrosome and cilium in tubular cells.

Glomerular cysts may indicate familial **glomerulocystic disorders**.

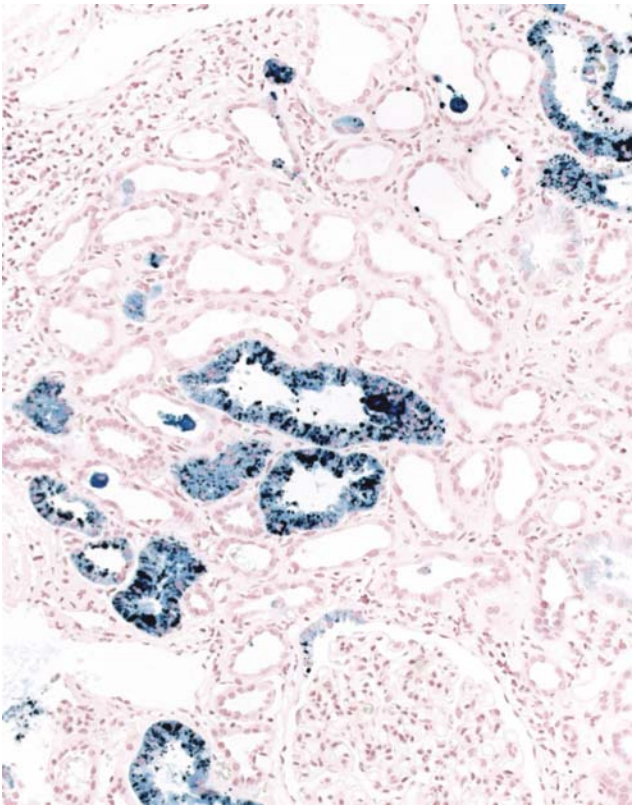

**Fig. 8.15** Cortex in a renal biopsy specimen from a man of 19 with chronic renal failure, the nephrotic syndrome, and sickle cell disease. Perls' Prussian blue stain shows deposition of iron in tubular cells. The glomerular disorder that accounts for the nephrotic syndrome has the pattern of subendothelial membranoproliferative glomerulonephritis. These findings are complications of sickle cell disease

## *Is There Evidence of a Tubular Disorder?*

**Paraproteinemias** may have several effects on the kidney, although they may have none at all, because paraproteins are common in the elderly, and may be coincidental with any other renal disorder.

The commonest effect they have is tubular damage as a result of consequences of filtered light chains, which is called **myeloma kidney** or **light chain cast nephropathy** or similar names. This is easy to detect if there are characteristic casts, meaning deposits within the lumen of tubules that appear dry, cracked, and more palely stained than usual casts. Myeloma casts are surrounded by giant cells (Figs 7.40 and 7.41). Usual casts are seen in virtually any kidney, especially if there is tubular damage, and appear moist, intact, and without a cellular response around them, although there may be red blood cells or leucocytes mixed in with them. In

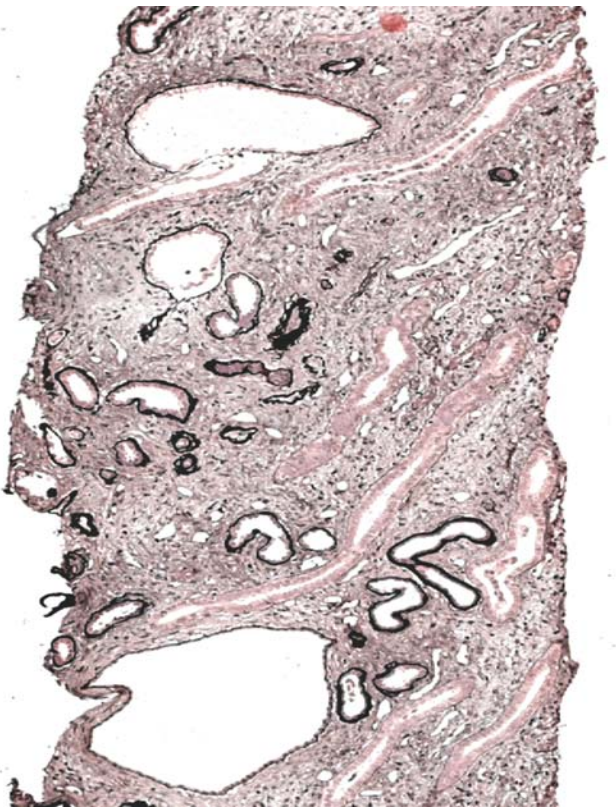

**Fig. 8.16** Medulla in a renal biopsy specimen from a man of 30 with chronic renal failure and small, symmetrical kidneys. There is chronic damage with cysts. No cysts were seen in the cortex. These findings suggest medullary cystic disease

myeloma, the typical casts may be sparse or undetectable in a biopsy specimen, and the diagnosis of myeloma kidney may be given by immunohistologic study to detect kappa and lambda light chains, which shows deposition of one type in tubular epithelium (Figs 7.42 and 7.43).

Myeloma kidney should be considered by the pathologist as a possible diagnosis in any specimen from an old person with otherwise unexplained renal failure, either acute or chronic.

Other effects of abnormal immunoglobulins on the kidney include **amyloid** of AL type (Figs 6.49, 6.63–6.67, and 6.74–6.76). This usually presents with the nephrotic syndrome, and the renal biopsy specimen may give the first hint of a disorder of immunoglobulins. Another effect may be seen if the abnormal immunoglobulins are **cryoglobulins**, which means that they can precipitate in the plasma in certain conditions (Figs 7.31–7.33). Cryoglobulinemic effects on the kidney usually present with acute renal failure. Another effect of abnormal immunoglobulins is the nodular glomerulosclerosis of **light chain glomerulopathy**, which resembles

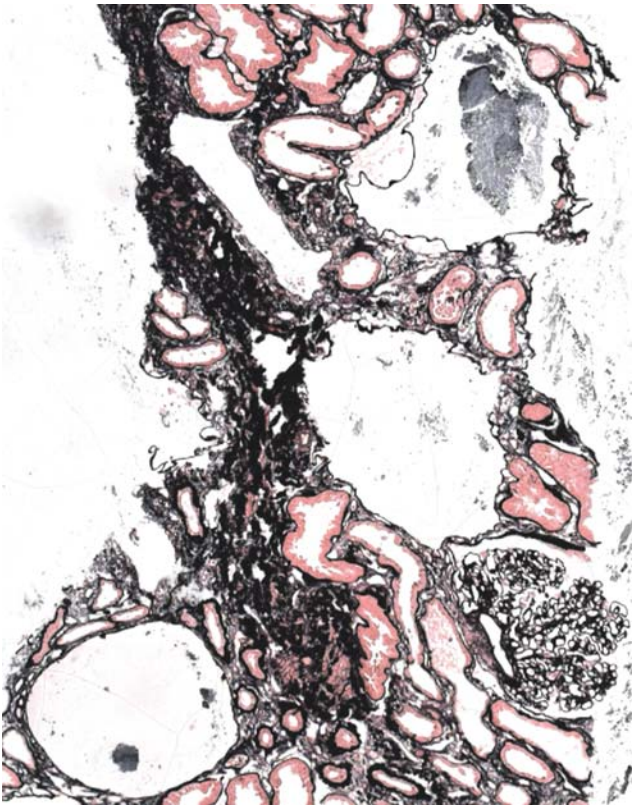

**Fig. 8.17** Cortex in a renal biopsy specimen from a man of 20 with chronic renal failure. There are cysts about the size of glomeruli, and elsewhere remnants of tufts are seen in cysts. This appears a glomerulocystic disorder, rather than an early form of autosomal dominant polycystic kidney disease

diabetic glomerulopathy, and usually presents with proteinuria and chronic renal failure (Figs 6.45–6.48).

Deposits of various **chemicals** may be seen in biopsy specimens. A few calcified deposits within tubules are common, but **calcification** of tubular basement membranes or interstitial tissues is uncommon, and suggests hypercalcemia (Fig. 8.18). This may be coincidental, or may itself be the cause of renal damage. Extensive calcification may be seen in some disorders of tubular function (Fig. 8.19). **Oxalate crystals** are within tubules and are birefringent, which means they appear bright when the specimen is examined between crossed polariser and analyser (Figs 7.46 and 7.47). Such crystals may indicate poisoning by antifreeze, or oxalosis, which may be the result of a genetic disorder, or the consequence of increased oxalate absorption from the intestines. More commonly, oxalate deposition is a complication of other renal disorders that cause acute tubular damage. In cystinosis, **cystine crystals** are also birefringent, but, unlike oxalate crystals, are within cells (Fig. 8.20).

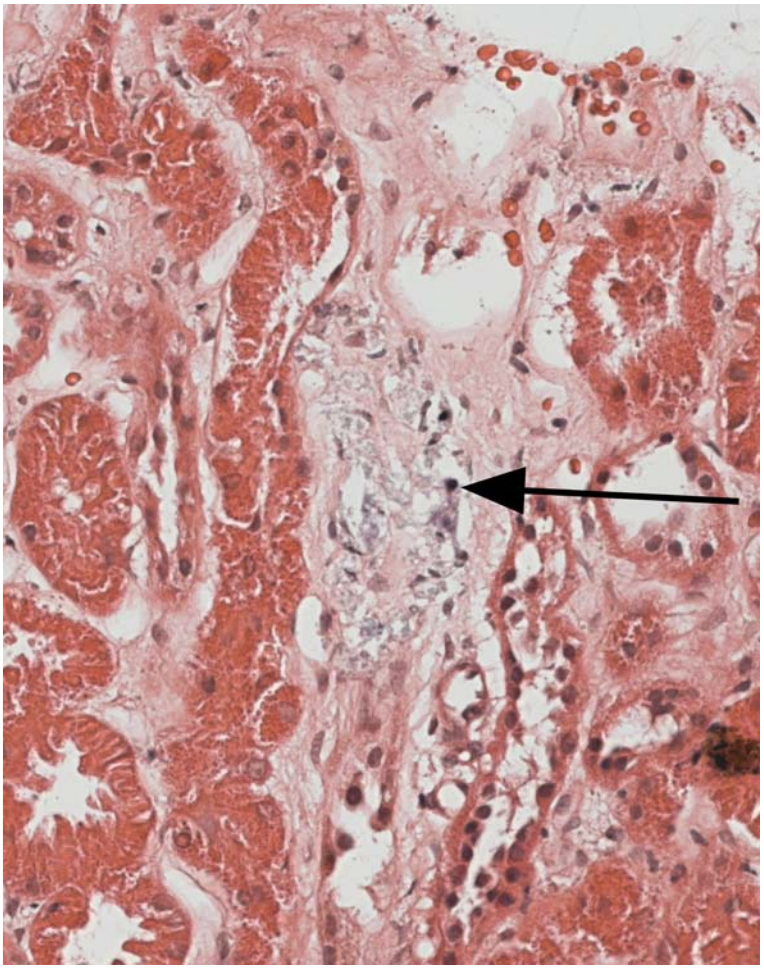

**Fig. 8.18** Cortex in a renal biopsy specimen from a woman of 37 with chronic renal failure, sarcoid, and hypercalcemia. There are calcified deposits in a band of atrophic tubules (arrowed)

Tubular atrophy may be due to **drugs or toxins**, such as lithium or lead, but the pathologist is unlikely to be able to identify the cause even if there is a history of exposure to a relevant drug or toxin. Chinese herb nephropathy appears due to a toxin aristolochic acid. Balkan endemic nephropathy may also be from the effects of tubular toxins from plants or fungi.

**Fanconi syndrome** is sometimes seen when there is damage to proximal tubules, with failure to reabsorb some substances from the glomerular filtrate, such as glucose, phosphate, amino acids, and small proteins, which appear in the urine. There is usually renal failure as well. Inherited diseases can produce this, but most are rare. The commonest is cystinosis, although mitochondrial disorders and many others may be found. Acquired disorders can also give Fanconi syndrome, but few have

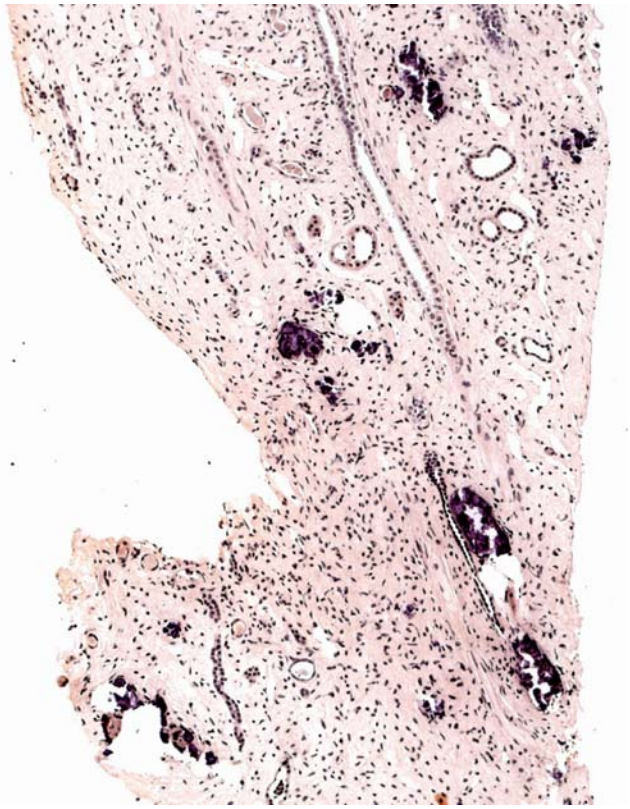

**Fig. 8.19** Medulla in a renal biopsy specimen from a woman of 45 with chronic renal failure, medullary calcification on imaging, normal serum calcium concentration, and distal renal tubular acidosis. Intratubular and interstitial deposits of calcified material are seen in this section, which is stained by Congo red with hematoxylin counterstain

characteristic structural features in tubules. These include the nephrotic syndrome and paraproteinemias occasionally, and effects of drugs, particularly anti retroviral drugs used to treat HIV infection, and chemotherapeutic agents used in cancer (Fig. 8.21).

## *Is There Evidence of an Interstitial Nephritis?*

Acute interstitial nephritis with active damage to tubules may be seen when the clinical problem is acute or acute on chronic renal failure, rather than truly chronic renal failure (Figs 7.34 and 7.35).

**Granulomas** may be seen in renal biopsy specimens. These are well-defined microscopic collections of macrophages with or without necrosis, giant cells, and other cells such as lymphocytes. Granulomatous interstitial nephritis may be seen

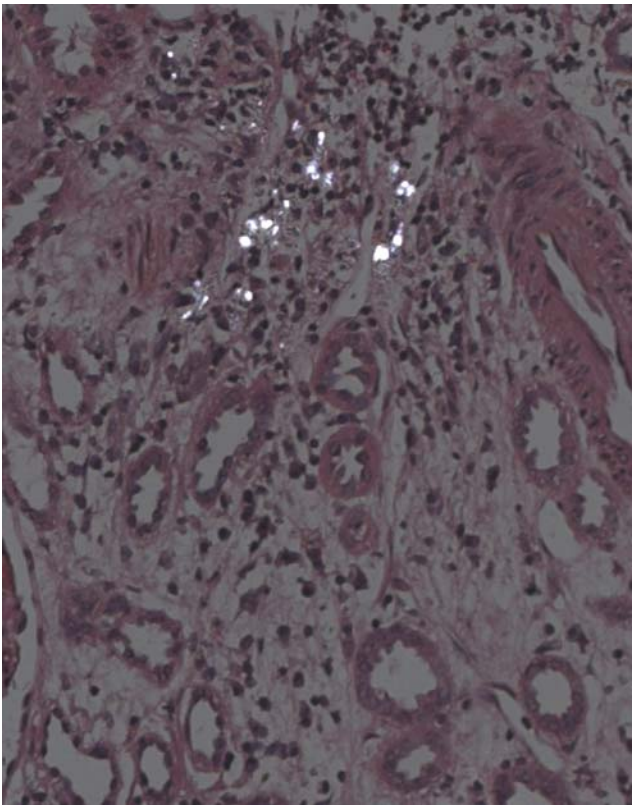

**Fig. 8.20** Cortex in a biopsy specimen of a renal allograft present for nearly 2 years in a woman of 18, who had had chronic renal failure due to cystinosis. Examination of the section between polariser and analyser that are nearly crossed shows birefringent crystals of cystine within macrophages that are infiltrating the graft

in sarcoid or tuberculosis when the tubular damage is mostly chronic (Figs 7.38 and 8.11), and as a response to drugs, such as penicillins, and in immunodeficiency states when the tubular damage is mostly acute (Fig. 7.37). True granulomas are not seen in the kidney in Wegener's granulomatosis, despite the name.

The term late interstitial nephritis may be used when the pathologist is confident that there is no other explanation of late renal damage. In practice, this should be a rare diagnosis, because to be sure of it there must have been an earlier biopsy specimen which showed acute interstitial nephritis. The pathologist should make it clear that the term is not used in the same sense as the discredited term chronic interstitial nephritis, often applied to any late changes in the kidney. Sjögren's syndrome of dry mouth and eyes and other clinical features may be associated with interstitial nephritis, and usually the renal damage is late and inactive at the time of diagnosis (Fig. 7.39).

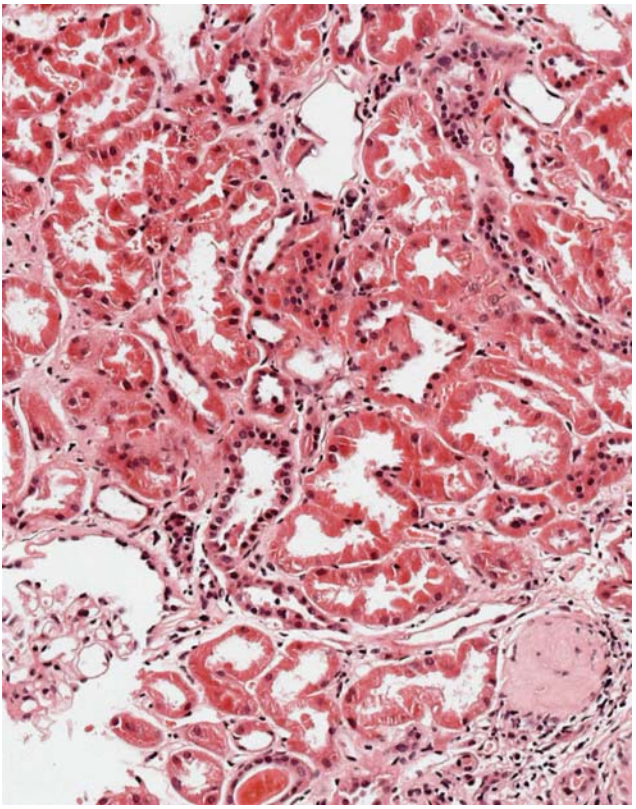

**Fig. 8.21** Cortex in a renal biopsy specimen from a man of 54 with chronic renal failure, slight proteinuria, and clinical evidence of Fanconi syndrome. He had been treated with chemotherapy for a lymphoma. There is patchy chronic damage with acute tubular damage seen as irregularity of cell size and a few abnormal nuclei, but there are no structural clues to the cause of the damage. Guido Fanconi (1882–1979), pronounced *fan-ko-nee*, was a Swiss pediatrician. His name is given to several conditions as well as the tubular disorder

## Summary: Chronic Renal Failure

Most people with chronic renal failure do not have a renal biopsy.

Chronic renal failure is associated with chronic abnormalities in tubules, the most important of which is atrophy.

In adults, many renal biopsy specimens show evidence of chronic renal damage due to something other than a glomerular disorder. Findings include chronic ischemic damage, problems with urinary drainage, problems in the renal medulla, cystic diseases, tubular disorders, and late stages of interstitial nephritis, including granulomatous disorders.

Most of the rest have IgA nephropathy, diabetic glomerulopathy, or segmental sclerosing glomerular conditions, which are often a complication of reduced renal mass.

In biopsy specimens in children, many have evidence of a nonglomerular disorder.

## Further Reading: Chronic Renal Failure

D'Agati VD, Jennette JC, Silva FG. Non-Neoplastic Kidney Diseases. Atlas of Nontumor Pathology, first series, fascicle 4. Washington, DC: American Registry of Pathology and Armed Forces Institute of Pathology, 2005. Chapters 2, 4, 16, 17, 20, 22.

Howie AJ. Nephrogenesis and developmental and genetic disorders of the urogenital tract. In: Burge DM, Griffiths DM, Steinbrecher HA, Wheeler RA, editors. Paediatric Surgery, second edition. London: Hodder Arnold, 2005: pp 415–421.

Jennette JC, Olson JL, Schwartz MM, Silva FG. Heptinstall's Pathology of the Kidney. Sixth ed. Philadelphia: Lippincott Williams and Wilkins, 2007. Chapters 10, 18, 19, 21, 22, 26.

# Chapter 9
# Indication for Biopsy: Hematuria

## Introduction to Hematuria

This means that hematuria is the main clinical abnormality, with or without proteinuria under the nephrotic range, with **normal renal excretory function**, with or without hypertension. If there is the nephrotic syndrome, or if function is abnormal, the approach to the study of the specimen is considered in Chapters 6, 7, and 8, as appropriate.

Hematuria is a common reason for renal biopsy, although different nephrologists have different criteria for biopsy. Many do not biopsy people without proteinuria.

Especially in children, there may be a **family history** of hematuria, or hematuria may be found on testing the urine of parents and siblings.

Often the pathologist is not told on the request form how the hematuria was detected, and whether there is only microscopic hematuria, or episodes of macroscopic hematuria, or both macroscopic and microscopic hematuria, and how much proteinuria there is. Because the information given to the pathologist about such things as type of presentation and family history may be incomplete, study of renal biopsy specimens in hematuria is described without distinction between macroscopic hematuria and microscopic hematuria, or between hematuria with and without proteinuria, or between those with and without a family history.

Loin pain with hematuria is a clinical syndrome that the pathologist should investigate in the way that all hematuria is investigated. Loin pain/hematuria syndrome is not a pathologic diagnosis.

## Detection of Hematuria

Macroscopic hematuria is seen as discoloration of the urine, which may be any colour between red and dark brown. People noticing this change in their urine usually seek medical advice.

Microscopic hematuria is detected by **urinalysis**, using dipsticks, which are dipped in urine, and change colour if blood is present. Usually, this test is repeated a few times at intervals, to make sure that it is not just a transient finding.

Apparently healthy people who may have their urine tested include pregnant women, and people who have a medical examination, for instance, before entry

A. J. Howie, *Handbook of Renal Biopsy Pathology.*

into various occupations, or when they apply for life insurance, or as part of a health check, or when taking part in some sports. Relatives of people known to have a renal disorder may also be tested. Children's parents and siblings are usually much easier to test than relatives of adults, simply because children's close relatives are likely to live together and to come to a physician together. Sometimes medical students, medical practitioners, and others related to the medical profession discover urinary abnormalities in themselves by random testing.

Other people who may be found to have microscopic hematuria are those with illnesses, especially long lasting ones which lead them to see physicians frequently, and mean that they are likely to have their urine tested. Their illnesses may be related directly or indirectly to the kidney, such as hypertension, or not apparently related, such as rheumatoid arthritis. Because people can have more than one disease, they may have a renal disorder that is coincidental.

## Investigation of Hematuria

A renal biopsy is not done on every person with hematuria, and is only done after appropriate investigations to exclude other causes of hematuria. **Biopsy is usually done late, if at all**.

Urinary tract infection is excluded before a renal biopsy is done to study hematuria. In **adults**, there have almost always been several other investigations, such as cystoscopy and radiologic examination of the urinary tract, to exclude explanations of hematuria that are often called urologic causes. These include disorders of the prostate, carcinoma of the bladder, stones in the urinary tract, and carcinoma of the kidney.

In **children**, hematuria is investigated by ultrasonography and radiologic examination of the kidneys, because causes in the bladder are rare, and cystoscopy is not usually worthwhile.

Some centres make use of microscopy of urine to help to determine whether blood cells in the urine are from glomeruli, or from the rest of the kidney and the lower urinary tract. Red blood cells from glomeruli have abnormal shapes, and are called dysmorphic.

Study of renal biopsy specimens in hematuria is straightforward, and the pathologist can usually give a satisfactory diagnosis on these specimens. There are always a few specimens that have no abnormality detectable by every technique that the pathologist uses, and the explanation of hematuria remains undetermined.

## Value of a Renal Biopsy in Hematuria

Often the diagnosis in people with hematuria makes no immediate difference to the clinical management if urologic causes have been excluded. Some nephrologists think that a biopsy is unnecessary.

Renal biopsy may be justified in hematuria for these reasons:

1. The specimen may show a disorder that requires a change in management, such as active vasculitic glomerulonephritis.
2. The diagnosis gives an important indication of prognosis, and so does the extent of chronic renal damage at the time of biopsy. There is a risk of progression to renal failure in IgA nephropathy, for instance, even if there is no chronic damage in the kidney at the time of biopsy, although other conditions such as thin glomerular basement membrane disease should not progress, and the person with this condition should have a normal life span. The amount of chronic damage is a guide to likely length of survival of renal function.
3. There are important genetic implications of some disorders with hematuria, particularly hereditary nephropathy of Alport type.

## Common Findings in Hematuria

When all people with hematuria of apparently renal origin have a renal biopsy, common findings are these.

In **adults**, most specimens in hematuria show either IgA nephropathy or thin glomerular basement membrane disease. Others usually have no abnormality that can be detected by the combination of orthodox light microscopy, immunohistology, and electron microscopy. The few remaining ones have a variety of disorders, including lupus nephritis, which can give any clinical renal abnormality.

In **children**, most specimens in hematuria show one of three disorders, thin glomerular basement membrane disease, IgA nephropathy, or hereditary nephropathy of Alport type. Others mostly have no detectable significant abnormality.

The relative frequency of disorders is different whether or not there is proteinuria with the hematuria. In adults, most specimens in hematuria without proteinuria show thin glomerular basement membrane disease, but in children, especially those aged under 10 years, any of the three common disorders may have hematuria alone. The commonest finding in specimens taken for hematuria with proteinuria is IgA nephropathy in adults, while children with hematuria and proteinuria usually have either IgA nephropathy or hereditary nephropathy of Alport type.

## Approach to the Study of Renal Biopsy Specimens in Hematuria

**Most specimens taken to investigate hematuria look normal or close to normal on orthodox light microscopy**, when the age of the person biopsied is taken into account, and provided that renal function is normal (Figs 5.1, 5.10, and 9.1).

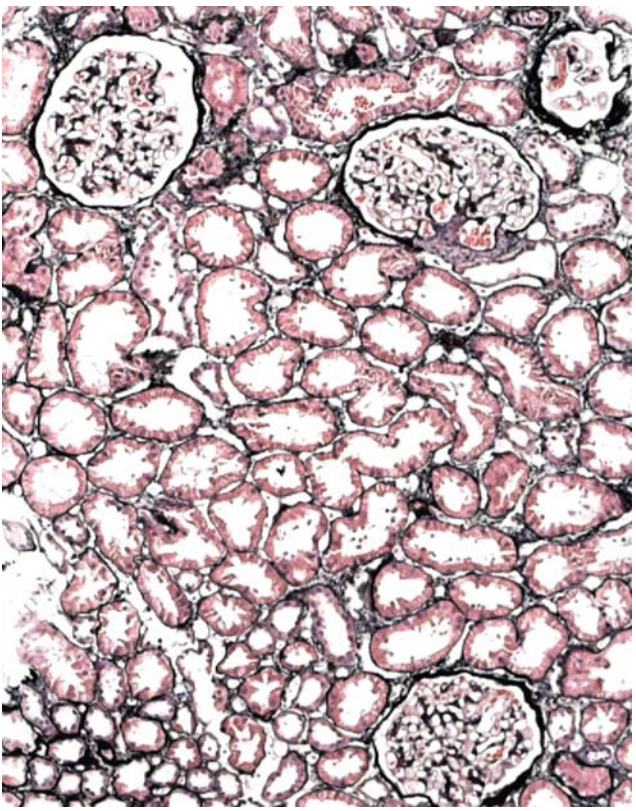

**Fig. 9.1** Cortex in a renal biopsy specimen from a woman of 35 with hematuria and proteinuria. This is virtually normal on orthodox light microscopy, but shows IgA nephropathy on immunohistologic study. IgA nephropathy is sometimes called Berger's disease. The name is almost always pronounced *bur-ger*, with a hard *g*, although the French pronunciation, *ber-zhay*, is perhaps more appropriate. In 1968, Jean Berger (born 1930), Professor of Pathology at the Necker Hospital in Paris, France, with his colleague Nicole Hinglais, who was an electron microscopist, reported the finding of IgA by immunofluorescence in 25 renal biopsy specimens. This was in a note of six short paragraphs, with no references (Berger J, Hinglais N. Les dépôts intercapillaires d'IgA-IgG. *Journal d'Urologie et de Nephrologie* 1968; **74:** 694–695). This tiny paper was largely overlooked, and the significance of IgA deposition in glomeruli did not become widely appreciated until 1969, when Berger presented his findings at a meeting of the Transplantation Society (Berger J. IgA glomerular deposits in renal disease. *Transplantation Proceedings* 1969; **1:** 939–944). The terms Berger's disease and Berger's nephropathy seem to have been first used in print in 1973. Berger was also the first to describe dense deposit disease, in 1963

## Initial Assessment of Orthodox Light Microscopic Sections

The diagnosis in hematuria mainly depends on findings of immunohistology and electron microscopy. Examination of orthodox light microscopic sections is to assess **the extent of irreversible damage**, which alters the prognosis, and to ensure

that there are no **unexpected findings**. These include segmental glomerular changes of vasculitic type (Figs 7.12 and 7.18) and active interstitial nephritis (Fig. 7.34).

On orthodox light microscopic sections, there are often hints that the diagnosis may be IgA nephropathy or hereditary nephropathy of Alport type, rather than thin glomerular basement membrane disease. There may be more irreversible tubular damage than expected for the age, glomeruli may have definite mesangial expansion, and there may be segmental changes in glomeruli, particularly irregular areas of sclerosis at various sites in glomeruli (Fig. 8.1). Foamy cells in tissues outside glomeruli are often a striking feature in hereditary nephropathy of Alport type, even when there is little or no proteinuria (Fig. 9.2). Foamy cells can be seen in other conditions such as IgA nephropathy and membranous nephropathy, but generally when there is heavy proteinuria. Often the pathologist cannot easily determine if foamy cells are in tubules or in interstitial tissues.

The diagnosis can hardly ever be made in hematuria by examination of orthodox light microscopic sections alone.

### *Assessment of Immunohistologic Sections: Is There IgA Nephropathy?*

The next crucial investigation in hematuria is immunohistology. If this shows deposition of IgA in mesangium, the diagnosis is likely to be **IgA nephropathy** (Figs 8.2 and 9.3 – 9.6). **Only one glomerulus is needed to give the diagnosis of IgA nephropathy** (Fig. 4.8). The mesangial immunostaining begins sharply where the arterioles pass through Bowman's capsule (Figs 8.2 and 9.4).

Often IgM and complement are also deposited in mesangium. Using an immunoperoxidase method, IgG is not found in typical IgA nephropathy, but may be seen using an immunofluorescence method. If IgG is found with IgA in mesangium by immunoperoxidase, this suggests **lupus nephritis**, which is almost the only other disorder in which IgA is found, if Henoch-Schönlein nephritis is regarded as part of IgA nephropathy, in its widest sense. C1q is more often found in lupus nephritis than in IgA nephropathy, and may help to discriminate between them if IgG is found on immunofluorescence. Lupus nephritis is usually diagnosed clinically or serologically before renal biopsy.

## Diagnosis of IgA Nephropathy

The typical presentation of IgA nephropathy is with macroscopic hematuria at the time of an upper respiratory tract infection, characteristically without the delay between the infection and the urinary abnormality that occurs in acute postinfective glomerulonephritis. Hematuria or proteinuria, or both, may be detected in many other ways. At diagnosis, there may be chronic renal impairment or accelerated hypertension. **IgA nephropathy hardly ever presents with the nephrotic syndrome**.

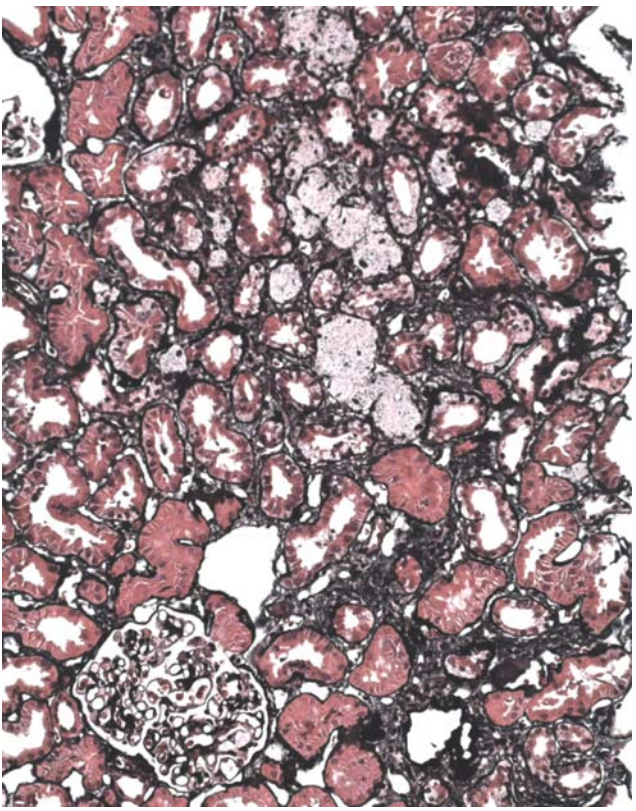

**Fig. 9.2** Cortex in a renal biopsy specimen from a woman of 17 with hematuria and proteinuria. This is not normal on orthodox light microscopy, and has a little chronic damage with many foamy cells, probably both in tubules and in interstitial tissues. Electron microscopy shows hereditary nephropathy of Alport type.

Alport's syndrome was suggested by R F Shaw and R A Glover in 1961 as a suitable name for the condition of familial renal disease with deafness, to honour Cecil Alport who described a family in 1927 (Alport AC. Hereditary familial congenital haemorrhagic nephritis. *British Medical Journal* 1927; **1:** 504–506). The name is pronounced *awl-port* or *al-port*. Arthur Cecil Alport (1880–1959) was born in South Africa, and qualified in medicine in Edinburgh, United Kingdom. In 1922, he was appointed second assistant to the medical unit at St Mary's Hospital Medical School in London, which he left in 1937 to become professor of medicine in Cairo, Egypt. The family he described had already been reported four times, by L G Guthrie in 1902, G Kendall and A F Hertz in 1912, Hertz again in 1923 but after a change of surname to Hurst, and J Eason, G L M Smith and G Buchanan in 1924. The observation had been made that males were more affected than females, but Alport was the first to mention deafness in the family. In 1968, M D Crawford and P J Toghill reported that they had traced the family described by Alport, and found that the disease had disappeared from it. The characteristic changes in glomerular basement membranes were first described in 1972. Electron microscopy was never done on glomeruli in Alport's family

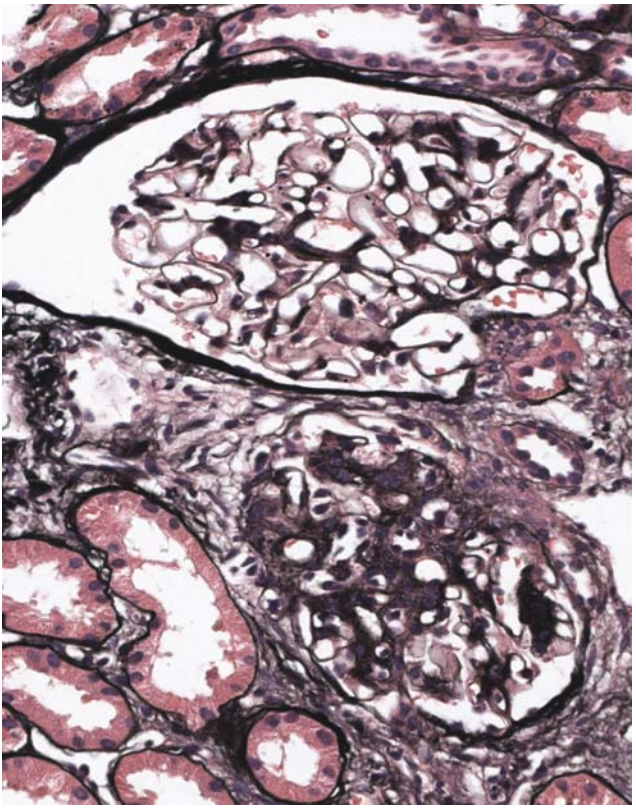

**Fig. 9.3** Glomeruli in a renal biopsy specimen from a woman of 28 with hematuria and proteinuria. These have different amounts of mesangial expansion, and one has a segmental area of sclerosis. Immunohistologic findings are illustrated in **Fig. 9.4**, and show IgA nephropathy

IgA nephropathy usually has abnormalities of glomeruli visible on orthodox light microscopy, but sometimes can appear to have normal glomeruli (Fig. 9.5). The most common abnormality is mesangial expansion to different extents (Figs 8.1 and 9.3). Various classifications of the glomerular appearances have been made. In practice, these are of little clinical use, compared with the prognostic information given by assessment of the amount of chronic damage in the kidney, for instance, by measurement of the index of chronic damage (Fig. 5.6).

IgA nephropathy is probably a consequence of abnormal glycosylation of IgA1 molecules in plasma, which leads to their deposition in mesangium. This is likely to have genetic causes, and indeed IgA nephropathy occasionally runs in families. There is a high risk of progression to renal failure, although this may take a long time, meaning decades, if the kidney is close to normal at the time of diagnosis.

The pathologist cannot differentiate between the common type of IgA nephropathy and the type that is associated with various disorders, particularly chronic liver diseases, such as alcoholic cirrhosis, in which there may be reduced clearance

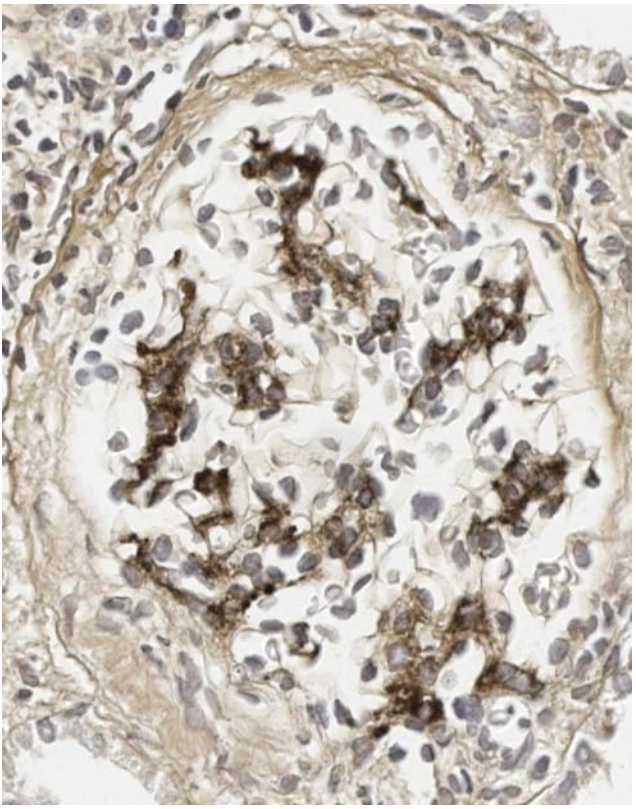

**Fig. 9.4** Glomerulus in the renal biopsy specimen from the woman of 28, which is illustrated in **Fig. 9.3**. An immunoperoxidase method to detect IgA shows mesangial deposition, and gives the diagnosis of IgA nephropathy

of IgA1 from plasma. IgA nephropathy is one of several conditions seen in HIV infection, and may also be associated with dermatitis herpetiformis, celiac disease, inflammatory diseases of joints, and several other diseases in which the renal disorder may just be coincidental. Some people with IgA nephropathy have a raised concentration of IgA in the blood, but IgA nephropathy is not the only explanation of this change, and the pathologist should not be influenced by knowledge of the serum IgA concentration when a renal biopsy specimen is assessed.

## Henoch-Schönlein Nephritis

Occasionally, there may be **glomerular abnormalities of vasculitic type** in IgA nephropathy, and these may occur with or without systemic features, such as a rash or joint symptoms (Figs 7.25–7.27, 9.7, and 9.8). Useful terms for this finding are **vasculitic IgA nephropathy** and **Henoch-Schönlein nephritis**, rather than

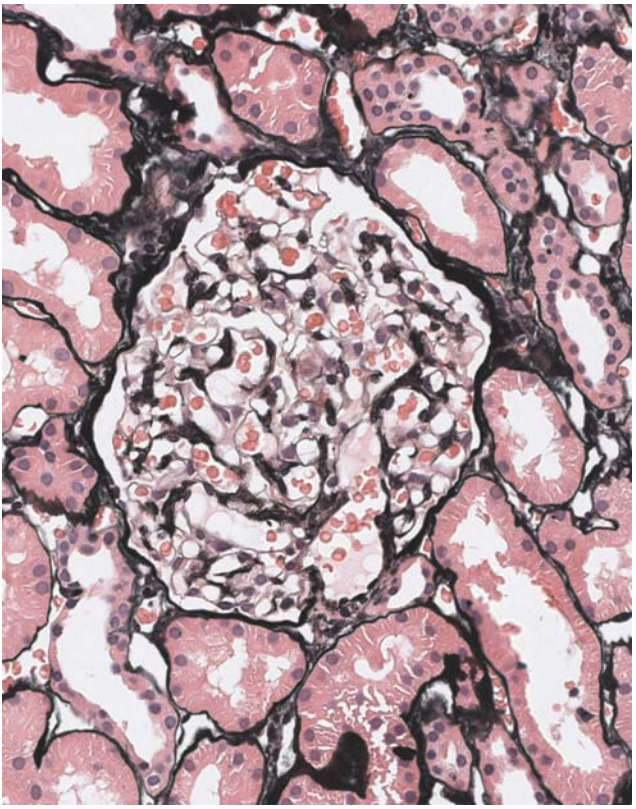

**Fig. 9.5** Glomerulus in a renal biopsy specimen from a man of 54 with microscopic hematuria, but no proteinuria. This is virtually normal on orthodox light microscopy, but shows IgA nephropathy on immunohistologic study, illustrated in **Fig. 9.6**

**Henoch-Schönlein purpura**, which is a clinical syndrome with various combinations of a rash, joint problems, gastrointestinal bleeding, acute renal failure, and hematuria. Biopsy of the skin or gastrointestinal tract in Henoch-Schönlein purpura shows a leukocytoclastic vasculitis with IgA in the walls of small blood vessels.

IgA nephropathy and Henoch-Schönlein nephritis are almost certainly the same condition. Henoch-Schönlein nephritis can be regarded as an acute vasculitic episode in IgA nephropathy, and is less common than IgA nephropathy not complicated by vasculitic glomerulonephritis. In adults, biopsy specimens showing Henoch-Schönlein nephritis are about one-sixth of the number that show uncomplicated IgA nephropathy.

The possible combinations of pathologic and clinical findings can be summarised in this way in conditions associated with IgA in glomeruli, which can be regarded as IgA nephropathy in its widest sense.

**IgA nephropathy**, without vasculitic glomerular lesions, may be found in a renal biopsy specimen when clinically there is apparently pure renal disease with

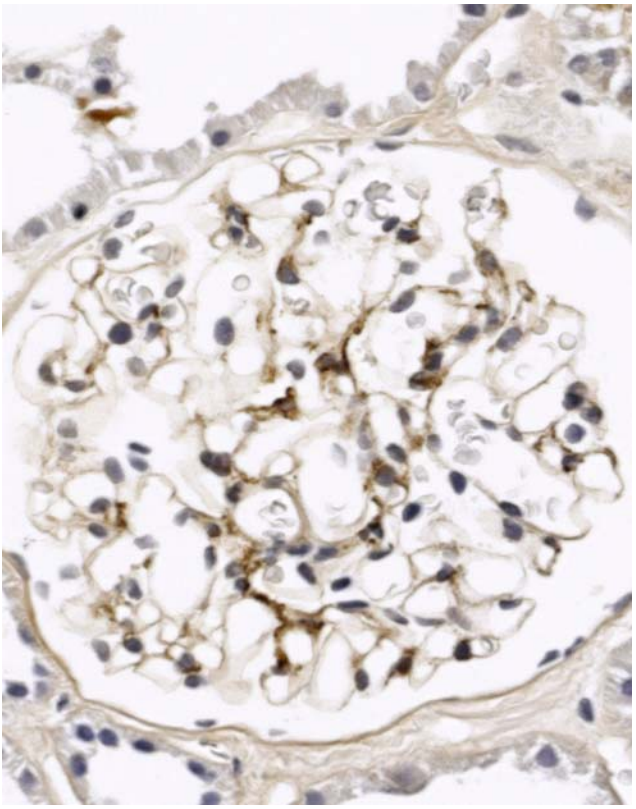

**Fig. 9.6** Glomerulus in the renal biopsy specimen from the man of 54, which is illustrated in **Fig. 9.5**. An immunoperoxidase method to detect IgA shows light mesangial deposition, and gives the diagnosis of IgA nephropathy. Definite deposition of IgA of any intensity in glomeruli is significant

hematuria and proteinuria, or when there is clinical Henoch-Schönlein purpura (Figs 4.8, 8.1, 8.2, 9.1, and 9.3–9.6). In adults, about nine-tenths with this finding do not have clinical Henoch-Schönlein purpura.

**Henoch-Schönlein nephritis**, or IgA nephropathy with vasculitic glomerular lesions, may be found in a renal biopsy specimen when there is clinical Henoch-Schönlein purpura, or when clinically there is apparently pure renal disease with hematuria and proteinuria (Figs 7.25–7.27, 9.7, and 9.8). In adults, about half with this finding have clinical Henoch-Schönlein purpura, and half do not.

**Clinical Henoch-Schönlein purpura** may be found in a renal biopsy specimen to have either Henoch-Schönlein nephritis or IgA nephropathy, without vasculitic glomerulonephritis (Fig. 9.7). In adults, there are approximately equal numbers of these findings.

**IgA-associated disease apparently confined to the kidney, with hematuria and proteinuria,** may be found in a renal biopsy specimen to have either IgA

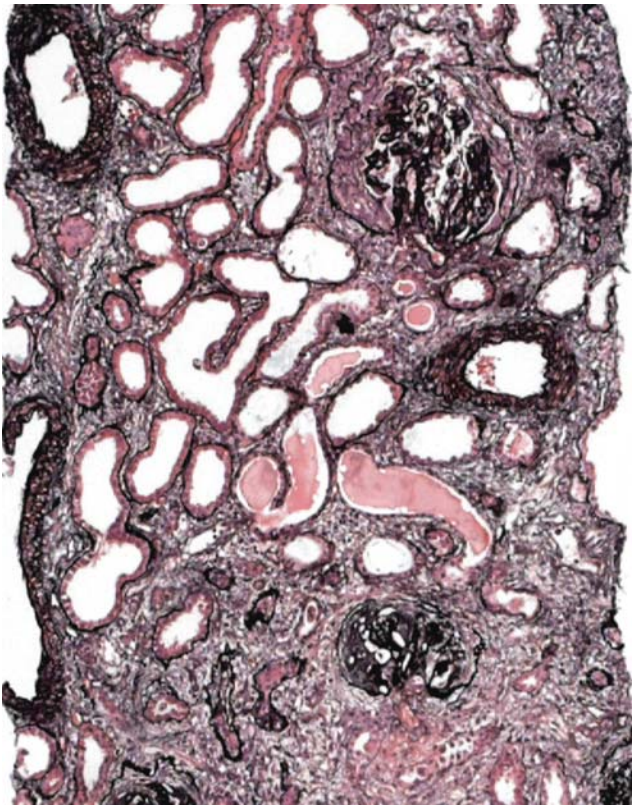

**Fig. 9.7** Cortex in a renal biopsy specimen from a woman of 34 with hematuria, proteinuria, hypertension, clinically acute renal failure, and a rash. There is marked acute and chronic damage, and a surviving glomerulus shows mesangial expansion with healing segmental vasculitic lesions. There is IgA deposition in glomeruli on immunohistologic study. Features are those of late and active Henoch-Schönlein nephritis

nephropathy, without vasculitic glomerulonephritis, or Henoch-Schönlein nephritis (Figs 4.8, 7.25–7.27, 8.1, 8.2, 9.1, 9.3–9.6, and 9.8). In adults with these clinical features, most, about nine-tenths of them, do not have Henoch-Schönlein nephritis, but this means that Henoch-Schönlein nephritis is occasionally found in someone with no systemic features of Henoch-Schönlein purpura (Fig. 9.8).

Often children with typical clinical features of Henoch-Schönlein purpura do not have a renal biopsy, and are expected to get better. Biopsy may be done if there is heavy proteinuria at onset, or if proteinuria persists.

In the report, the pathologist should give the diagnosis as IgA nephropathy or Henoch-Schönlein nephritis, include the proportion of glomeruli with active vasculitic lesions, and give an assessment of the amount of irreversible damage in glomeruli and tubules.

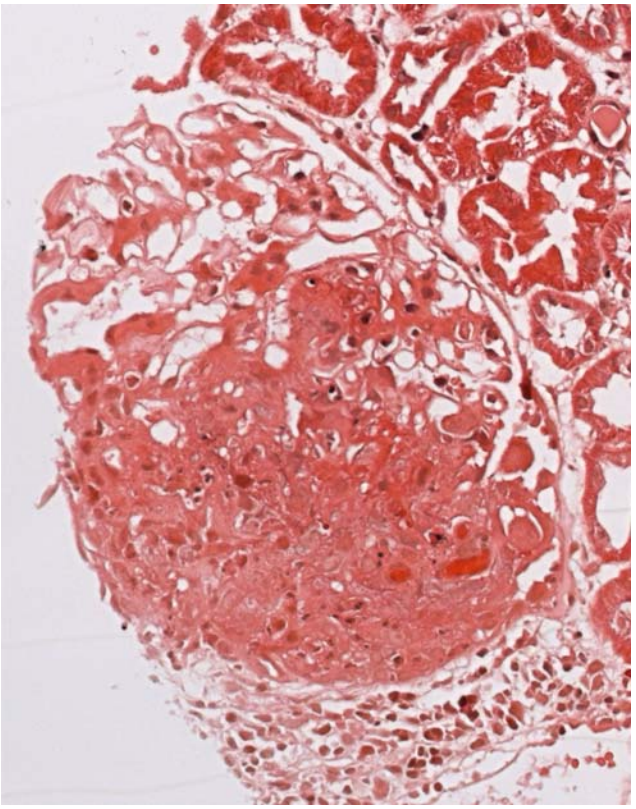

**Fig. 9.8** Glomerulus in a renal biopsy specimen from a man of 26 with hematuria and proteinuria found on routine screening, without any other findings on medical examination. There is a large segmental vasculitic lesion with mild mesangial expansion in the rest of the tuft. Immunohistologic study shows IgA deposition in glomeruli. This is unexpected Henoch-Schönlein nephritis, without any systemic features of Henoch-Schönlein purpura

## *If IgA Nephropathy Has Been Excluded, Is There an Abnormality on Electron Microscopy?*

If IgA nephropathy is excluded by immunohistology, and there is no other identifiable abnormality on light microscopy, the next investigation is electron microscopy. For pathologists without access to an electron microscope, specimens without IgA nephropathy, and with only changes attributable to age, can be reported to show kidney with no significant abnormality on light microscopy. The chance that a serious progressive disease has been missed is slight in adults, although there is a chance in children of early or mild hereditary nephropathy of Alport type.

The most likely finding on electron microscopy is **thin glomerular basement membrane disease**. This is one of the few disorders of any organ in which the name describes the structural findings.

## Diagnosis of Thin Glomerular Basement Membrane Disease

The reason for the renal biopsy is persistent microscopic hematuria in a person of either sex and of any age. There may be a family history of microscopic hematuria, or hematuria may be found by testing urine of relatives, but there should be no history of renal failure in the family. Macroscopic hematuria and proteinuria may occur, but are unusual. Thin glomerular basement membrane disease is common, and has been found in about one in 20 apparently normal people. The abnormality can occur with other disorders of the kidney.

If the diagnosis is correct, and if they have no other condition, such as hypertension, people with thin glomerular basement membrane disease should have normal renal function for the rest of their life. This outlook is different from that of people with either IgA nephropathy or hereditary nephropathy of Alport type, who may progress to renal failure.

The renal biopsy specimen looks normal on orthodox light microscopy, when the age of the person biopsied is taken into consideration (Figs 5.1, 5.7, and 5.10). This means that in middle aged and old people, there may be signs of chronic ischemic damage. There is no deposition of IgA in glomeruli on immunohistologic study. There may be deposition of IgM in mesangium, but if basement membranes are thin on electron microscopy, this immunohistologic finding can be ignored.

On electron microscopy, basement membranes appear strikingly thin. Usually measurement is not necessary, because there is such a definite difference from normal thickness, with which the pathologist should be familiar from examination of specimens with IgA nephropathy, for example (Figs 6.6 and 9.9). Membranes are uniform, without irregularities of the epithelial surface, and without signs of deposits. Usually a prominent lamina densa is seen in the centre of the membrane, although this is not seen in normal membranes. In children aged below 10 years, normal controls should be matched by age, because the glomerular basement membrane increases in thickness until then.

The pathologist should remember that glomerular capillary loops are three-dimensional structures, and a random section can show basement membranes with any apparent thickness from the true minimum to any width at right angle to the minimum. Parts of the membrane where it appears to be sectioned perpendicularly are easily detected by the sharpness of the image of cytoplasmic membranes of endothelial and epithelial cells on each side, and these parts give the most accurate impression of the thickness. If necessary, the thickness can be measured here.

Measurement is difficult to do properly, because ideally this requires adequate numbers of random samples and suitable control measurements, all compared with measurements from calibration grids photographed at the same magnification on the electron microscope. This is tedious, is rarely done thoroughly, and is not usually necessary, because most examples of thin glomerular basement membrane disease can be diagnosed by simple inspection. Because the definition of thin glomerular basement membrane disease is arbitrary, and accurate measurement is difficult, the most important thing for the pathologist to do in equivocal specimens is to exclude other explanations of hematuria.

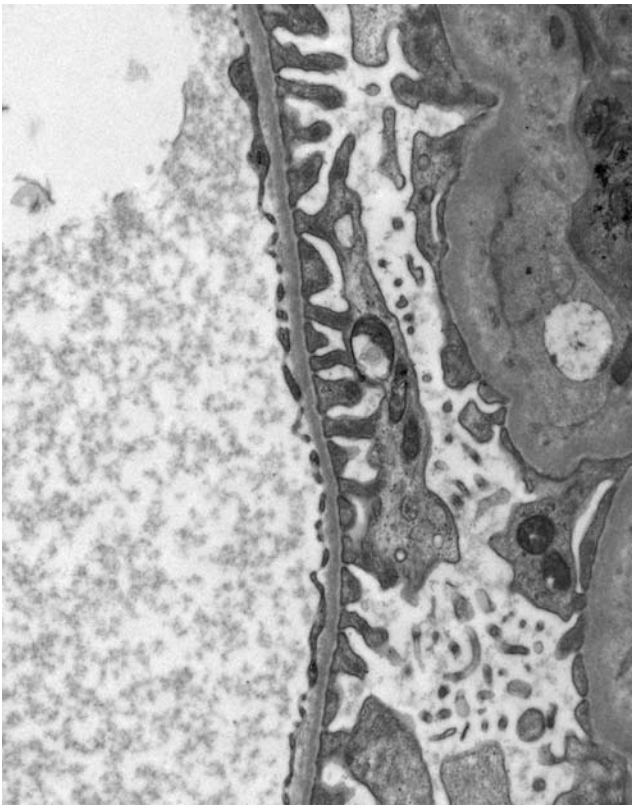

**Fig. 9.9** Electron micrograph of part of the glomerular basement membrane in a renal biopsy specimen from a woman of 60 with persistent microscopic hematuria, but no proteinuria. This is uniformly thin, with a thickness of about 150 nm. Compared with normal basement membranes in **Fig. 6.6**, photographed at the same magnification, this membrane is not only thinner, but also has a more obvious lamina densa in the middle. Features are those of thin glomerular basement membrane disease

One problem is the specimen with basement membranes of different thicknesses, in places definitely thin but elsewhere apparently normal, without irregularity of the epithelial surface. This may be called patchy thin glomerular basement membrane disease.

If there is an irregular outer surface on basement membranes, the diagnosis is hereditary nephropathy of Alport type.

## Diagnosis of Hereditary Nephropathy of Alport Type

This is not a single disease. The same pathologic appearances can be produced by many genetic abnormalities of type four collagen, which is found in glomerular basement membranes.

Most people with this condition have an abnormality on an X chromosome, which means that the disease is sex linked, carried by women who may appear unaffected, and phenotypically worse in males. There are other types of inheritance, autosomal recessive and autosomal dominant, and even in the sex linked type, the clinical features and severity vary between families. Often the disorder is found on investigation of a boy with hematuria, and there is a family history of deafness and renal failure in male relatives. There may be proteinuria, and occasionally this can be in the nephrotic range.

In the sex linked disorder, the alpha five chain of collagen type four is defective. In the other types, the alpha three chain or alpha four chain is defective. Lack of one of these chains leads to nonexpression of the others in glomerular basement membranes. In hereditary nephropathy of Alport type, glomerular basement membranes lack the Goodpasture antigen, which is in the noncollagenous domain of the alpha three chain of collagen type four, and is recognised by antibodies in Goodpasture's disease (Figs 7.29 and 7.30). There is a likelihood that many people with thin glomerular basement membrane disease have a heterozygous defect in alpha three or alpha four chains of collagen type four, but such defects do not prevent expression of the Goodpasture antigen in glomerular basement membranes in thin glomerular basement membrane disease.

In hereditary nephropathy of Alport type, a renal biopsy specimen may range in orthodox light microscopic appearances from normal in a young person who has the disorder but is biopsied at an early stage, or in a woman who is a carrier of an abnormal X chromosome, to severely abnormal with extensive tubular atrophy, segmental and global sclerosis of glomeruli, and many foamy cells in the cortex (Fig. 9.2). Immunohistologic study shows no deposition of IgA in glomeruli.

Electron microscopy shows that basement membranes are not uniformly thin, and have an irregular epithelial surface (Figs 9.10 and 9.11). There are thick areas as well as thin, patches of complex splitting of the lamina densa, sometimes called basket weave pattern, and inclusions of electron dense particles in the basement membrane.

These features are often well developed in boys and young men, but may be slight in girls or women, in whom the pathologist may be in doubt whether the diagnosis is hereditary nephropathy. The changes usually become more marked with time, and a definite diagnosis may require another renal biopsy, a few years after the first. Each family with hereditary nephropathy of Alport type has a different genetic abnormality. There is no simple genetic screening test that at present helps to decide whether equivocal pathologic findings are those of hereditary nephropathy.

In hereditary nephropathy of Alport type, glomerular basement membranes lack the Goodpasture antigen, which can be identified by various antibodies. There are also antibodies that can be used immunohistologically to identify various chains of collagen type four, such as the alpha five chain. Such antibodies may be helpful in diagnosis, because they react with normal basement membranes, but may not react with basement membranes in hereditary nephropathy (Figs 9.12 and 9.13). Some antibodies may also be useful in skin biopsy specimens. One of the two X chromosomes is randomly inactivated in female cells, and this may give patchy

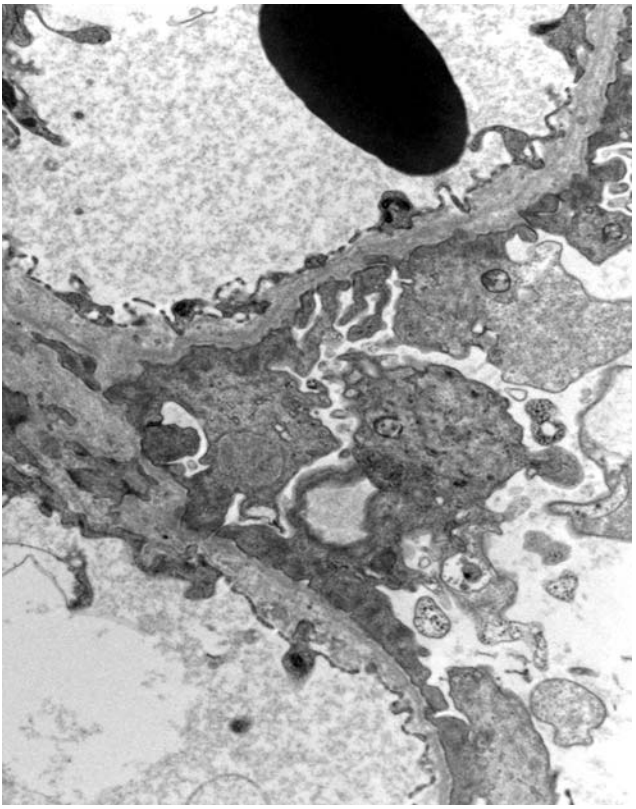

**Fig. 9.10** Electron micrograph of glomerular basement membranes in a renal biopsy specimen from a woman of 28 with persistent microscopic hematuria and proteinuria. Her brother was on renal replacement therapy, but the cause of his renal failure was not known. The membranes have an irregular outer aspect, a range of thickness, and splitting of the lamina densa. These are features of hereditary nephropathy of Alport type. An image at higher magnification is shown in **Fig. 9.11**

expression of collagen chains in glomeruli of women with a mutation giving the sex linked form of hereditary nephropathy of Alport type. This may cause difficulties with interpretation of immunohistologic findings. Antibodies to chains of collagen type four and the Goodpasture antigen should react normally in thin glomerular basement membrane disease (Fig. 9.12).

## Other Findings in Hematuria

If orthodox light microscopy has shown only age-related changes, immunohistology has excluded IgA nephropathy, and electron microscopy has shown glomerular basement membranes of uniform normal thickness, the pathologist can give

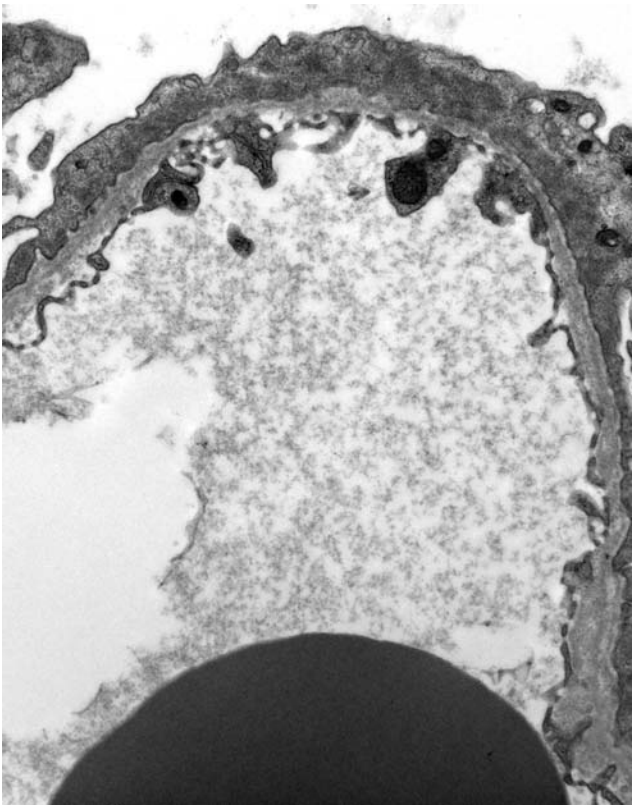

**Fig. 9.11** Electron micrograph of part of a glomerular basement membrane in the renal biopsy specimen from the woman of 28 with hereditary nephropathy of Alport type, which is illustrated in **Fig. 9.10**. This is at the same magnification as the normal basement membrane in **Fig. 6.6** and the thin basement membrane in **Fig. 9.9**. The basement membrane has an irregular outer aspect, variable width with thick and thin areas, splitting of the lamina densa, and small inclusions

the diagnosis as kidney with no detectable significant abnormality in the biopsy specimen. This does not mean that the kidney is normal because there may be an explanation of hematuria that has been missed, such as a vascular abnormality or a urologic disorder.

In both adults and children, most renal biopsy specimens taken for investigation of hematuria should be interpretable with this approach. The relatively few others may show such things as diabetic glomerulopathy, lupus nephritis, and segmental sclerosing conditions. Often, the clinical information given to the pathologist on the request form in these is incomplete or wrong. For example, the underlying disease may not be mentioned, or there may be chronic renal failure, or the main nephrologic problem may be proteinuria in the nephrotic range rather than hematuria.

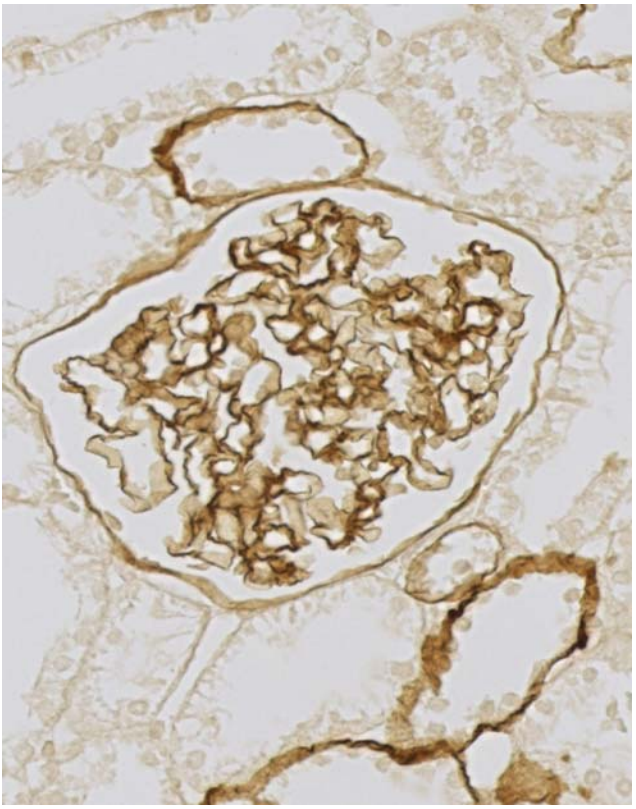

**Fig. 9.12** Cortex in a renal biopsy specimen from a woman of 40 with thin glomerular basement membrane disease. This is stained by an immunoperoxidase method with an antibody to the Goodpasture antigen. The antigen is detected in basement membranes of the glomerular tuft, Bowman's capsule, and a few tubules. This distribution is normal, unlike the findings in hereditary nephropathy of Alport type, illustrated in **Fig. 9.13**

## Summary: Hematuria

A renal biopsy is not done on every person with hematuria, and is only done after appropriate investigations to exclude other causes of hematuria.

Most specimens taken to investigate hematuria look normal or close to normal on orthodox light microscopy when the age of the person biopsied is taken into account.

In children, most specimens in hematuria show one of three disorders: thin glomerular basement membrane disease, IgA nephropathy, or hereditary nephropathy of Alport type.

In adults, most specimens in hematuria show either IgA nephropathy or thin glomerular basement membrane disease.

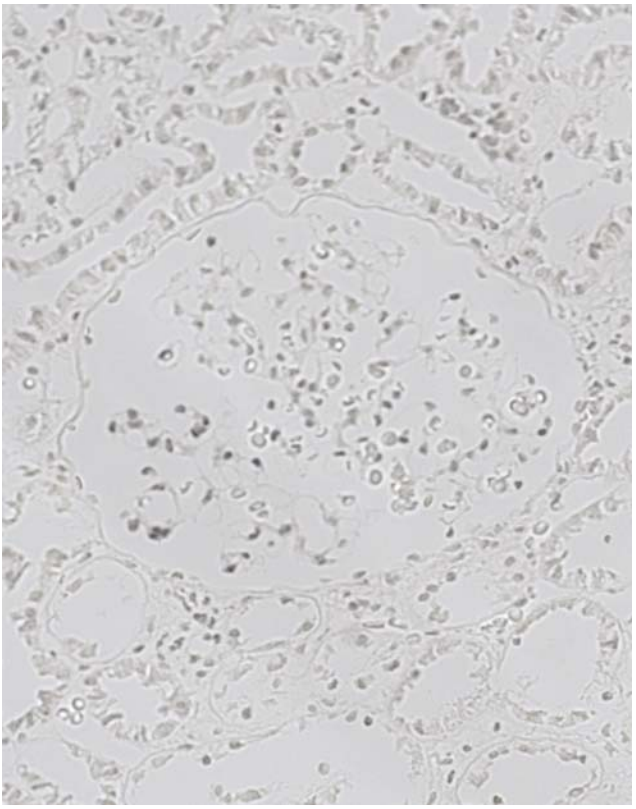

**Fig. 9.13** Cortex in the renal biopsy specimen from the woman of 17 with hereditary nephropathy of Alport type that is illustrated in **Fig. 9.2**. This is stained by an immunoperoxidase method with the antibody to the Goodpasture antigen that is illustrated in **Fig. 9.12**. No Goodpasture antigen is found in either glomerular or tubular basement membranes. Similar findings are expected with antibodies against alpha three and five chains of collagen type four

## Further Reading: Hematuria

D'Agati VD, Jennette JC, Silva FG. Non-Neoplastic Kidney Diseases. Atlas of Nontumor Pathology, first series, fascicle 4. Washington, DC: American Registry of Pathology and Armed Forces Institute of Pathology, 2005. Chapters 4, 12.

Jennette JC, Olson JL, Schwartz MM, Silva FG. Heptinstall's Pathology of the Kidney. Sixth ed. Philadelphia: Lippincott Williams and Wilkins, 2007. Chapters 10, 11.

# Chapter 10
# Indication for Biopsy: Proteinuria

## Introduction to Proteinuria

This is used in this chapter to mean proteinuria above normal amounts, but below the nephrotic range, under 3 g or 3.5 g total protein output in the urine per 24 h in adults, or the equivalent when expressed as protein/creatinine or albumin/creatinine concentration ratios. This may be called **asymptomatic proteinuria**.

The person biopsied is assumed to have no edema, renal failure, or hematuria, although there may be hypertension. Edema indicates the nephrotic syndrome, which is covered in Chapter 6. If renal excretory function is not normal, the biopsy specimen should be analysed as in Chapters 7 and 8. If renal function is normal, but there is also hematuria, Chapter 9 should be consulted.

The pathologist relies upon the information written on request forms, and ideally expanded by conversation with a physician. Some biopsy specimens apparently from people with only asymptomatic proteinuria may actually be from people with other features of renal disease as well, but the other features have been overlooked or unreported. This may explain unusual or unexpected findings in these specimens.

## Types of Proteinuria

The nephrotic syndrome always indicates a glomerular disorder, but **glomerular proteinuria**, caused by increased glomerular permeability to albumin and other plasma proteins, can be below the nephrotic range, and does not always lead to the nephrotic syndrome.

Protein can be found in the urine for reasons other than structural abnormalities of the glomerulus. These reasons include the following:

1. **Tubular proteinuria** of low molecular mass proteins, smaller than albumin, normally found in plasma, such as immunoglobulin light chains, beta two microglobulin, retinol binding protein, and alpha one microglobulin, that are normally filtered by glomeruli and reabsorbed by tubules. When there is a tubular abnormality, such as poisoning by the metals cadmium, lead, and mercury, these proteins appear in the urine. Other substances may also appear in the urine in

A. J. Howie, *Handbook of Renal Biopsy Pathology.*

these circumstances, including glucose, phosphate, and amino acids. This is called Fanconi syndrome (Fig. 8.21).

2. **Overflow proteinuria** of an increased amount in plasma of low molecular mass proteins, which are normally filtered by glomeruli and reabsorbed by tubules, but which overwhelm the reabsorptive capacity of tubules. An example is leak of immunoglobulin light chains in some types of paraproteinemia. These light chains in the urine are called Bence Jones proteins (Fig. 6.45).
3. **Nephrogenic proteinuria** of proteins produced by the kidney. This includes the main protein found in normal urine, Tamm-Horsfall protein, produced by the ascending limb of the loop of Henle, proteins secreted by abnormal kidney, such as IgA in acute pyelonephritis, and enzymes, such as N acetyl beta D glucosaminidase, released from cells in tubular damage.
4. Others, including artefactual proteinuria caused by addition of protein such as egg albumin to otherwise normal urine, and orthostatic proteinuria, found in some people on standing or after exercise, but not when they have been lying down. This influence of posture on proteinuria is the reason why testing for proteinuria is sometimes recommended in a urine sample taken on awakening, especially in children.

## Value of a Renal Biopsy in Proteinuria

The diagnosis in proteinuria does not often affect clinical management in the short term. The main value is to allow the nephrologists to know what is the disease and its severity, and in this way to decide the likely long-term outcome.

Not every person found to have proteinuria has a renal biopsy. Some nephrologists are reluctant to use this investigation in persistent asymptomatic proteinuria with no other abnormality. One of the commonest conditions associated with proteinuria is known to be transient. This is **pre-eclampsia** in the third trimester of pregnancy, and renal biopsy is hardly ever done, because delivery of the baby will be followed by resolution of the proteinuria (Figs 10.1 and 10.2).

## Findings in Proteinuria

Renal biopsy specimens in proteinuria are the most difficult for a pathologist to investigate. There are many possible findings, sometimes no definite abnormality can be detected, and some diagnoses are unsatisfactory. These specimens are by no means so straightforward to investigate as those in the nephrotic syndrome.

If a specimen appears normal, the diagnosis should not be given as minimal change nephropathy. This diagnosis should only be used **when there is the nephrotic syndrome**, or **there is evidence that the person biopsied is just recovering from the nephrotic syndrome**.

In **adults**, the commonest single finding is a segmental sclerosing condition. Most others have IgA nephropathy, diabetic glomerulopathy, lupus nephritis,

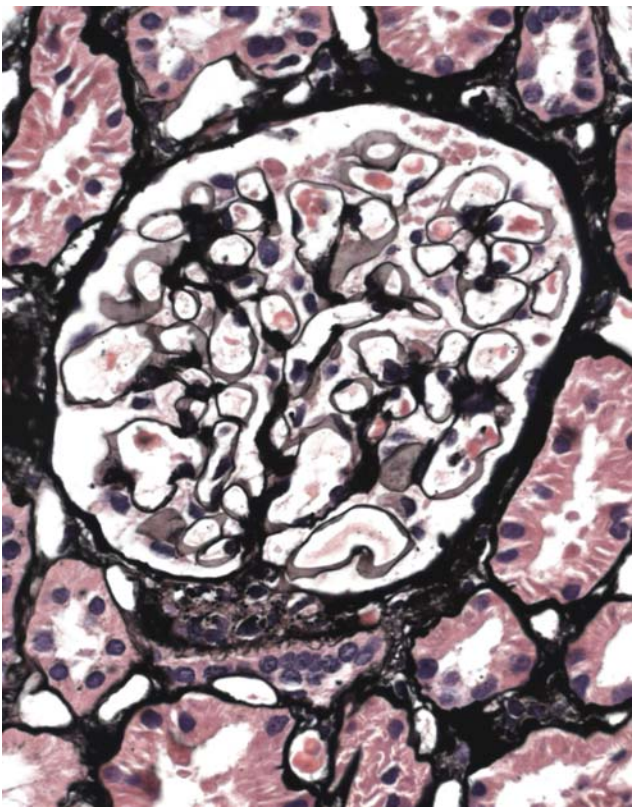

**Fig. 10.1** Apparently normal glomerulus in a renal biopsy specimen from a man whose age was not given to the pathologist, but who had asymptomatic proteinuria. This image is at the same magnification as the one in **Fig. 10.2** to emphasise the changes in that figure

membranous nephropathy, or thin glomerular basement membrane disease. Asymptomatic proteinuria on its own is an unusual finding in several of these disorders. Membranous nephropathy, for instance, almost always presents with the nephrotic syndrome. Thin glomerular basement membrane disease and IgA nephropathy are almost always associated with hematuria.

In **children**, renal biopsy in proteinuria is uncommon, but the most frequent findings are Henoch-Schönlein nephritis, a segmental sclerosing condition, and no detectable abnormality.

## Approach to Study of Renal Biopsy Specimens in Proteinuria

**Most specimens taken for investigation of proteinuria appear normal or close to normal on initial inspection** when the age of the person biopsied is taken into account, and provided that renal function is normal. Initial inspection at low power will show whether there is more chronic damage than expected for the age, in which

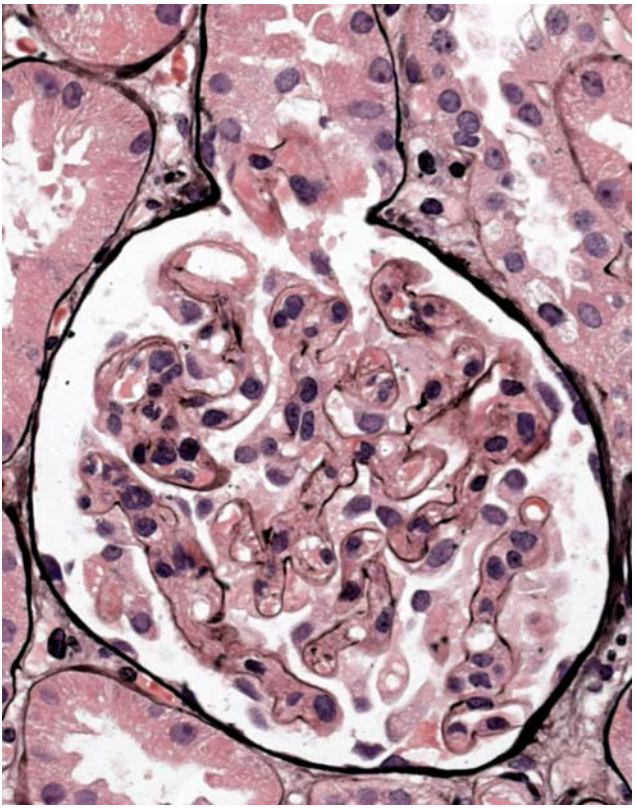

**Fig. 10.2** Glomerulus, photographed at the same magnification as the one in **Fig. 10.1**, in a renal biopsy specimen from a woman of 36, who had proteinuria apparently related to pre-eclampsia, but also had a stroke at delivery. The biopsy was to exclude vasculitis, of which there is no evidence. There is marked endothelial swelling, and part of the tuft has prolapsed into the tubular opening. These are typical features of pre-eclamptic changes in glomeruli. Proteinuria disappeared soon afterwards

case the specimen can be analysed as in Chapter 8 on the assumption that there is chronic renal failure. A common finding in proteinuria is a segmental sclerosing condition, and this should be sought first. Serial sections of the specimen are valuable, because only one segmental abnormality has to be found to have an important effect on interpretation.

## *Is There a Segmental Glomerular Disorder?*

Typically, in proteinuria, a segmental abnormality is genuinely **focal**, which means it appears to affect a few glomeruli but not all (Figs 8.4 and 8.5). In the nephrotic syndrome, although segmental sclerosing abnormalities are often called focal segmental

glomerulosclerosis, the abnormalities are usually in every glomerulus, which makes the condition diffuse rather than focal (Figs 6.27 and 6.28). The pathologist is usually able to be more helpful to nephrologists by a description of the extent of segmental changes, rather than by unqualified use of the vague and ambiguous term focal segmental glomerulosclerosis.

In **truly or genuinely focal segmental sclerosing conditions**, the glomerular changes may be at any position in the tuft. The rest of the tuft often appears normal or close to normal in cellularity, but may be enlarged (Fig. 8.4). On immunohistologic study, there is likely to be deposition of IgM in segmental abnormalities, and sometimes in mesangium (Fig. 8.5). Truly focal segmental sclerosing abnormalities persist, but generally, if there is any clinical progression with increase of proteinuria and development of renal impairment, this is slow.

**Reduced glomerular numbers**, equivalent to reduced nephron numbers or reduced renal mass, can produce proteinuria and segmental sclerosing glomerular lesions from effects of glomerular overload or hyperfiltration or hyperperfusion (Figs 5.13 and 8.3). This is the explanation of segmental lesions seen in some kidneys apparently damaged by chronic ischemia, such as in so-called hypertensive nephrosclerosis (Fig. 5.5). This may be the explanation of most or all examples of truly or genuinely focal segmental sclerosing disorder. Mechanisms could include an absolute reduction in number of nephrons from a congenital cause, even though the kidneys appear normal size on imaging, and severe obesity, in which there may be a relative reduction in number of nephrons, which is disproportionately small compared with the body mass.

Segmental sclerosing abnormalities may complicate many conditions, some of which may present with proteinuria. Before a truly or genuinely focal segmental sclerosing condition is diagnosed, these other conditions should be excluded. Examples of these are **IgA nephropathy** (Figs 8.1, 8.2, 9.1, and 9.3–9.6) and **membranous nephropathy** (Figs 6.8–6.14), both of which are diagnosed mainly by immunohistologic findings. The pathologist should give the diagnosis as that of the underlying condition, rather than focal segmental glomerulosclerosis combined with the other condition.

An important condition for the pathologist to consider in these circumstances is **hereditary nephropathy of Alport type**. Electron microscopy is necessary to investigate this possibility, which should be looked for especially in children with proteinuria, and in adults with a family history of renal disorders (Figs 9.2, 9.10, and 9.11).

## *Does the Request Form Give Information About a Systemic Disorder?*

In adults, **diabetic glomerulopathy** should be easy to diagnose from information on the request form about diabetes mellitus, and from typical changes in glomeruli (Figs 6.34–6.44). **Lupus nephritis**, similarly, is almost always suggested by infor-

mation on the request form (Figs 6.51– 6.62). In children, **Henoch-Schönlein nephritis** should be easy to diagnose from clinical information, and from the immunohistologic finding of IgA in glomeruli (Figs 7.25–7.27, 9.7, and 9.8).

## *Does the Specimen Appear Normal or Nearly Normal on Light Microscopy?*

A practical problem in investigation of proteinuria is the specimen that appears normal or nearly normal on light microscopy, without signs of segmental abnormalities, nor of diagnosable conditions, such as IgA nephropathy. There may be mesangial expansion, but this is not usually severe, and there is no doubling of glomerular capillary loops, which is found in subendothelial membranoproliferative glomerulonephritis. Such a specimen often has IgM in mesangium on immunohistologic study.

Electron microscopy occasionally shows **thin glomerular basement membrane disease**, which may present with proteinuria alone, either genuinely or more likely spuriously, because hematuria was present but was not mentioned on the request form (Figs 5.1, 5.7, 5.10, and 9.9). Electron microscopy may also show glomerular basement membranes that are regularly thickened, and indicate early **diabetic glomerulopathy** (Fig. 6.44), or irregularly thickened and thinned with an irregular outer aspect, and indicate **hereditary nephropathy of Alport type** (Figs 9.10 and 9.11).

If electron microscopy shows glomerular basement membranes of normal thickness, there may be apparent fusion of foot processes of epithelial cells, although this is a response to proteinuria not a cause of it. To give a satisfactory name to this condition is difficult for the pathologist. Sometimes, glomeruli appear large. This suggests the possibility that there are changes attributable to effects of reduced glomerular numbers, even though no segmental lesions are seen in the specimen, and the kidneys may appear normal in size on clinical imaging (Figs 10.3 and 10.4). The clinical course is likely to be persistence of proteinuria, with gradual development of segmental sclerosing lesions in glomeruli and tubular atrophy accompanied by renal impairment, especially if hypertension develops.

The term **IgM nephropathy**, or similar terms such as IgM mesangial glomerulonephritis, is sometimes used, although these terms are used in different ways and may not apply to one condition. Even if they do apply to one condition, it is not understood. Some pathologists use these terms when there are segmental sclerosing abnormalities, and some confine them to specimens without segmental changes. Several conditions, including minimal change nephropathy and thin glomerular basement membrane disease, have IgM detectable in mesangium, and so this finding alone has little significance. A sensible course for a pathologist is to use terms such as IgM nephropathy only when necessary, when no other diagnosis is available. Even truly focal segmental sclerosing glomerulonephritis is a preferable term, if appropriate.

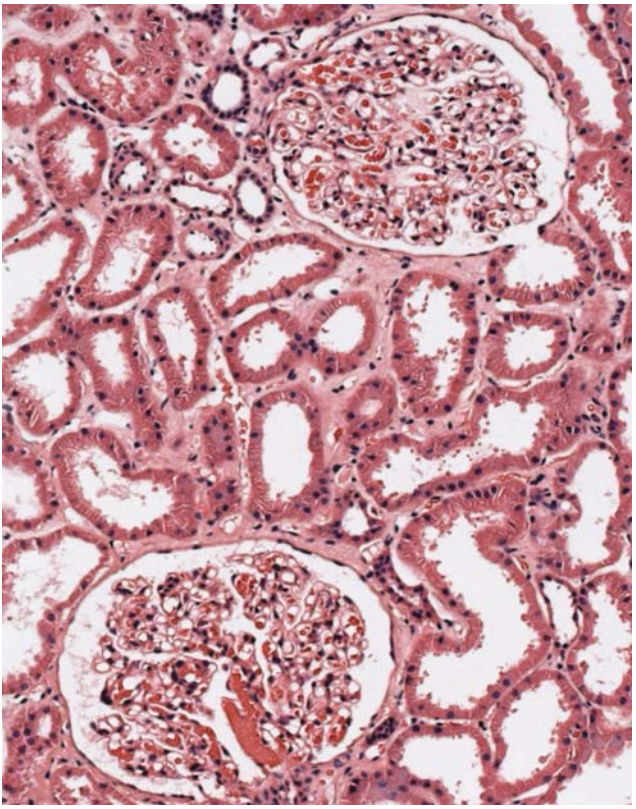

**Fig. 10.3** Cortex in a renal biopsy specimen from a woman of 34 with persistent proteinuria, first detected in pregnancy a few years before the biopsy. The kidney appears nearly normal, but glomeruli are a little enlarged, and have slight mesangial expansion. Immunohistologic study is illustrated in **Fig. 10.4**, and shows deposition of IgM in mesangium. Electron microscopy shows normal glomerular basement membranes. This is probably an early stage of overload glomerular changes

## The Unsatisfactory Nature of the Terms Mesangial Proliferative Glomerulonephritis, and Focal or Segmental Proliferative Glomerulonephritis

Some pathologists use the diagnosis mesangial proliferative glomerulonephritis. This seems to be applied to a variety of conditions, and is accordingly unsatisfactory. Another reason why this should be avoided, if possible, is that a person speaking to a pathologist or reading a report may confuse this term with mesangiocapillary or membranoproliferative glomerulonephritis (Figs 6.50, 6.82, and 6.84).

With thorough investigation, most renal biopsy specimens can be given a less vague diagnosis, such as IgA nephropathy (Figs 8.1, 8.2, 9.3, and 9.4), lupus nephritis (Figs 6.51–6.62), acute postinfective glomerulonephritis (Figs 6.20, 6.79,

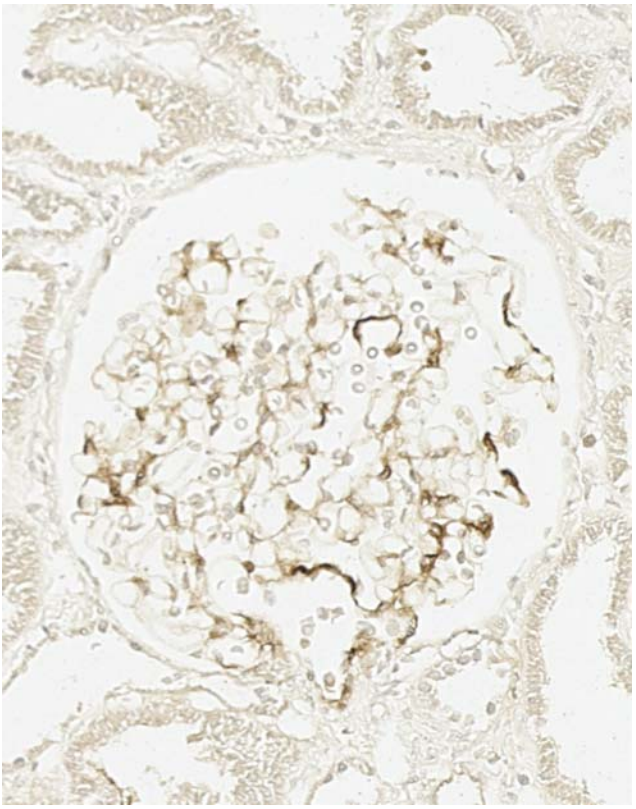

**Fig. 10.4** Cortex in the renal biopsy specimen from the woman of 34, which is illustrated in **Fig. 10.3**, examined by an immunoperoxidase method to detect IgM, which is found in mesangium

and 6.81), diabetic glomerulopathy (Figs 6.34– 6.44), early classic segmental sclerosing glomerulonephritis (Figs 6.23, 6.25, and 6.26), light chain glomerulopathy (Figs 6.45– 6.48), fibrillary-immunotactoid glomerulopathy (Figs 6.77 and 6.78), and hypoxic glomerular changes (Fig. 8.6).

Rare conditions that may give the appearance of mesangial expansion include nail patella syndrome, fibronectin nephropathy, and collagen type three nephropathy. Some pathologists use the diagnosis C1q nephropathy, but this condition is not well defined.

Similar problems occur with the diagnosis focal or segmental proliferative glomerulonephritis.

With adequate investigation, most renal biopsy specimens can be given a more precise diagnosis, such as IgA nephropathy or Henoch-Schönlein nephritis (Figs 7.25–7.27, 8.1, 8.2, 9.3, and 9.4), vasculitic glomerulonephritis (Figs 7.12–7.18, 7.23, and 7.28), and early classic segmental sclerosing glomerulonephritis (Figs 6.23, 6.25, and 6.26).

## Summary: Proteinuria

Renal biopsy specimens in asymptomatic proteinuria on its own are the most difficult for a pathologist to investigate.

Most specimens taken for investigation of proteinuria appear normal or close to normal on initial inspection.

A common finding is a segmental sclerosing condition, and this should always be sought in proteinuria.

Otherwise, there is a variety of conditions that can be found in proteinuria.

## Further Reading: Proteinuria

D'Agati VD, Jennette JC, Silva FG. Non-Neoplastic kidney diseases. Atlas of Nontumor pathology, first series, fascicle 4. Washington, DC: American Registry of Pathology and Armed Forces Institute of Pathology, 2005. Chapters 6, 18.

Jennette JC, Olson JL, Schwartz MM, Silva FG. Heptinstall's Pathology of the Kidney. Sixth ed. Philadelphia: Lippincott Williams and Wilkins, 2007. Chapters 5, 17.

# Chapter 11
# Indication for Biopsy: Renal Allograft

## Introduction to Renal Allograft Biopsy Specimens

Most renal allograft biopsies are taken because of **impaired excretory function** called **graft dysfunction**. This could be called acute or chronic renal failure, as appropriate, although these terms are rarely used following transplantation. The extreme cases are when the graft has not functioned at all or has completely lost function.

**Allograft** means a graft from a human donor who is not genetically identical with the recipient. Allo- is from the Greek for other. Graft comes from the Greek for a stylus or style, an instrument used for writing on wax tablets, from the resemblance between its shape and that of shoots of plants inserted to grow in other plants, which is how grafting began. Virtually all transplanted kidneys are **allografts**, and that is the word used in this text.

An **isograft** is much rarer. Iso- is from the Greek for equal. This graft is from a donor genetically identical with the recipient, which means that the pair are monozygotic or identical twins. The recipient has no immune response against the graft, and immunosuppression is not necessary. A successful graft between identical twins in 1954 in Boston, Massachusetts, had a great effect, because it showed that kidney transplantation was feasible, even though it was not the first human transplant, as is sometimes said. A **xenograft**, from the Greek for foreign, is a graft from a donor of a different species to the recipient. Xenografts are experimental at the moment, but had been tried in people before 1954, as had allografts. An **autograft**, from the Greek for self, is removal of a person's own kidney and replacement in the body, but this is not a procedure that will cure chronic renal failure.

Transplanted kidneys are from people whose brainstem has died, called cadaveric donors, or from living people. Cadaveric kidneys are removed either while the donor is on a ventilator, and the kidneys are still perfused with oxygenated blood, or after circulation has stopped, in a non heart beating donor. Potential live donors are usually investigated thoroughly, to make sure they have no condition of the kidneys or other organs that would be a contraindication to transplantation. This may reveal an abnormality that requires investigation by renal biopsy, analysed as in the appropriate chapter, depending on the indication for biopsy.

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## Reasons for Biopsy of an Allograft Other than Dysfunction

There are a few other reasons for biopsy of an allograft or potential allograft.

1. Sometimes a kidney is sampled after surgical removal, **to see if it is suitable to be transplanted**.

   Renal transplantation is rarely an emergency. After removal, a kidney is perfused with a suitable solution to remove blood and is kept cold in ice. The interval between perfusion and preparation of the kidney for transplantation is the **cold ischemic time**, which is ideally under 24 h but if necessary can be longer, and some kidneys have been grafted more than 48 h after removal. Outcome of the transplant is slightly worse if the cold ischemic time is over 24 h. The **warm ischemic time** is the interval between removal of the kidney from ice, and opening of the vascular clamps to perfuse the graft with blood. The shorter this time is, the less damage the kidney is likely to have.

   If a pre-transplant sample is taken, the pathologist usually has time to have sections prepared of the specimen embedded in paraffin wax rather than frozen sections, which are ready more quickly than paraffin sections but are less satisfactory for detailed microscopy. The kidney may be from a donor known or suspected to have significant renal disease, and the pathologist may be able to diagnose this and give an assessment of whether the disease and the amount of chronic damage make transplantation undesirable. This is a matter of opinion rather than of established rules, but the amount of chronic damage that has to be present before the outcome is affected is much more than is usually seen in transplanted kidneys (Fig. 11.1).

   Sections of frozen material may be necessary in an emergency. The surgeon may have noted a lesion when the kidney is finally prepared for transplantation, and the potential recipient is under a general anesthetic. The pathologist may diagnose a neoplasm or an early stage of adult polycystic kidney disease, which are usually contraindications to transplantation.
2. A sample of a kidney is often taken by the surgeon **immediately after the kidney has been grafted**, either as a wedge of the capsular surface or as a needle biopsy.

   This is called an implantation biopsy, or post perfusion biopsy, or 30 min biopsy, or other terms. Such a specimen is useful, because the pathologist can determine the condition of the transplanted kidney, particularly the extent of chronic damage and state of the blood vessels, which may have evidence of chronic intimal thickening, atherosclerotic embolism, or hyalinosis (Figs 5.15, 11.2, and 11.3). Knowledge of this **pre-existing damage** helps the pathologist to interpret changes in later specimens. The specimen is also useful to show who has received a graft and when they received it. Ideally, the pathologist should be informed about the original renal disease in the recipient, although the surgeon may not know this.

   Sometimes, the surgeon gives details of the donor, such as age, sex, and cause of death if it was a cadaveric donor, or whether it was a living donor. These specimens often show globules of cytoplasm in the lumen of tubules,

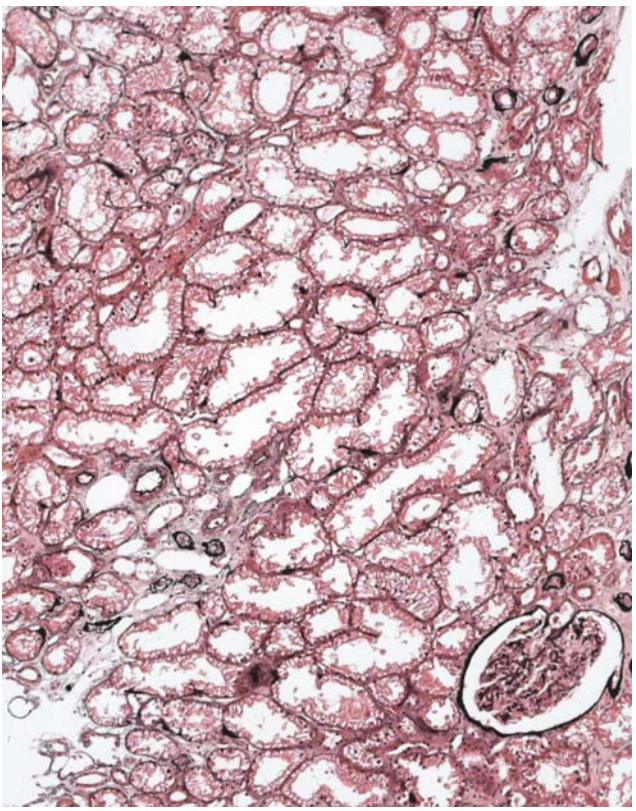

**Fig. 11.1** Cortex in a wedge biopsy specimen of kidney removed after death from a man of 34, who had a head injury, severe loss of blood, and progressive renal impairment over a few hours before death. The biopsy was to see if the kidney could be transplanted. There is a little tubular atrophy, and most tubules show acute damage with flattened epithelium. Tubules also have fine vacuolation, which is consistent with use of mannitol. The pathologist recommended that the kidney should be used. The kidney was transplanted into a man of 48. Although there was no function for 10 days, the graft worked well afterwards

particularly proximal tubules, that may reflect autolysis, but seem to have no significance related to graft function. This is sometimes called preservation injury, or ischemia/reperfusion injury. Proximal tubules may have fine vacuolation of their cytoplasm if the donor had had cerebral edema treated with the osmotic diuretic mannitol, but this change also seems to have no significance related to graft function (Fig. 11.1). Despite these and other changes, the pathologist may be able to identify features of genuine acute tubular damage, which must have been present in the donor (Figs 7.3 and 7.4). The significance is that a graft with this damage is likely to take longer to function than one without the damage.

There may be an unsuspected glomerular disorder, or something else (Fig. 4.9). If every implantation biopsy specimen is investigated thoroughly, thin glomerular basement membrane disease may be found in about one in 20

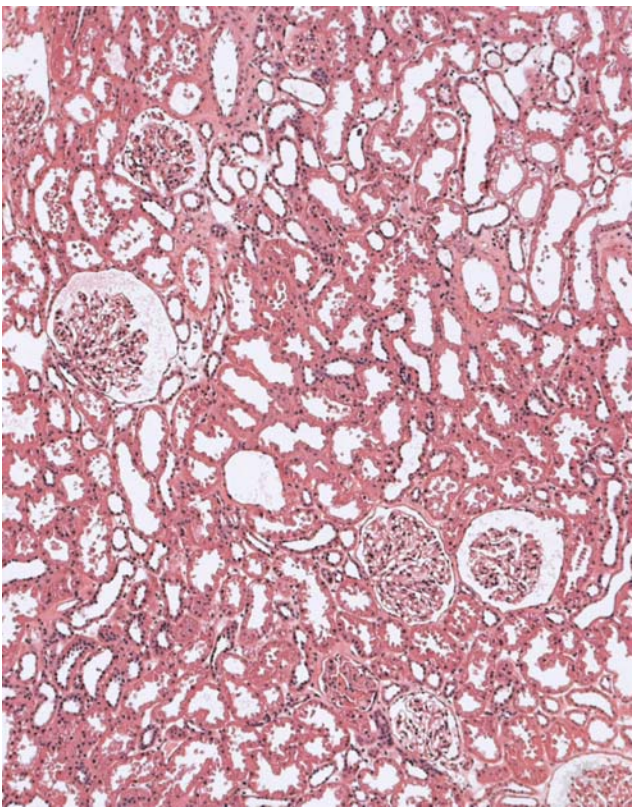

**Fig. 11.2** Cortex in a wedge biopsy specimen of kidney taken at the time of transplantation into a woman of 24 from a boy of 16, who died of a subarachnoid hemorrhage. The kidney appears normal, and the graft worked well

samples, while other conditions, such as IgA nephropathy or diabetic glomerulopathy, will be found less commonly. Identification of such conditions is helpful in interpretation of later specimens, but whether pre-existing glomerular disorders have a significant effect on outcome of a graft by themselves is doubtful. The amount of chronic damage associated with those disorders, or arising from other factors such as ischemia, is more important in prognosis. Even the amount of chronic damage is less important in outcome than immunologic, vascular, ureteric, and other problems that develop after transplantation. Some conditions should get better after transplantation. For instance, IgA should disappear from glomeruli in a kidney from a donor with IgA nephropathy, provided that the recipient does not also have IgA nephropathy.

3. Occasionally, if a surgeon is operating on a graft for reasons such as ureteric or vascular problems, a biopsy is taken **just because the surgeon is there**.
4. Some centres take biopsies at set intervals after transplantation, irrespective of renal function. These are called **protocol** biopsy specimens.

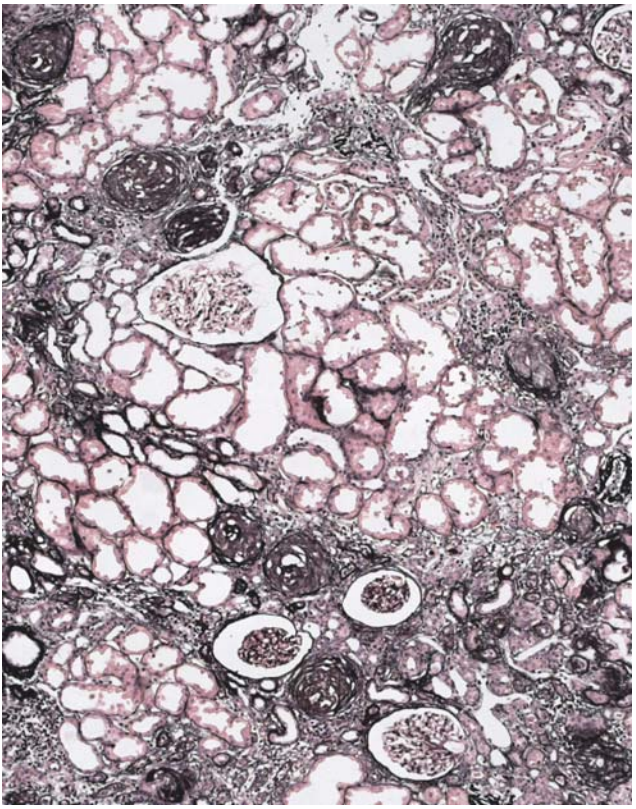

**Fig. 11.3** Cortex in a wedge biopsy specimen of kidney taken at the time of transplantation into a woman of 46 from a woman of 57, who died of a brainstem infarct. There is extensive chronic ischemic damage. Neither this kidney nor the other one from the same donor worked well. An index of chronic damage (**Fig. 5.6**) of 40 % or more indicates that graft survival is likely to be shorter than average. In this specimen, the index of chronic damage is 46 %

5. Allografted people may have **a renal problem other than abnormal excretory function**, or as well as abnormal excretory function, such as the nephrotic syndrome, and this may be the reason for the biopsy.

## Value of Biopsy of a Renal Allograft

The most common reason for surgeons or nephrologists to take an allograft biopsy specimen is to determine whether there is evidence of a significant immunologic reaction by the recipient against the graft, which is traditionally called **rejection**. This is one of the few circumstances in which a pathologist's report can have a decisive immediate influence on clinical management, and may help to save a graft that otherwise would have been lost, or help to avoid unnecessary treatment, or indicate

the need for further investigations. Biopsy is much better done before treatment of rejection, rather than afterwards, when the pathologist may not be able to say whether or not there had been significant rejection.

## Technical Handling of Renal Allograft Biopsy Specimens

Specimens taken for investigation of graft dysfunction should be considered urgent, and processed and sectioned with the shortest possible delay. The same set of sections that is prepared for other specimens can be cut, and the pathologist should be given the sections stained by hematoxylin and eosin. **Most conditions of immediate clinical significance can be assessed on sections stained by hematoxylin and eosin**, even if only provisionally.

Most specimens need only orthodox light microscopic stains for adequate assessment. The full set should be prepared, to allow the pathologist to see many sections, and to make use of the stains in interpretation, for instance in judgment of the extent of tubular atrophy. Immunohistologic study or electron microscopy may occasionally be required, to investigate such things as possible viral infection, or possible recurrence of the original renal disease in the graft.

Cortex is required to allow the pathologist to assess allograft biopsy specimens. How much is required is a matter of judgment. The Banff group, so called because their meeting at Banff in Canada in 1991 was the first of a regular series at various sites, suggested in 1997 that an adequate specimen had at least ten glomeruli and at least two arteries. The minimum requirement was seven glomeruli and one artery, with at least two cores of cortex or two areas of cortex on the same core, studied with multiple sequential sections, 3–4 μm thick, on seven slides, three stained with hematoxylin and eosin, three with either periodic acid Schiff or periodic acid-methenamine silver, and one with a connective tissue stain.

## Approach to the Diagnosis in Renal Allograft Biopsy Specimens

The single most important piece of information that the pathologist needs on the request form with a biopsy specimen from a renal allograft is how long the kidney has been in the recipient.

The two common decisions that a pathologist should make are whether there is **significantly active, acute rejection that may respond to treatment**, and whether there is **chronic damage that will not respond to treatment**. Generally, the first problem arises in specimens taken soon after transplantation, meaning in the first few weeks, and the second problem in specimens taken long after transplantation.

Another problem for the pathologist is to decide whether there is any other identifiable reason for graft dysfunction.

Most specimens can be given a satisfactory diagnosis by a pathologist. An important rule is that **there may be more than one condition in a specimen**.

Traditionally, rejection is divided into acute and chronic, although the pathogenesis of chronic rejection is not understood, and this may not be an immunologic process at all.

### *Is There Evidence of Acute Rejection?*

Before satisfactory identification of blood group and histocompatibility antigens of the potential donor and recipient, and cross-matching procedures between cells from the donor, such as lymphocytes, and serum from the recipient, there were examples of **hyperacute rejection** caused by an immediate response of antibodies in the recipient against the endothelium in the kidney. Soon after the vascular anastomoses were completed and blood was allowed to perfuse the graft, this became discolored and never worked, and the pathologist saw thrombus in glomerular capillaries, either in an implantation specimen or in a specimen taken within a few days of transplantation. In theory, hyperacute rejection should not occur these days, but may still be seen if there have been technical problems with matching donor and recipient (Fig. 11.4).

## Antibody-mediated Rejection

Hyperacute rejection is the most dramatic type of **antibody-mediated rejection**, which may be seen in a form that can be called **delayed hyperacute** or **accelerated acute rejection**. This may be due to antibodies in the recipient against HLA or non-HLA antigens in the graft. Pre-existing antibodies could have been induced in a recipient by blood transfusion, pregnancy, or previous transplantation. If antibody-mediated rejection occurs, these antibodies either were not evident on the cross-matching procedures, or were detected but considered insignificant. New antibodies against the graft may also develop, despite immunosuppression.

This type of rejection often occurs in the first few weeks after transplantation, and a biopsy specimen shows many neutrophils adherent to the endothelium of capillaries between tubules, and often in glomeruli as well (Fig. 11.5). A marker that there has been a reaction between antibodies and endothelium is **C4d**, which is an inactivated form of the complement component C4. C4d detected by an immunohistologic method on the endothelium of intertubular capillaries is sometimes considered evidence of antibody-mediated rejection, especially if C4d is widespread (Fig. 11.6).

Interpretation of the clinical significance of C4d deposition is not straightforward. For example, extensive deposition is almost always found in recipients who have been apparently depleted of antibodies to A or B blood groups or HLA antigens to allow them to receive an ABO or HLA incompatible graft, and yet many have an uncomplicated outcome after transplantation. C4d may also persist for several days after rejection has been treated (Fig. 11.7).

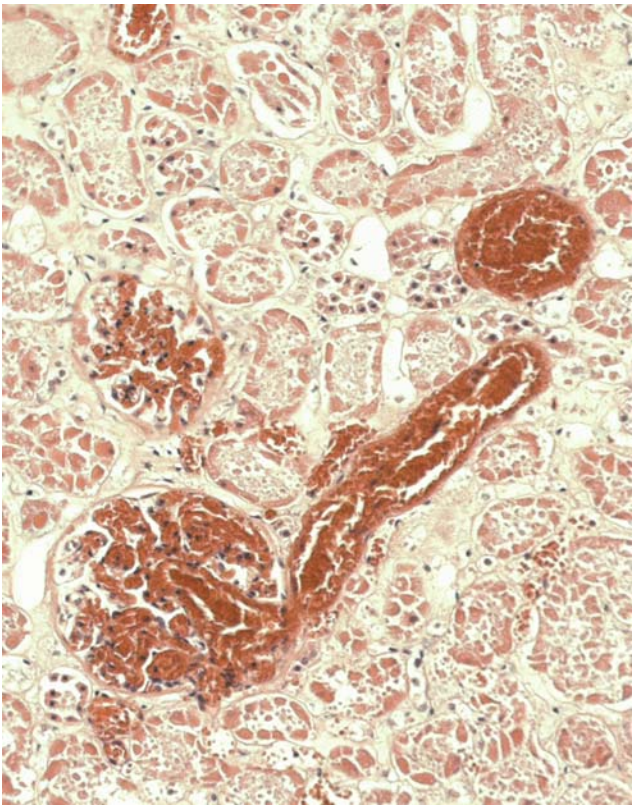

**Fig. 11.4** Cortex in a nephrectomy specimen removed 7 days after transplantation into a man of 63. The donor and recipient had a close match on HLA typing, but could not be directly tested for histocompatibility, because no lymphocytes were available from the donor. The graft never worked. There is thrombosis in glomeruli and small vessels with the appearances of hyperacute rejection

Although the Banff group recommended that every renal allograft biopsy specimen should be examined immunohistologically using an antibody to C4d, there is contradictory evidence whether this is justified in routine practice. The test is probably only useful when there are clinical or pathologic suggestions that there may be antibody-mediated rejection.

Diagnosis of antibody-mediated rejection should not be made on the finding of C4d alone. There should also be changes in a biopsy specimen such as neutrophils in intertubular capillaries and thrombosis in glomeruli, and the recipient should be shown by immunologists to have antibodies against donor antigens. The clinical importance of this diagnosis is that treatment may be required that is different from treatment of conventional rejection.

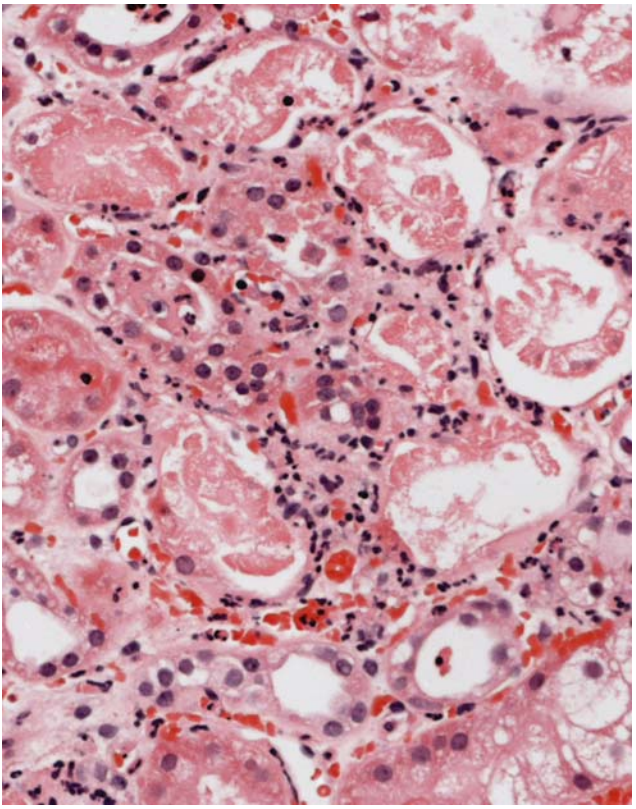

**Fig. 11.5** Cortex in a needle biopsy specimen of kidney taken 4 days after transplantation into a man of 25. There was no graft function. Tubules show severe acute damage, with a heavy infiltrate of neutrophils in intertubular capillaries. Immunoperoxidase staining for C4d is shown in **Fig. 11.6**, and helped to suggest the diagnosis of antibody mediated rejection

## Conventional Acute Rejection

Conventional **acute rejection** takes two forms that can occur independently or together, and can be seen with antibody-mediated rejection. The forms are **acute cellular rejection**, sometimes called acute tubular and interstitial rejection or acute tubulo-interstitial rejection, and **acute vascular rejection**. These days, acute vascular rejection is uncommon, particularly in its severe form. Acute rejection is commonest soon after transplantation, within the first few weeks, but can occur at any time after transplantation, for instance if there is a change in dose or type of immunosuppressive drugs. About one quarter of transplant recipients have at least one episode of acute rejection.

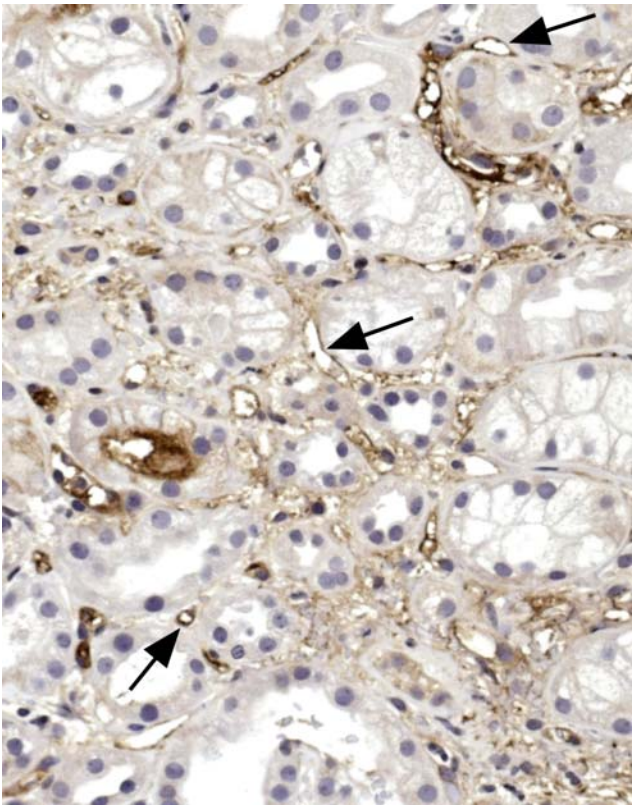

**Fig. 11.6** Cortex in the biopsy specimen from the man of 25 shown in **Fig. 11.5**, stained by an immunoperoxidase method for C4d. This is seen on the endothelium of many intertubular capillaries, some of which are arrowed. Before the transplant, there was a close HLA match between donor and recipient, and recipient serum had no cytotoxic effect on donor lymphocytes. When the biopsy findings suggested antibody mediated rejection, further immunologic investigation showed that the recipient had an antibody to an HLA class two antigen, found on donor B cells, but not included in routine HLA typing. The man had had a previous renal transplant, which had the same class two antigen as the new donor

## Diagnosis of Acute Cellular Rejection, also Called Acute Tubulo-interstitial Rejection

**Acute cellular rejection**, in its more severe stages, is easy to diagnose. Sometimes, sections appear dark even before the pathologist looks at them with a microscope. At low magnification, there is an infiltrate of inflammatory cells, patchily or uniformly throughout the cortex (Fig. 11.8). At high power, the cells are mostly lymphocytes, and there is acute damage to tubules, which are separated by the inflammatory infiltrate and edema (Fig. 11.9). Inflammatory infiltrates are not considered significant if they are in areas of fibrosis, such as in the subcapsular cortex if there is chronic ischemic damage or in connective tissues around arcuate vessels (Fig. 11.10).

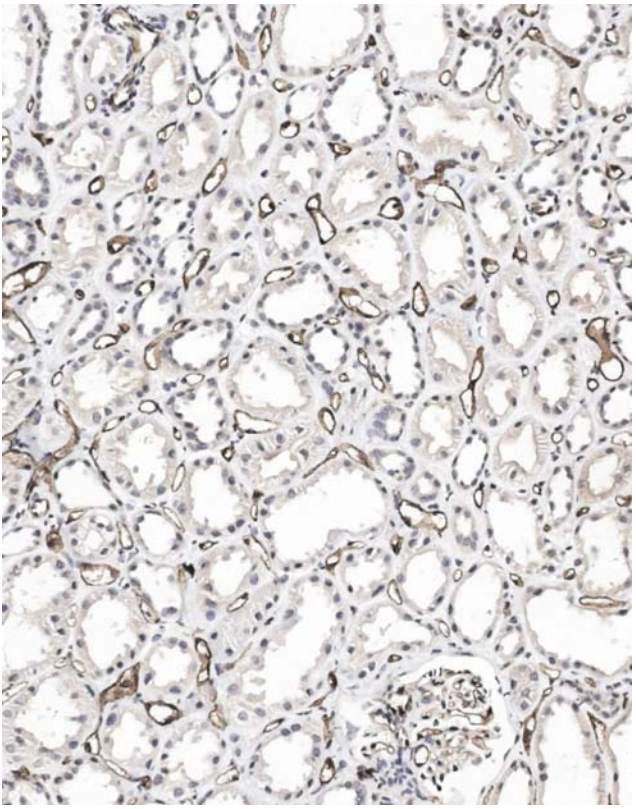

**Fig. 11.7** Cortex in a needle biopsy specimen of kidney taken 2 weeks after transplantation into a woman of 43. Vascular access to allow hemodialysis was becoming so difficult that a cadaveric kidney was accepted for transplantation, even though the recipient had antibodies to HLA class two antigens in the donor. With extra immunosuppression at transplantation, graft function was satisfactory until 9 days after transplantation, when there was a swollen, tender kidney with oliguria and a marked rise in serum creatinine concentration. Biopsy was not done at that time, because there was a fear of rupture of the graft. Intensive treatment for presumed antibody-mediated rejection produced clinical improvement in symptoms, but not in renal function. The biopsy specimen is stained by an immunohistologic method for C4d, and shows extensive deposition in the endothelium of intertubular capillaries, but without any other evidence of rejection. The graft recovered function without additional treatment

Acute cellular rejection is a reaction against antigens on tubular cells by T lymphocytes, particularly CD8 positive cytotoxic cells. The feature that is the strongest indicator of this type of rejection is infiltration of lymphocytes across tubular basement membranes to lie inside the tubular epithelium (Fig. 11.9). This is often called tubulitis. A lymphocytic infiltrate is disregarded in atrophic tubules, which are recognised by reduction in size of the tubules, with thickening of their basement membrane.

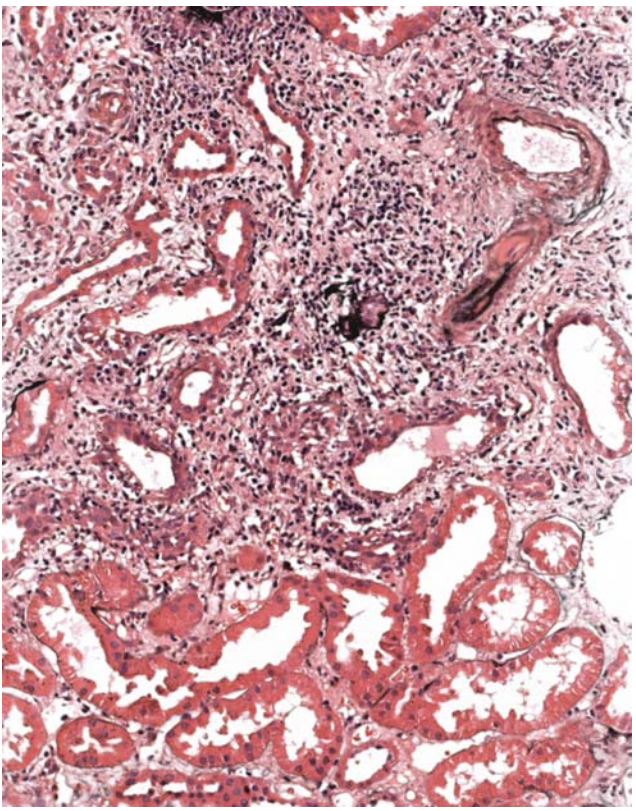

**Fig. 11.8** Cortex in a needle biopsy specimen of kidney taken 6 days after transplantation into a man of 35. Initial function was satisfactory, but then deteriorated. There is a lymphocytic infiltrate with edema. Tubules are acutely damaged, and there is an infiltrate of lymphocytes into them. Features are those of significant acute cellular rejection

## Diagnosis of Significant Acute Cellular Rejection

The problem is that acute cellular rejection is not all or none. There is a gradation from no cellular infiltrate to widespread infiltration of the cortex. The extent of lymphocytic infiltration of tubules varies widely, even in the same specimen. A difficulty for the pathologist is to decide when the features are those of acute cellular rejection of sufficient intensity to be clinically significant. This means that the immunologic response is producing enough damage to give renal dysfunction and that treatment of the response is likely to allow the kidney to recover.

The distinction between significant acute cellular rejection and a clinically insignificant cellular infiltrate is arbitrary. Grading schemes have been devised to try to standardise interpretation of changes in renal allograft biopsy specimens. At the moment, these schemes largely depend upon guesswork and the opinion of the pathologist rather than upon measurement or strictly objective criteria.

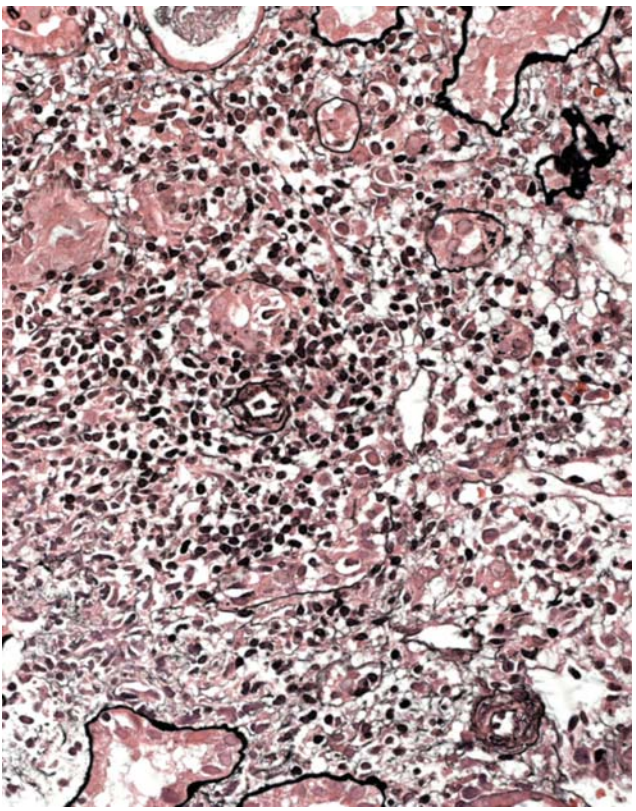

**Fig. 11.9** Cortex in a needle biopsy specimen of kidney taken 2 months after transplantation into a man of 24. Function was satisfactory, but suddenly deteriorated. There is a lymphocytic infiltrate with edema. Tubules are acutely damaged, and there is an infiltrate of lymphocytes into them, obscuring the epithelium in several tubules. Features are those of significant acute cellular rejection

In the scheme suggested by the Cooperative Clinical Trials in Transplantation (CCTT), the threshold for diagnosis of **clinically significant acute cellular rejection** is that the mononuclear cell inflammatory infiltrate occupies at least 5 % of the cortical area, by guesswork, and that in the most heavily infiltrated areas there are at least three tubules with an infiltrate of lymphocytes in ten serial microscopic fields with a ×40 objective. The original scheme stated that there must also be at least two of these three additional features, edema, tubular degeneration or injury, and reactive lymphoblasts, although these features are not necessary when the biopsy is taken for graft dysfunction, but may be useful in interpretation of protocol biopsy specimens.

In the scheme suggested by the Banff group in 1997, the threshold for diagnosis of **clinically significant acute cellular rejection** is that at least 25 % of the cortical area, by guesswork, has an inflammatory infiltrate, and there are at least four lymphocytes within a tubule in more than one area. In the Banff scheme, there is no

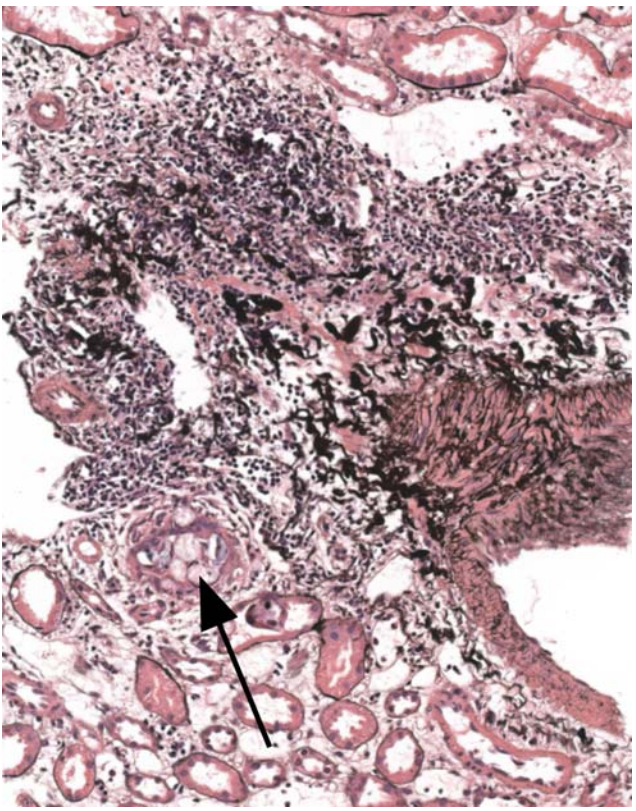

**Fig. 11.10** Cortex in a needle biopsy specimen of kidney taken 8 days after transplantation into a man of 17. There was no function. There are dense clusters of lymphocytes at the corticomedullary junction around arcuate vessels, but these are disregarded in assessment of rejection. There is no evidence of significant rejection in the cortex. A few tubules contain crystals (arrowed), a feature of acute tubular damage

requirement for edema, tubular degeneration or injury, and reactive lymphoblasts. Also, in the Banff scheme, changes between roughly the CCTT threshold and the Banff threshold for clinically significant acute cellular rejection are called borderline or suspicious for rejection, except that the lower limit for the Banff scheme is that the inflammatory infiltrate occupies at least 10 % of the cortical area, by guesswork.

The borderline category is not helpful to surgeons or nephrologists who are looking for guidance to help their decision whether to treat rejection. For this reason, the pathologist should take the responsibility and say whether the changes are significant or not. The Banff category of borderline or suspicious for rejection usually indicates clinically significant acute cellular rejection in renal allograft biopsy specimens, other than those from grafts that have been treated for rejection shortly before the biopsy, or those that are protocol biopsy specimens. The pathologist should know whether either of those conditions applies to a particular specimen, and can report accordingly, for instance that there seems to have been significant acute cellular rejection with an apparent response to treatment.

Acute cellular rejection is identical in appearance to acute interstitial nephritis (Figs 7.34 and 7.35). In theory, an allograft could have an acute interstitial nephritis as an allergic response to a drug, but no pathologist with the tests routinely available would be able to differentiate this with certainty from acute cellular rejection.

## Diagnosis of Acute Vascular Rejection

**Acute vascular rejection** is easy to diagnose. **Any features of it that the pathologist is confident are present are enough to indicate clinically significant rejection**, even if only one artery is affected.

These features are widening of the space between the endothelium and the underlying tissues in arteries of any size, with infiltration of lymphocytes into this space (Figs 11.11 and 11.12). This abnormality is sometimes called intimal arteritis, intimal vasculitis, endarteritis, or arterial endothelialitis. The infiltrating cells are mostly T lymphocytes of both CD4 and CD8 types. Changes in the intima of venules and veins are not considered significant (Fig. 11.13).

Acute vascular rejection is an easier diagnosis to make than acute cellular rejection, because any definite features of acute vascular rejection are significant, no matter how small or scarce. Not even the full circumference of an artery has to be affected (Fig. 11.11). Compared with acute cellular rejection, acute vascular rejection is generally more difficult to treat, less likely to return to normal, and more likely to leave significant chronic damage, and no definite features of it should be ignored or considered insignificant.

Another feature that may be seen in acute rejection is a glomerular disorder called **acute allograft glomerulopathy**. Glomeruli appear hypercellular, with swollen endocapillary cells and an infiltrate of lymphocytes (Fig. 11.14). This is uncommon, usually occurs shortly after transplantation, and is often associated with signs of significant rejection, particularly acute vascular rejection.

Acute vascular rejection is considered **severe** when affected arteries have damage in the media as well as in the intima. Specifically, there is fibrinoid necrosis of the media, with or without infiltration of inflammatory cells into the media. There may be thrombosis in these vessels. Severe acute vascular rejection is often accompanied by interstitial hemorrhage, and sometimes by necrosis of parts of the kidney (Fig. 11.15). This type of rejection is particularly likely to cause irreversible damage to a graft, but is rare, and in practice, virtually only seen when immunosuppression is withdrawn.

## Summary of Acute Rejection

The pathologist should use one of five diagnoses related to acute rejection. These are antibody-mediated rejection, significant acute cellular rejection, acute vascular rejection, severe acute vascular rejection, and no evidence of significant acute rejection.

The three diagnoses of rejection, other than the antibody-mediated type, correspond to types one, two, and three, respectively, in the CCTT and Banff systems,

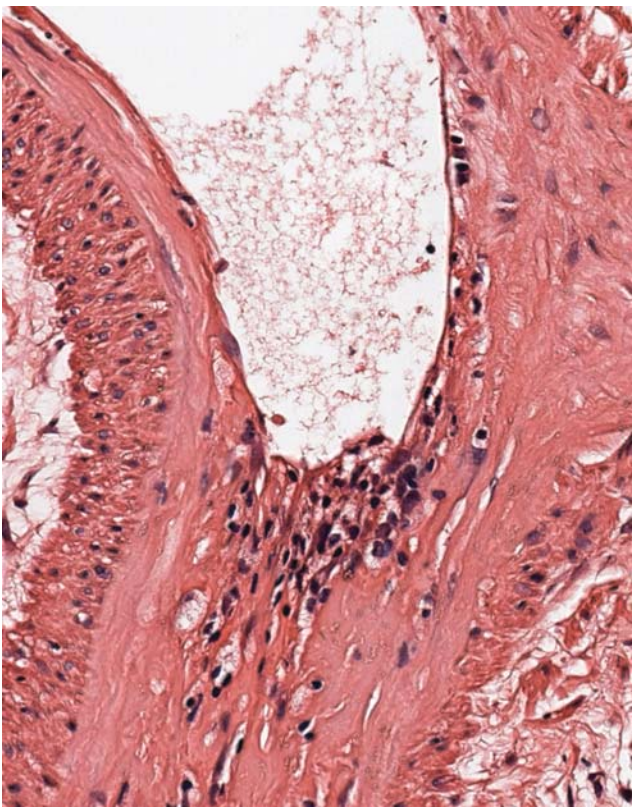

**Fig. 11.11** Cortex in a needle biopsy specimen of kidney taken 13 days after transplantation into a woman of 43 from a woman of 50, who died of a subarachnoid hemorrhage. Initial function was satisfactory, but then deteriorated. An arcuate artery has pre-existing chronic intimal thickening from the donor. There are lymphocytes under the endothelium in places, a sign of acute vascular rejection

although these have different criteria to separate significant and insignificant acute cellular rejection.

More elaborate schemes, such as those suggested by the Banff group, are ways of recording and grading the great variety of changes that can be seen in allografts. In general, these are poorly reproducible between pathologists, and of little or no clinical use.

## *Is There Any Other Acute Abnormality Instead of Acute Rejection, or in Addition to It?*

If an allograft is not working, there is a structural disorder of tubules, as there is in any kidney with acute renal failure.

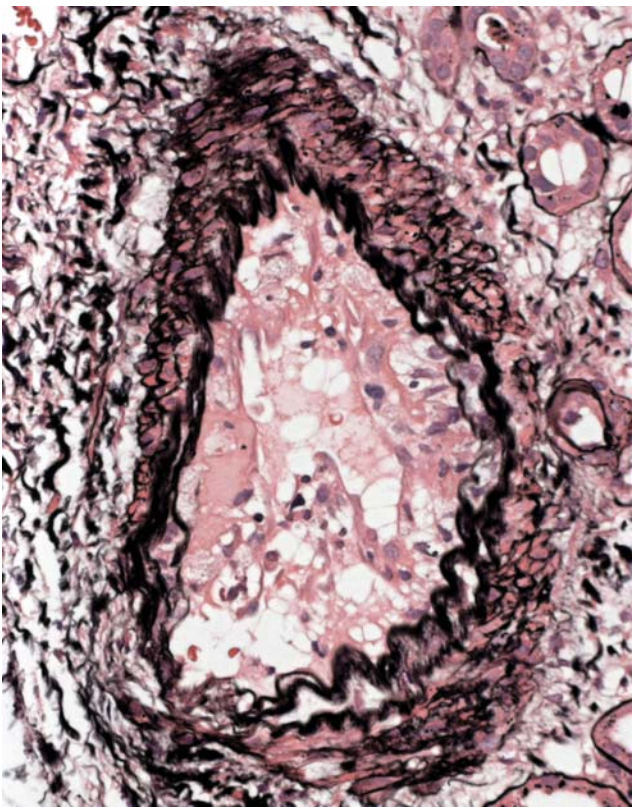

**Fig. 11.12** Cortex in a needle biopsy specimen of kidney taken 10 days after transplantation into a man of 33. There was no function. An artery has loose intimal swelling with an infiltrate of lymphocytes. Features are those of acute vascular rejection

In the early stages after transplantation, a common clinical problem is delayed graft function. The main differential diagnosis is between significant acute rejection as a cause of acute tubular damage, and acute tubular damage without significant rejection, almost always called acute tubular necrosis by nephrologists and surgeons.

**Acute tubular damage** is inevitable to some extent after transplantation, although it may be so clinically insignificant that the graft works immediately. Acute tubular damage is likely to be more severe and longer lasting in grafts from cadaveric donors rather than living donors, in grafts from cadaveric donors who had extensive trauma or prolonged hypotension or whose heart was not beating at the time of removal of the kidney, and in grafts with particularly long cold or warm ischemic times (Fig. 11.16).

Both acute rejection and pure acute tubular damage can occur at any time after transplantation, and usually there is an explanation in the clinical history. An episode of acute rejection long after transplantation may be due to a change in immunosuppression, such as failure of the recipient to take drugs. An episode of pure acute

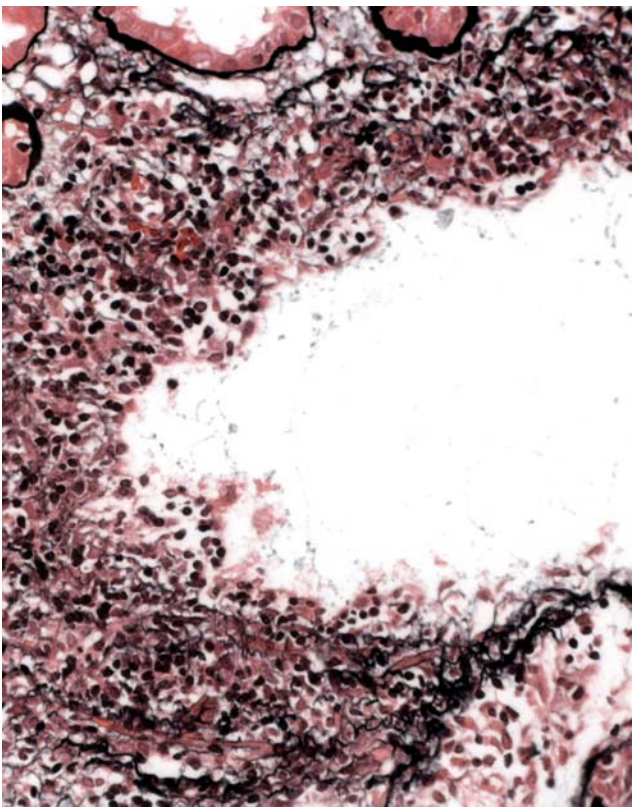

**Fig. 11.13** Cortex in the needle biopsy specimen of kidney taken 2 months after transplantation into the man of 24 with significant acute cellular rejection, which is illustrated in **Fig. 11.9**. A vein has an infiltrate under its endothelium, but this is not a sign of acute vascular rejection

tubular damage may be due to an event such as a myocardial infarct or an episode of sepsis with hypotension and underperfusion of the graft.

Other conditions that may occur especially in the early stages after transplantation include **infarction** and **infection**.

**Infarction** may be due to thrombosis in large arteries or veins, although this is now rare, or to severe acute vascular rejection, which is also rare, and should have characteristic changes in arteries (Fig. 11.15). Thrombus may be seen in small vessels as a complication of acute or chronic rejection, often without infarction (Fig. 11.17). Infarction may occur in part of the graft if one pole has its own artery separate from the main artery, and the accessory artery has not been anastomosed to a recipient artery, or if there is thrombosis only of some vessels. The affected part undergoes infarction (Fig. 11.18). The pathologist should report only that the tissue in the biopsy specimen is infarcted, not that the whole graft is infarcted. This is an example of the general rule that **a biopsy specimen may not be representative of the whole kidney**.

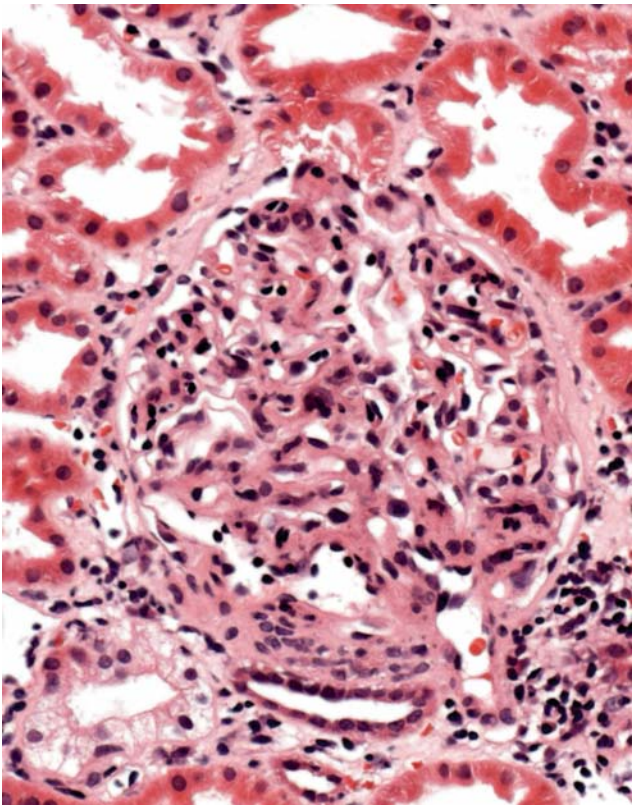

**Fig. 11.14** Glomerulus in a needle biopsy specimen of kidney taken 6 months after transplantation into a woman of 41, whose immunosuppressive drugs had been reduced. The glomerulus appears hypercellular with endothelial swelling, an infiltrate of lymphocytes, some of which are clustered and appear to run together, and prolapse into the tubular opening. Features are those of acute allograft glomerulopathy. There is evidence of acute cellular rejection elsewhere in the specimen

**Infection** of a graft may be ascending infection with pus in tubules, sometimes with evidence of bacteria or fungi (Fig. 7.36). Purulent infections and tuberculosis can also be carried to the graft in the blood, and there may be purulent infection around a graft (Fig. 4.3).

**Cytomegalovirus** infection is common as a systemic infection, but is now unusual in the graft itself. Large, infected cells with intranuclear inclusions may be seen in glomeruli or tubules, and can be confirmed to contain cytomegalovirus by immunohistologic study (Figs 11.19 and 11.20).

Another viral infection is with **BK virus**, a polyomavirus related to simian virus (SV) 40, and which can be detected immunohistologically using antibodies to SV40. BK virus initially infects transitional epithelium of the urinary tract and cells of the collecting duct, to produce large, distorted nuclei, containing indistinct inclusions

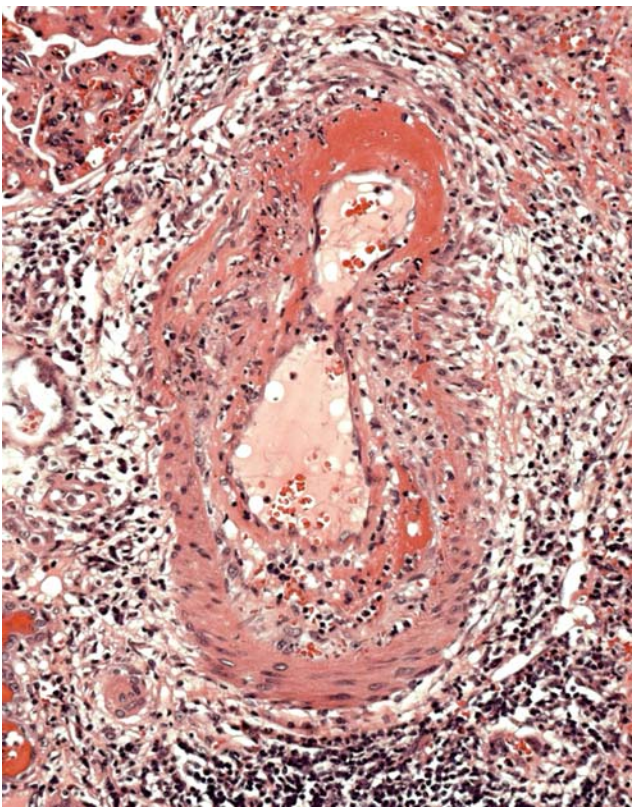

**Fig. 11.15** Cortex in a nephrectomy specimen from a woman of 22 removed 19 months after transplantation, and after immunosuppression had been withdrawn. An artery has fibrinoid necrosis, a sign of severe acute vascular rejection

(Figs 11.21 and 11.22). There is usually a chronic inflammatory response around infected tubules.

## *Is There Evidence of Chronic Rejection?*

Gradual loss of graft function is still a common problem, despite advances in control of acute rejection. The median survival of function is under 10 years, although the aim should be to have adequate function until the recipient dies of a cause unrelated to the kidney. Decline in function may be a sign of so-called chronic rejection, one feature of which is a disorder of blood vessels that can be called **chronic vascular rejection**. Although this is usually seen years after transplantation, changes may begin to appear within a few weeks of grafting.

This is a condition in which arteries develop concentric intimal thickening, without an inflammatory infiltrate in the intima (Fig. 11.23). The intimal changes do

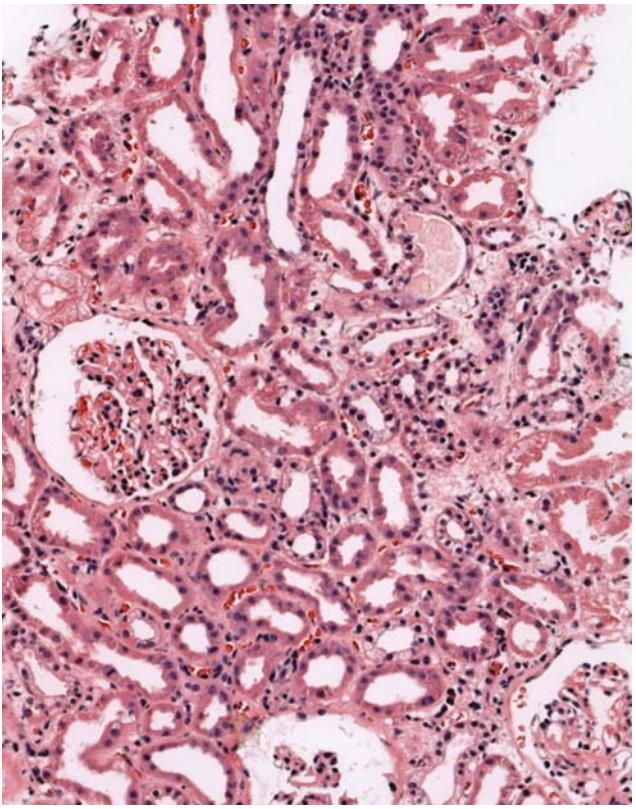

**Fig. 11.16** Cortex in a needle biopsy specimen of kidney taken 11 days after transplantation into a woman of 43. There was a period of hypotension, and there was no renal function. The graft is viable, and shows acute tubular damage without evidence of significant rejection

not have concentric rings of elastin fibres, and in this way can be differentiated from the chronic intimal thickening caused by age and hypertension (Fig. 11.24). Sometimes, there is an appearance of a new artery inside the old, with muscular media and internal elastic lamina (Fig. 11.25). There may be intimal foamy cells.

Usually, the affected arteries are larger than those included in biopsy specimens. Because of this, the pathologist may see no direct evidence of the arterial changes, and the diagnosis is suspected from changes in tubules, which show atrophy as a result of ischemia, and glomeruli, which may be shrunken, also from ischemia. Large renal veins may have similar changes to those in arteries, but these are unlikely to be seen in a biopsy specimen. Intertubular capillaries may have thickening and multilayering of their basement membrane, and deposition of C4d in their wall.

Glomeruli may also show **chronic allograft glomerulopathy**. There is mesangial expansion and doubled basement membranes, not always globally, often with areas of segmental sclerosis (Fig. 11.26). On immunohistologic study, there is slight

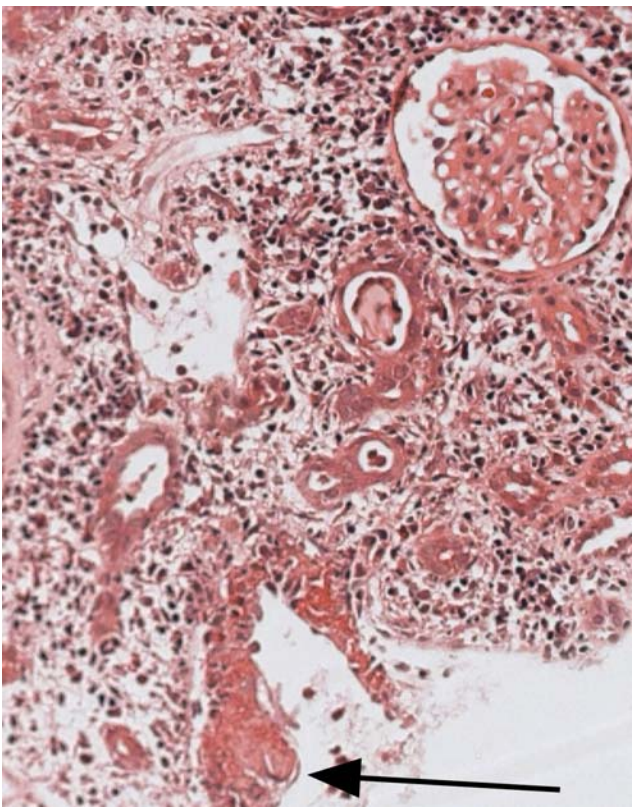

**Fig. 11.17** Cortex in a needle biopsy specimen of kidney taken 3 months after transplantation into a man of 24. There is evidence of significant acute cellular rejection with a thrombus in a small vein

deposition of IgM and complement in mesangium and subendothelial areas. On electron microscopy, glomeruli show subendothelial areas widened by material that lacks immune deposits (Fig. 11.27). This glomerulopathy may be accompanied by proteinuria, which is occasionally heavy enough to be in the nephrotic range.

In chronic rejection, there may be collections of lymphocytes, but these are in atrophic areas, and there is no sign of the active tubular damage that indicates significant acute cellular rejection. A few grafts have heavy infiltrates of plasma cells. Although this is sometimes called plasma cell-rich acute rejection, the infiltrates are mostly in areas with tubular atrophy rather than acute tubular damage, and there is usually little or no response to conventional treatment for acute cellular rejection.

Acute rejection can coexist with chronic rejection. In practice, a pathologist may have difficulty in deciding whether a lymphocytic infiltrate, in a graft with chronic damage, is a sign of significantly active cellular rejection. A feature which suggests significant acute cellular rejection is the presence of acute tubular damage in areas of lymphocytic infiltration, with lymphocytes inside tubules that are not atrophic (Fig. 11.28).

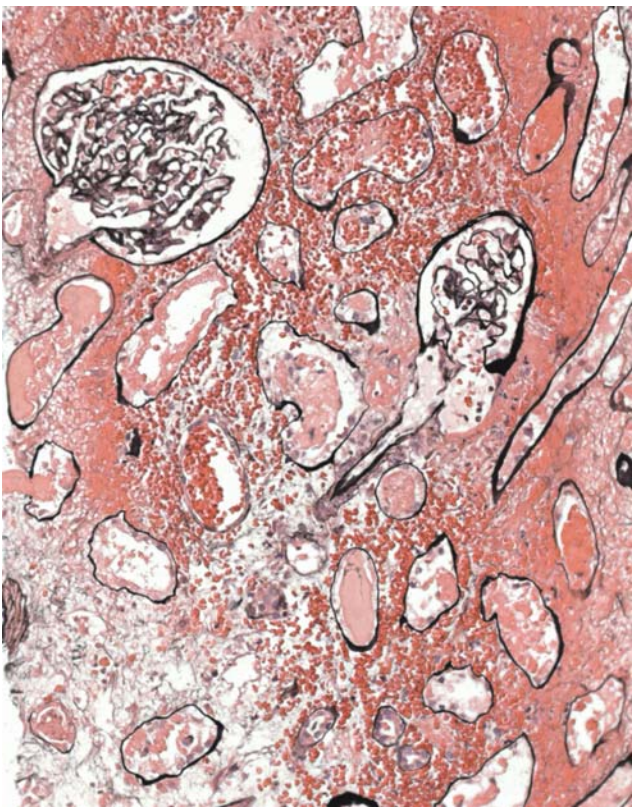

**Fig. 11.18** Cortex in a needle biopsy specimen of kidney taken 1 month after transplantation into a man of 37. There is hemorrhagic necrosis without evidence of acute vascular rejection. Only part of the kidney had venous thrombosis on radiographic investigation. The graft recovered function

## Differential Diagnosis of Late Damage in a Renal Allograft

Late damage in an allograft, meaning tubular atrophy in particular, does not only result from chronic rejection (Fig. 11.29). All late changes were grouped in the Banff system in 1991 under the term **chronic allograft nephropathy**. This was meant to be just a description, but the term was often taken to mean a specific diagnosis, synonymous with chronic rejection. For this reason, in 2005, the Banff group suggested that chronic allograft nephropathy should be no longer used.

Possible explanations of late damage in addition to chronic rejection are these.

1. **Damage may have been present in the kidney before transplantation**. The implantation biopsy specimen may help the pathologist to decide how much damage was pre-existing (Figs 5.15 and 11.3).
2. **Calcineurin inhibitors, used as immunosuppressants, have an ischemic effect on the kidney**. These drugs are tacrolimus and cyclosporine, whose

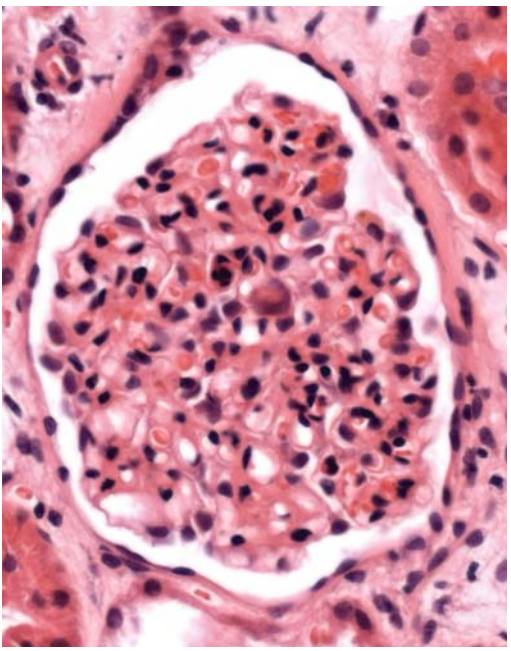

**Fig. 11.19** Glomerulus in a needle biopsy specimen of kidney taken 7 weeks after transplantation into a man of 53. There was acute graft dysfunction. Cytomegalovirus was detected in the blood. The biopsy specimen shows no evidence of significant rejection, but the glomerulus appears hypercellular, and contains large cells with atypical nuclei. Immunoperoxidase findings are shown in **Fig.** 11.20

Recommended International Non Proprietary Name is ciclosporin in the European Union. These may cause reversible acute tubular damage in the short term or irreversible tubular atrophy in the long term. These drugs may also produce fine vacuolation of tubular cells, often called isometric vacuolation, but similar changes may be seen in acute tubular damage from any cause, and as a result of mannitol treatment (Figs 5.9, 7.4, and 11.1). Calcineurin inhibitors may rarely cause a small vessel vasculopathy, also called thrombotic microangiopathy, of the type seen in the hemolytic uremic syndrome (Fig. 7.9). A pathologist cannot often diagnose acute effects of calcineurin inhibitors with confidence, and can only suggest toxicity as a possibility if other things, such as significant acute rejection, have been excluded (Fig. 11.30).

Arteriolar hyalinosis is a late complication of these drugs. This finding may be consistent with drug toxicity in children's grafts, but is often little help in adult kidneys, in which hyalinosis is common (Fig. 5.15). The hyalinosis produced by calcineurin inhibitors is sometimes claimed to be characteristic, because this bulges into the tissues around an arteriole, but this feature can be seen in people not treated with these drugs (Fig. 11.31). The tubular atrophy produced by calcineurin inhibitors is often said to be accompanied by striped fibrosis, running

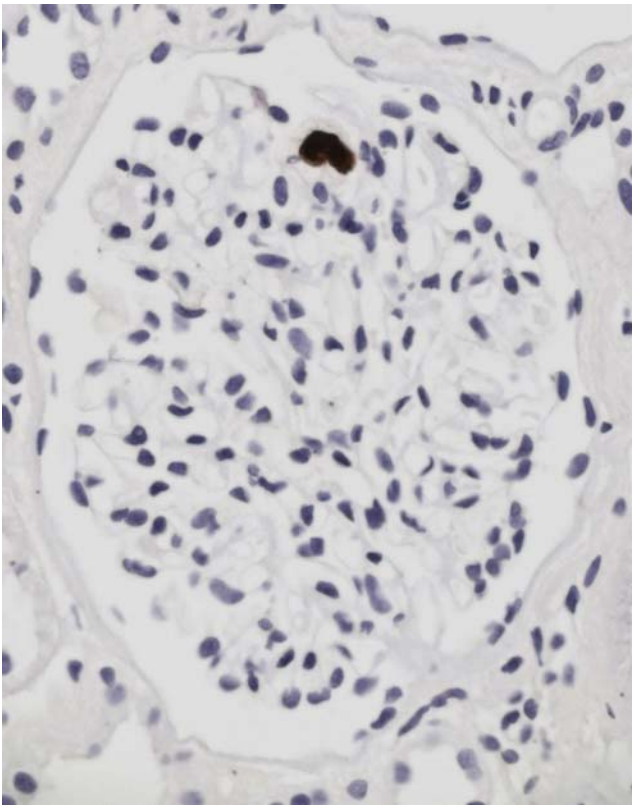

**Fig. 11.20** Glomerulus in the biopsy specimen from the man of 53 shown in **Fig. 11.19**. An immunoperoxidase method to detect cytomegalovirus shows a large, infected cell

radially through the cortex in the position of medullary rays. This may be seen in other conditions, and the drugs may give more widespread atrophy (Fig. 11.32). Glomeruli may have segmental sclerosis, which, again, can be seen in other conditions.

Although the late changes said to be characteristic of effects of calcineurin inhibitors may be seen in kidneys of people without a renal graft, treated with these drugs for another reason, such as after transplantation of a heart or liver, whether the changes are only produced by calcineurin inhibitors is unlikely (Fig. 2.1). There does not appear to have been a formal comparison between renal grafts examined at several years after transplantation, some treated with these drugs, and a control group treated only with other immunosuppressants. If the various late changes are seen, they are best reported to be consistent with effects of calcineurin inhibitors.

3. **There may be permanent damage to the graft from attacks of acute rejection**. This is more likely after acute vascular rejection than acute cellular rejection. Previous **infection** of the graft may also have produced chronic damage.

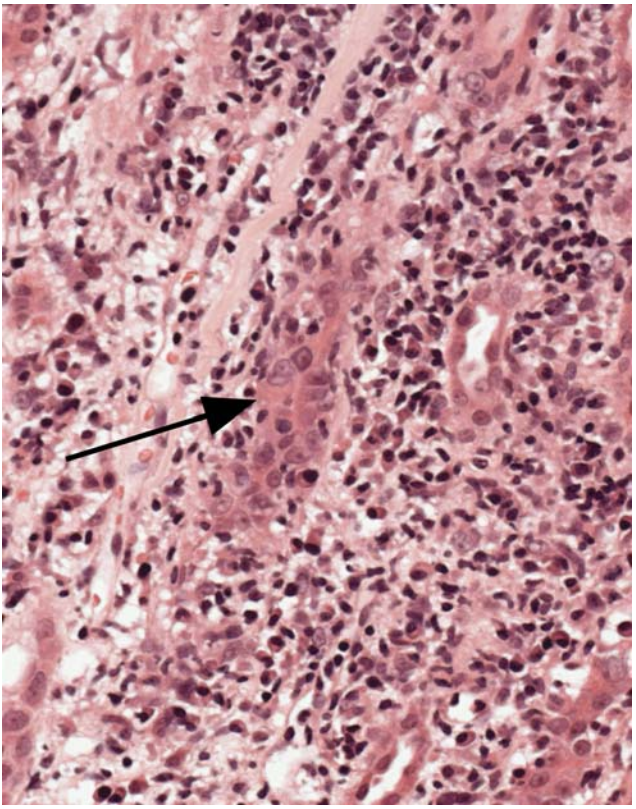

**Fig. 11.21** Cortex in a needle biopsy specimen of kidney taken 4 months after transplantation into a man of 62. There is a heavy chronic inflammatory infiltrate with abnormal nuclei in tubules, particularly the one arrowed. Immunoperoxidase findings are shown in **Fig. 11.22**

4. **The graft may have a disorder of its blood supply**, such as effects of hypertension, stenosis of the renal artery, or thrombosis of veins. Vascular problems cause ischemia, with acute and chronic effects, but there may be no indication in a biopsy specimen of the precise cause or causes of ischemia.
5. **The graft may have a disorder of its drainage**, such as urinary reflux or stenosis of the ureter. A clue to a drainage problem is the presence of pus in tubules (Fig. 7.36). Another clue is solid masses in interstitial tissues or veins of material that stains with periodic acid Schiff and contains few cells (Fig. 11.33). This material is precipitated Tamm-Horsfall protein (Fig. 11.34). These extratubular deposits, which include tubulo-venous ruptures, are seen in obstruction of the urinary tract, but can also be complications of acute rejection. In severe, acute obstruction, Tamm-Horsfall protein may reflux within tubules to precipitate in Bowman's space.
6. **Effects of reduced nephron number, with hyperfiltration and overload changes**, are likely, after any other process has caused loss of nephrons. These

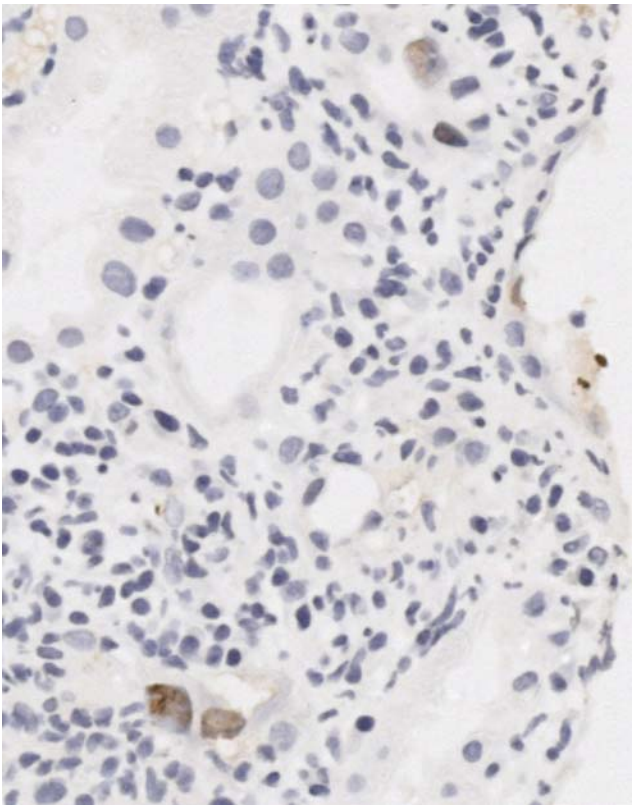

**Fig. 11.22** Cortex in the biopsy specimen from the man of 62 shown in **Fig. 11.21**. An immunoperoxidase method to detect polyomaviruses using an antibody to SV40 shows several infected tubular cells. This finding is consistent with BK virus infection. B and K were the initials of the first person, a renal allograft recipient, from whom the virus was isolated in 1971

effects in turn damage the remaining nephrons, and cause further loss, with progressive and irreversible decline in graft function.

Discrimination between explanations of chronic damage may be impossible for the pathologist. An important point to remember is that **more than one process may be occurring**, and this is probably the case in most long-standing grafts. With no clues, the pathologist should report that there is chronic damage to the graft, without evidence of significantly active rejection.

## *Is There a Glomerular Disorder?*

Glomerular disorders may be seen in an allograft. There are several possible explanations.

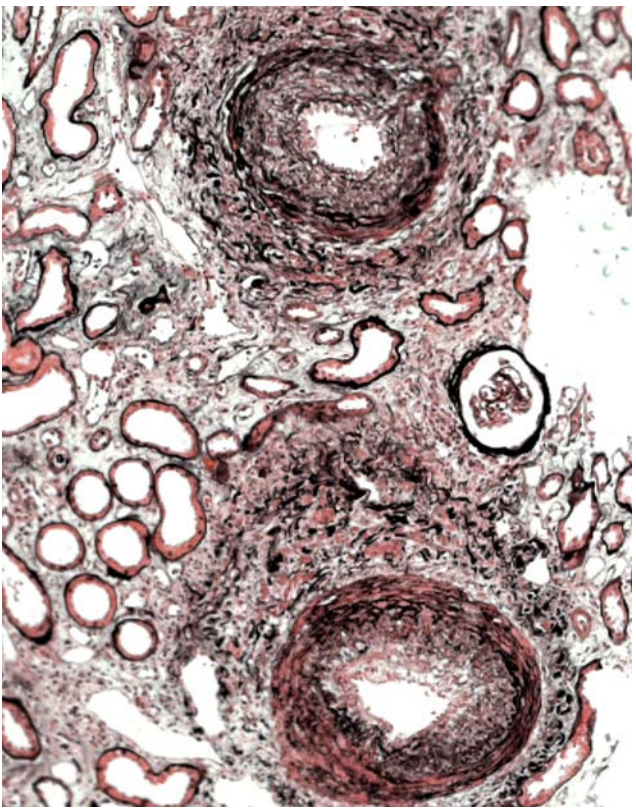

**Fig. 11.23** Cortex in a needle biopsy specimen of kidney taken 3 months after transplantation into a woman of 47. There is concentric intimal thickening in arteries with the appearances of chronic vascular rejection

1. **Pre-existing disease in the donor**. The implantation biopsy specimen should allow the pathologist to determine if the transplanted kidney had a glomerular disorder, such as IgA nephropathy. This can be assessed retrospectively if necessary.
2. **Acute allograft glomerulopathy** (Fig. 11.14).
3. **Chronic allograft glomerulopathy** (Figs 11.26 and 11.27).
4. **Infection**, such as by cytomegalovirus (Figs 11.19 and 11.20).
5. **Recurrence of a glomerular disorder**, known to be present in the recipient before transplantation. Many glomerular disorders are consequences of diseases of the immune system. Immunosuppression, used to prevent rejection, does not always protect the grafted kidney from the effects of the underlying immune disease.

Disorders that virtually always recur are dense deposit disease, also called membranoproliferative glomerulonephritis type two (Figs 6.16–6.18), fibrillary/

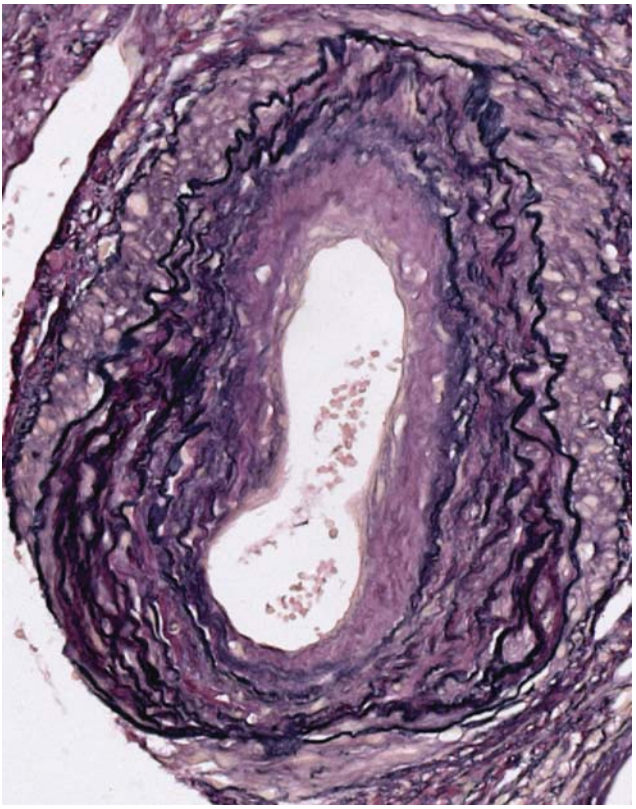

**Fig. 11.24** Artery in a nephrectomy specimen of kidney from a man of 69 removed 10 years after transplantation. An elastin hematoxylin van Gieson stain shows that the intima has two types of thickening, an outer ring of concentric elastin fibres, representing changes present before transplantation, and an inner ring of fibrous tissue without elastin fibres, representing chronic vascular rejection

immunotactoid glomerulopathy (Figs 6.77 and 6.78), and diabetic glomerulopathy (Figs 6.34–6.44). These rarely cause the graft to fail, at least in the short term. Some forms of atypical hemolytic uremic syndrome almost always recur, and almost always cause loss of the graft (Fig. 7.53).

Other disorders that frequently recur are IgA nephropathy and its associated condition, Henoch-Schönlein nephritis (Figs 7.25–7.27, 8.1, 8.2, 9.1, and 9.3–9.8), the classic type of focal segmental glomerulosclerosis associated with the nephrotic syndrome (Figs 6.25–6.28), vasculitic glomerulonephritis (Figs 7.12–7.24), amyloid (Figs 6.64–6.76), nodular light chain glomerulopathy (Figs 6.45– 6.48), and subendothelial membranoproliferative glomerulonephritis, in which heavy deposition of IgG, IgM, and complement in a subendothelial distribution allows discrimination from chronic allograft glomerulopathy (Figs 6.80 and 6.82). Electron microscopy

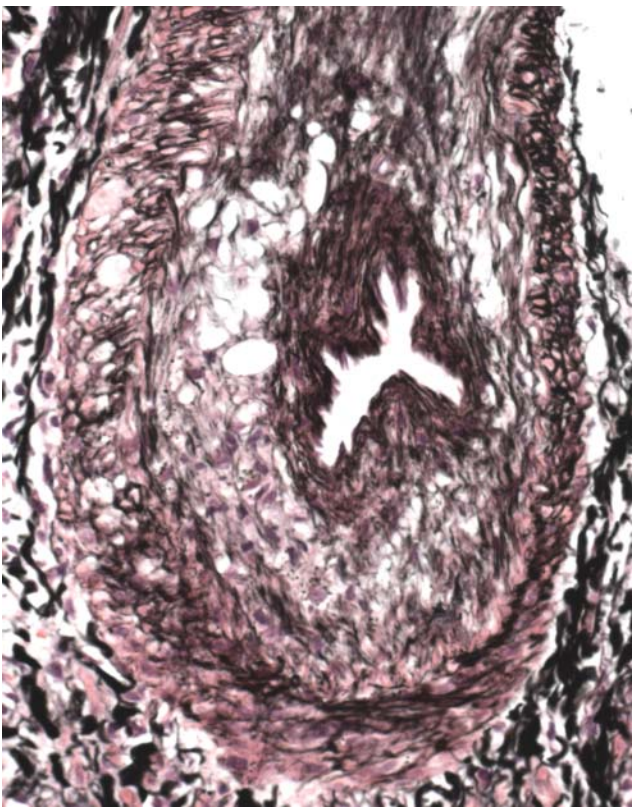

**Fig. 11.25** Artery in a needle biopsy specimen of kidney taken 10 months after transplantation into a man of 60. There is the appearance of a new muscular media around the lumen, separated from the original media by loose, poorly cellular tissue and the original internal elastic lamina. This is a feature of chronic vascular rejection

also differentiates these conditions and shows deposits in a subendothelial distribution in membranoproliferative glomerulonephritis (Fig. 6.84).

Lupus nephritis and membranous nephropathy do not often recur, and rarely cause loss of the graft. Goodpasture's disease only recurs if transplantation is done when the recipient still has antibodies to glomerular basement membranes (Figs 7.29 and 7.30).

In a similar way to glomerular disorders, metabolic diseases may recur. Genetic oxalosis recurs in grafts, unless the recipient has also had liver transplantation to treat the metabolic problem (Figs 7.46 and 7.47). Cystinosis does not recur, but cystine crystals may be carried into a graft by macrophages (Fig. 8.20). Fabry's disease probably does not recur. Cystic diseases do not recur.

6. **Development of a new glomerular disorder**, also called de novo glomerular disorder. This usually appears long after transplantation, and rarely causes graft loss by itself.

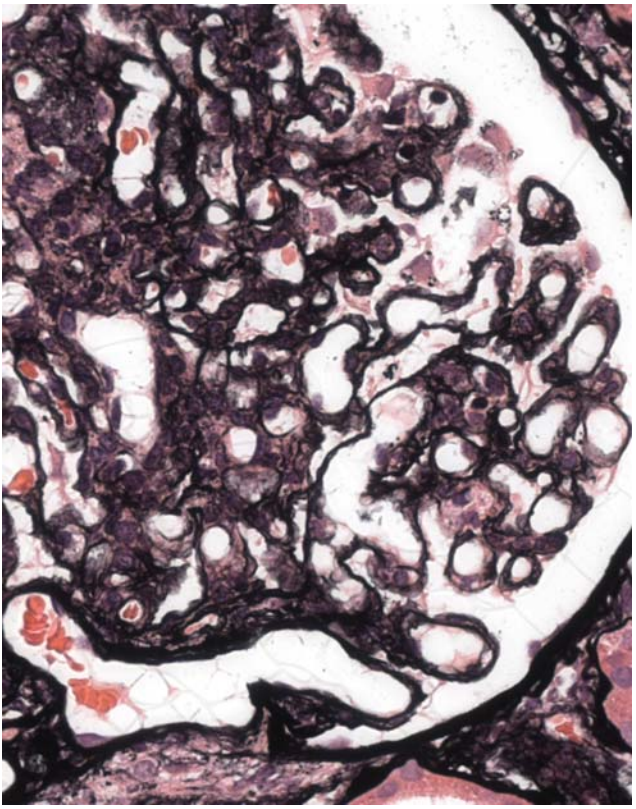

**Fig. 11.26** Glomerulus in a needle biopsy specimen of kidney from a man of 27 taken 17 years after transplantation. There is mesangial expansion, and several capillary loops have doubled basement membranes. These are features of chronic allograft glomerulopathy

Diagnosis requires knowledge of the recipient's original renal disease and recognition that the glomerular disorder is neither a recurrence nor chronic allograft glomerulopathy. The commonest is **membranous nephropathy** (Figs 6.8– 6.14). Hereditary nephropathy of Alport type does not recur in grafts, but recipients develop antibodies to part of the type four collagen molecule that they lack, which is the antigen detected by antibodies in Goodpasture's disease (Fig. 9.13). Grafts in recipients with hereditary nephropathy of Alport type can sometimes be shown to have linear deposition of IgG in glomerular basement membranes, but they hardly ever develop the vasculitic glomerulonephritis of Goodpasture's syndrome.

In a similar way, children with the Finnish type of congenital nephrotic syndrome, who do not express nephrin in their glomeruli, may develop antibodies against nephrin in the graft. These antibodies can produce the nephrotic syndrome.

A glomerular disorder that may develop long after transplantation is the type associated with hyperperfusion effects, or reduced glomerular numbers, with enlargement, segmental sclerosis often at the glomerular hilum, progressive loss of

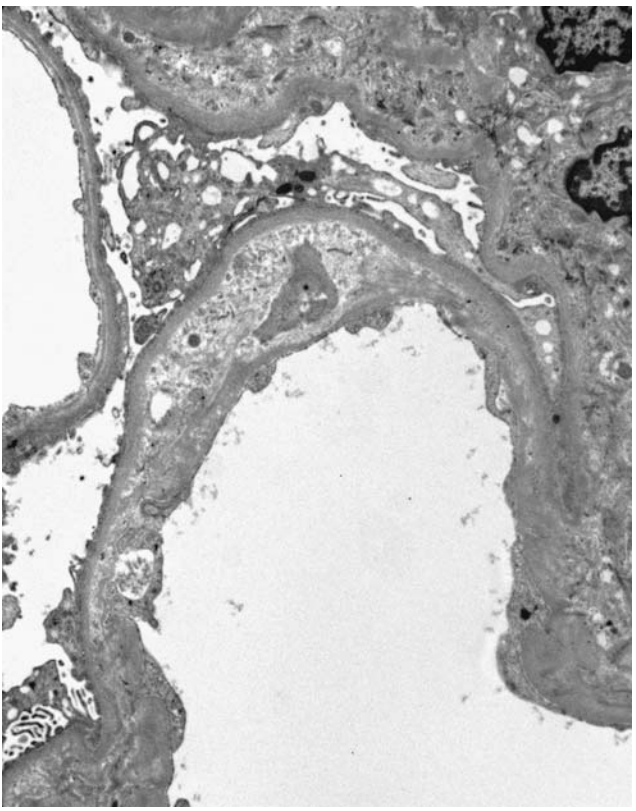

**Fig. 11.27** Electron micrograph of part of a glomerulus in a needle biopsy specimen of kidney from a woman of 31 taken 5 years after transplantation. In one capillary loop, there is loose material on the inside of the original basement membrane with formation of a new basement membrane next to the capillary lumen. This corresponds with the doubled basement membranes seen on light microscopy in chronic allograft glomerulopathy as in **Fig. 11.26**

glomeruli by global sclerosis, and proteinuria (Fig. 8.3). This may be the explanation of the segmental lesions reported as an effect of calcineurin inhibitors.

## *Is There Evidence of a Neoplastic Disorder, or Any Other Disorder?*

**Lymphomas** are rare in grafted kidneys. These are often called post transplant lymphoproliferative disorders, but are now classified in the same way as other lymphomas. They are usually a complication of Epstein Barr virus infection. This virus persists in B lymphocytes, and its replication is kept in check by T lymphocytes. Immunosuppression may release the virus from this control, and can lead to proliferation of B cell clones. There is an infiltrate of lymphoid cells, usually large and all the same (Fig. 11.35). These are B lymphocytes that express CD20 on immunohistologic study, with expression of markers of Epstein Barr virus infection (Fig. 11.36).

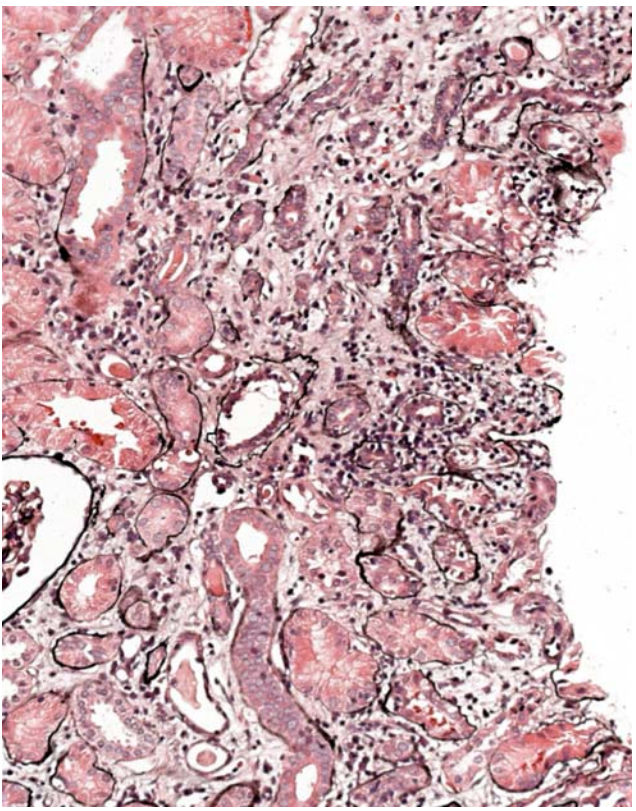

**Fig. 11.28** Cortex in a needle biopsy specimen of kidney from a woman of 18 taken 2 years after transplantation. There is chronic damage, but there is also evidence of significant acute cellular rejection

Grafts may develop other neoplasms, such as Kaposi's sarcoma or renal call carcinoma, and can show abnormalities that can occur in any kidney, such as cysts or amyloid (Fig. 6.63). Often, a thick fibrous capsule develops around a graft, and this makes biopsy difficult. A capsule may contain crystals or sutures from surgical procedures, surrounded by giant cells. There may be evidence around a graft of pre-existing disease in the recipient, such as amyloid derived from beta two microglobulin related to hemodialysis.

## Summary: Renal Allografts

Most renal allograft biopsies are done because of impaired excretory function, called graft dysfunction.

The two common problems for a pathologist are to decide whether there is significantly active, acute rejection that may respond to treatment, and whether there is chronic damage that will not respond to treatment.

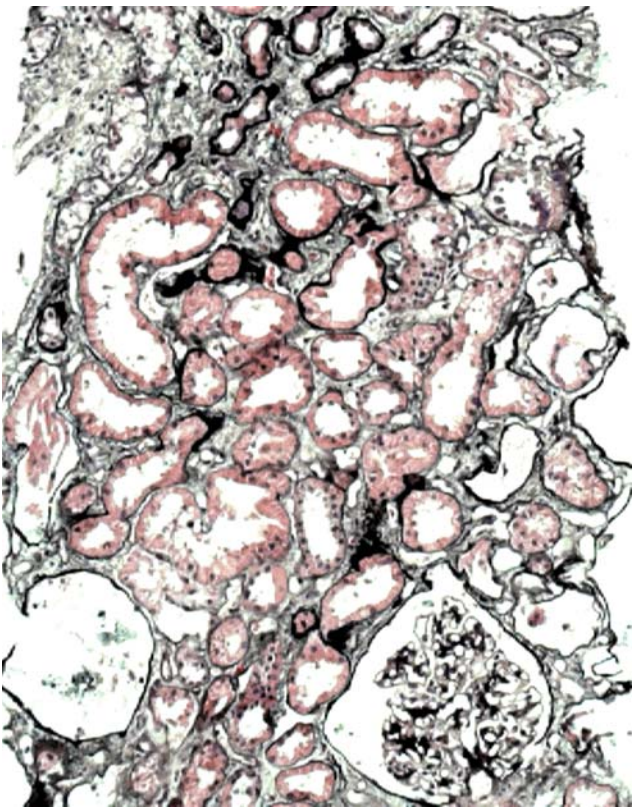

**Fig. 11.29** Cortex in a needle biopsy specimen of kidney taken 3 months after transplantation into a man of 40. There is chronic damage with atrophic tubules that contrast with surviving enlarged tubules, but there are no clues to the cause

There are five diagnoses related to acute rejection. These are antibody-mediated rejection, significant acute cellular rejection, acute vascular rejection, severe acute vascular rejection, and no evidence of significant acute rejection.

Late damage in an allograft, meaning tubular atrophy in particular, may result from chronic rejection, but there are several other possible explanations.

Other disorders that may occur in grafts include glomerular abnormalities that may be due to a variety of causes, vascular and ureteric problems, infections, and neoplasms.

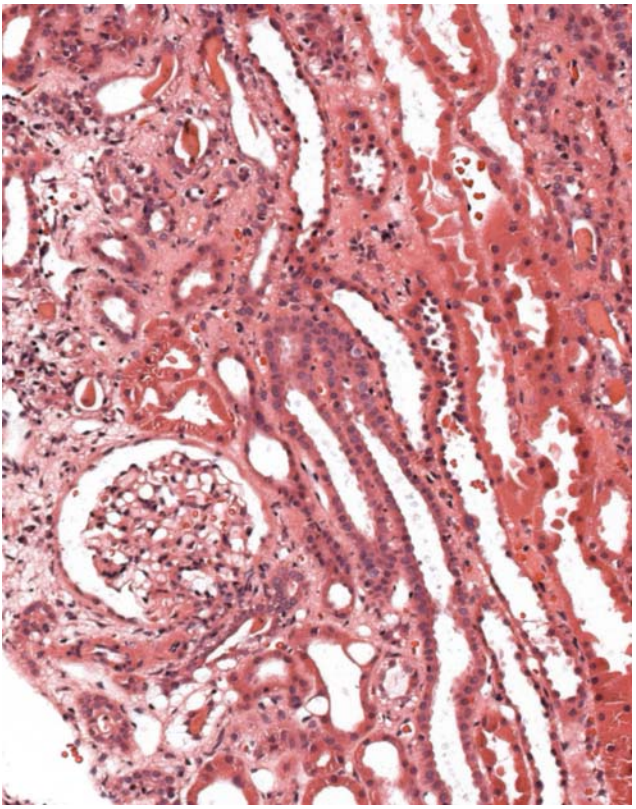

**Fig. 11.30** Cortex in a needle biopsy specimen of kidney taken 2 months after transplantation into a man of 44. There is a little chronic damage, but there is no evidence of significant acute rejection. The clinical diagnosis was cyclosporine toxicity. Function improved when the dose of cyclosporine was reduced

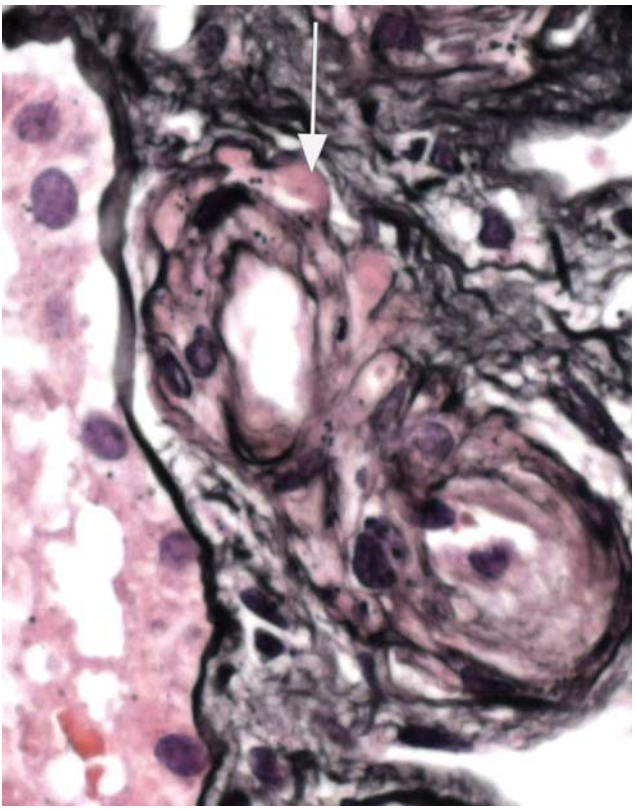

**Fig. 11.31** Arteriole in a needle biopsy specimen of kidney from a woman of 46 with chronic renal failure from a nonglomerulonephritic cause. Nodules of hyalinosis bulge into tissues around the arteriole. This is sometimes claimed to be a feature of effects of calcineurin inhibitors, but this woman had never been treated with these drugs

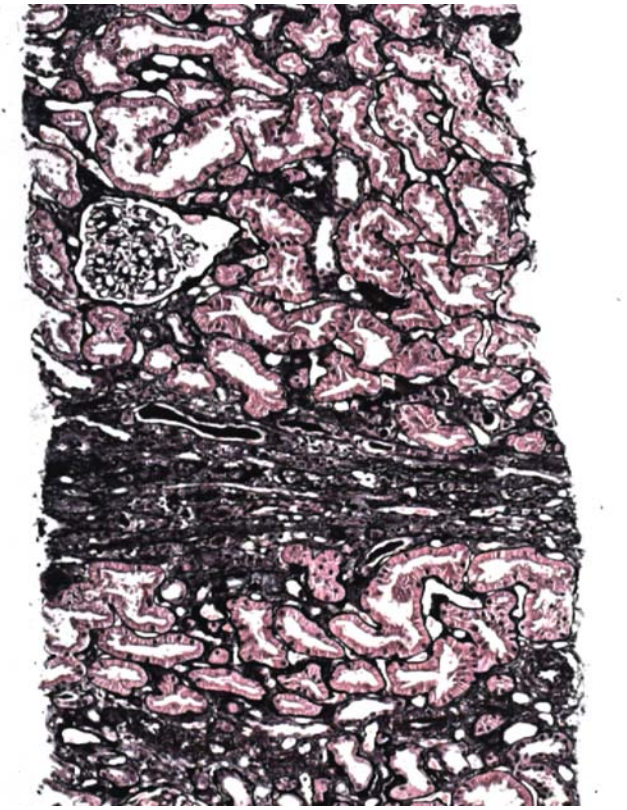

**Fig. 11.32** Cortex in a needle biopsy specimen of kidney from a woman of 67 with chronic renal failure from a nonglomerulonephritic cause. There are streaks of chronic damage running radially through the cortex in the position of medullary rays. This is sometimes called striped fibrosis, which is said to be characteristic of effects of calcineurin inhibitors. This woman had never been treated with these drugs

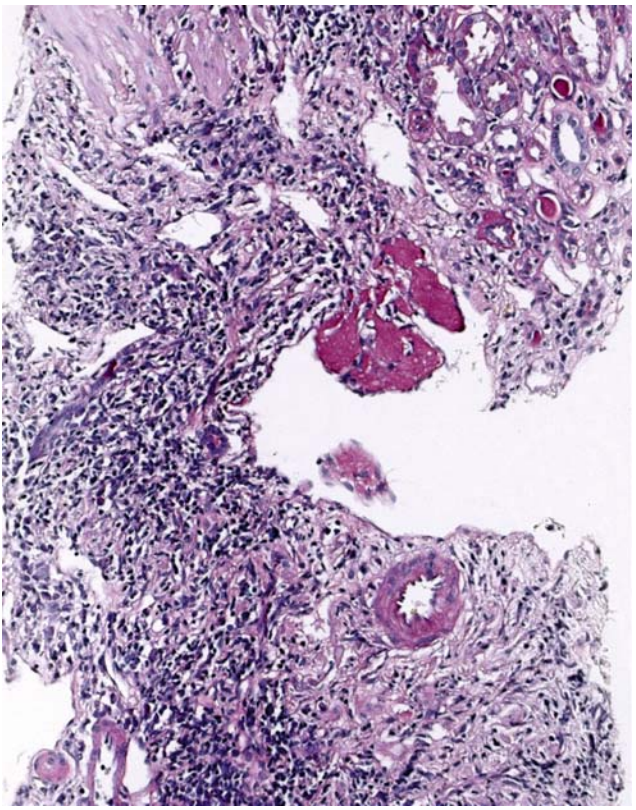

**Fig. 11.33** Cortex in a needle biopsy specimen of kidney taken 4 months after transplantation into a man of 51. On this section stained by periodic acid Schiff, there is material that protrudes into a vein. Tubulo-venous ruptures like this often suggest obstruction of the urinary tract, and previously there had been a temporary blockage of a urinary catheter in this man. The nature of the material is described in the legend to **Fig. 11.34**

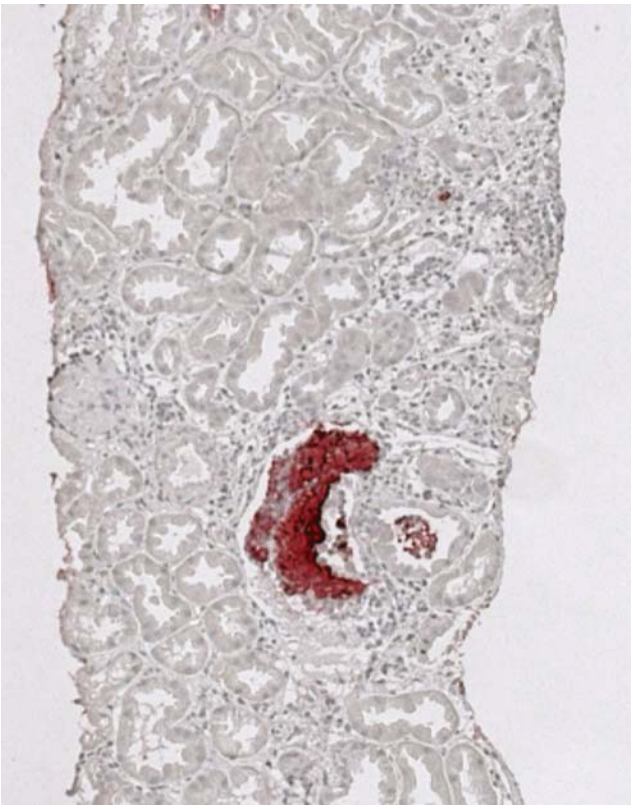

**Fig. 11.34** Cortex in a needle biopsy specimen of kidney taken 16 days after transplantation into a man of 53. An immunoalkaline phosphatase method to detect Tamm–Horsfall protein shows a deposit of the protein in a vein, suggestive of urinary obstruction with tubulo-venous rupture. There was ultrasonographic evidence of hydronephrosis. Tamm–Horsfall protein is the most abundant protein in normal urine, and is produced by the thick limb of the loop of Henle. Tamm, pronounced as it looks, and Horsfall, pronounced *horse-fawl* or *horse-fal*, described a protein purified from urine that reacted with viruses, because of its content of carbohydrates (Tamm I, Horsfall FL. A mucoprotein derived from human urine which reacts with influenza, mumps, and Newcastle disease viruses. *Journal of Experimental Medicine* 1952; **95:** 71–97). Igor Tamm (born 1922) and Frank Lappin Horsfall (1906–1971) were virologists at the Rockefeller Institute for Medical Research, New York, where Tamm later became a Professor of Virology. Horsfall became President and Director of the Sloan-Kettering Institute for Cancer Research. Friedrich Gustav Jacob Henle (1809–1885), pronounced *hen-lee*, was a German anatomist who reported loops in the medulla in 1862

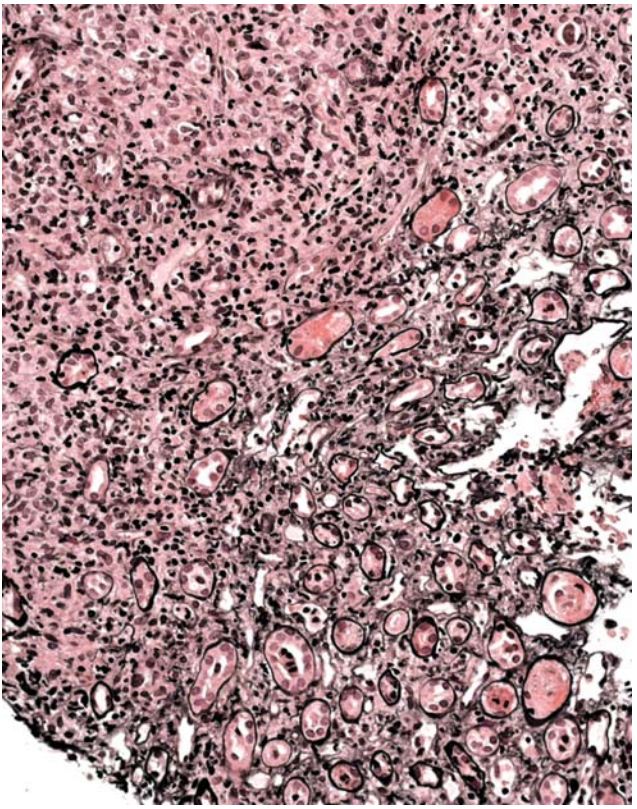

**Fig. 11.35** Medulla in a needle biopsy of kidney taken 12 weeks after transplantation into a man of 21. There is an infiltrate in half the field of large lymphoid cells, shown on immunoperoxidase staining to be B lymphocytes. Features are those of a lymphoma. Investigation of Epstein Barr virus is shown in **Fig. 11.36**

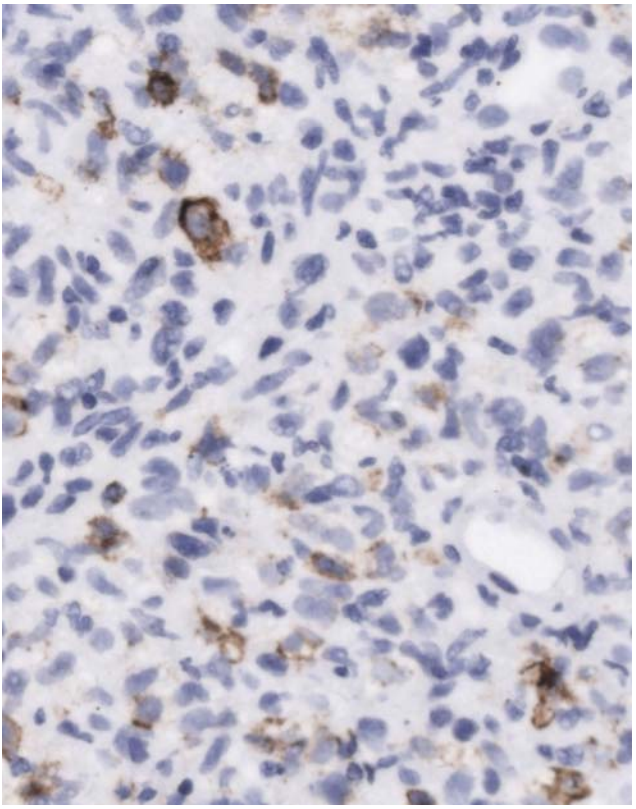

**Fig. 11.36** The lymphoid infiltrate shown in **Fig. 11.35**, examined by an immunoperoxidase method for a late membrane protein of Epstein Barr virus. Many cells express the viral antigen

## Further Reading: Renal Allografts

Colvin RB, Cohen AH, Saiontz C, et al. Evaluation of pathologic criteria for acute renal allograft rejection: reproducibilty, sensitivity, and clinical correlation. *Journal of the American Society of Nephrology* 1997; **8:** 1930–1941. This gives details of the system suggested by the Cooperative Clinical Trials in Transplantation.

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# Chapter 12
# Other Indications for Biopsy of Kidneys

## Introduction

Renal biopsy is hardly ever done other than to investigate the nephrotic syndrome, acute renal failure, chronic renal failure, hematuria, and proteinuria, and in various circumstances related to grafts.

## Investigation of the Kidney in Systemic Disease

Rarely, a renal biopsy is taken in vasculitis or in systemic lupus erythematosus, even though there are no clinical or chemical indications of renal abnormalities to see whether the disease has affected the kidney. Even a minor abnormality, such as microscopic hematuria, increases the chance that significant disease will be found in the kidney. In vasculitis, only one glomerulus with a vasculitic lesion has to be seen to give the diagnosis (Fig. 7.12).

## Investigation of Metabolic or Other Familial Disorders, and Disorders of Tubular Function

Especially in children, renal biopsy may be done to investigate suspected or known **metabolic disorders** or **other familial disorders**. Such disorders include cystic diseases, nail patella syndrome, hypokalemic conditions, and abnormalities of calcium or magnesium, or other minerals. **Disorders of tubular function** may be investigated by renal biopsy, such as those associated with tubular proteinuria and other features of Fanconi syndrome (Fig. 8.21) or renal tubular acidosis (Figs 7.39 and 8.19).

Biopsy specimens in most of these conditions show structural abnormalities to different extents, but generally they require investigation in specialised centres.

A. J. Howie, *Handbook of Renal Biopsy Pathology.*

## Assessment of Effects of Treatment on the Kidney

Renal biopsy may be done to determine whether a **treatment** has damaged the kidney, although its effects may not yet be apparent clinically. The most common example of this is in the nephrotic syndrome treated with calcineurin inhibitors, such as cyclosporine. A sign of the chronic ischemic effect of this drug on the kidney is the presence of atrophic areas, and there may be other features (Figs 2.1, 7.4, 7.9, and 11.30–11.32). If there has been a previous biopsy specimen, the pathologist can judge whether cyclosporine appears to have had a significant effect, especially in minimal change nephropathy, in which only age-related chronic damage would otherwise be expected. The pathologist may see a significant amount of chronic damage before clinical tests of excretory renal function detect renal impairment.

Cyclosporine may be the explanation of development of segmental sclerosing glomerular lesions in a person shown to have minimal change nephropathy in an earlier renal biopsy specimen.

## Investigation of a Renal Mass

Biopsy may be used in investigation of a **renal mass**. This is not done by nephrologists, and rarely done by urologists, whose opinion is usually requested. After appropriate imaging, partial or total nephrectomy is often performed on the assumption that the mass is a primary neoplasm of the kidney. Biopsy is usually avoided, because the findings are unlikely to change management, and there is a risk of dissemination of cancer along the biopsy track.

Biopsy may be considered if there is disseminated neoplasia to see whether there is a primary malignant neoplasm in the kidney, or whether the renal mass is a metastasis. Occasionally, there may be biopsy of a solitary renal mass to help to decide on the type of operation to be done. For instance, if a transitional cell carcinoma is suspected and then confirmed by biopsy, the surgeon may remove all the ureter as well as the kidney, rather than just the kidney.

The commonest finding in biopsy specimens of renal masses is **renal cell carcinoma**. Usually this appears a clear cell neoplasm, although sometimes the cells may be eosinophilic, or spindle shaped, or chromophobe, or there may be a mixture of appearances (Figs 12.1 and 12.2). Usually on immunohistologic study, a chromophobe carcinoma expresses E cadherin but not vimentin, while the opposite is found in a clear cell carcinoma.

The main differential diagnoses of a clear cell carcinoma of the kidney are **normal adrenal cortical tissue** and **an adrenocortical neoplasm** (Fig. 12.3). Adrenal gland is recognised by the presence of medulla and fine vacuolation in the cytoplasm of cortical cells. Adrenal gland and adrenocortical neoplasms do not express broad spectrum cytokeratins, epithelial membrane antigen, or CD10, but a renal cell carcinoma expresses these markers.

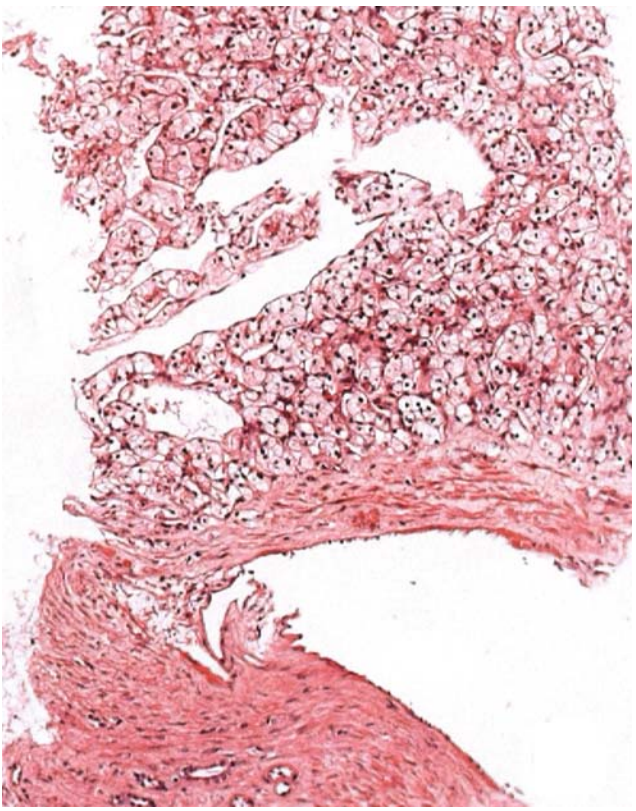

**Fig. 12.1** Needle biopsy specimen of a mass found incidentally in the kidney of a man of 70, during follow up after treatment of a hepatocellular carcinoma. There is a clear cell carcinoma, typical of renal cell carcinoma, with no resemblance to the hepatic neoplasm

Other renal neoplasms that may be seen include **transitional cell carcinoma** (Fig. 12.4), basophilic tubular neoplasms that are usually difficult to interpret in biopsy specimens (Fig. 12.5), or appearances suggestive of an **oncocytoma** (Fig. 12.6). An oncocytoma does not express CD10 or vimentin. An oncocytoma and some basophilic neoplasms are benign, but a sensible course for a pathologist is to remember that the biopsy specimen may not be representative of the whole mass, and that the sample may be from a renal cell carcinoma.

Biopsy may show other neoplasms, such as a lymphoma (Figs 4.2, 7.11, 11.35, and 11.36), or metastatic carcinoma (Fig. 12.7), although the kidney is an unusual site for metastasis from any malignant neoplasm. In someone with a known cancer, there may be evidence of a spread to the kidney in a renal biopsy specimen taken to investigate any of the usual indications for biopsy.

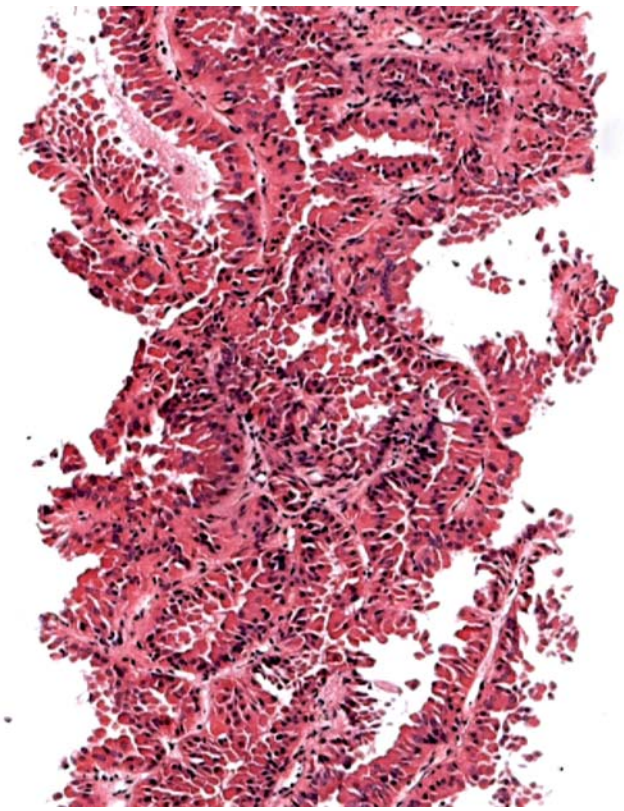

**Fig. 12.2** Needle biopsy specimen of a lesion in the kidney of a man of 67 found to have a complex cyst on radiographic investigation. There is a papillary eosinophilic neoplasm consistent with a renal cell carcinoma

## Chance Finding of a Neoplasm in a Renal Biopsy Specimen

Rarely a renal biopsy specimen taken for any reason may by chance contain a neoplasm, in a person not known to have cancer (Figs 4.9 and 12.8). About one specimen in 500 may show this. The lesion is likely to be no more than a few millimetres in diameter, because larger ones should be detected by investigations before the biopsy, such as intravenous urography or ultrasonography. If not metastatic (Fig. 4.9), the neoplasm may be papillary, cystic, or solid, and may have cells that are clear, eosinophilic, or basophilic. Although clear cells are a sign of a definite renal cell carcinoma (Fig. 12.1), most lesions found by chance do not consist of clear cells. Usually these are papillary adenomas, which occur with increasing frequency with age, and may be multiple and bilateral (Fig. 12.8).

After chance finding of a primary neoplasm, one course of action is for nephrologists or urologists to arrange detailed imaging of the kidney, and consider partial nephrectomy, if appropriate, if a lesion is seen. A mass under 5 mm diameter is

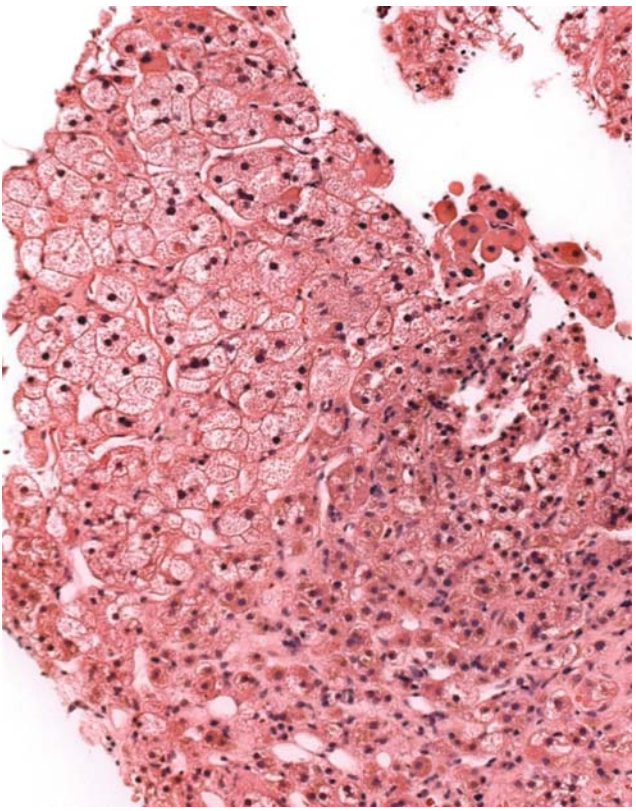

**Fig. 12.3** Adrenal cortex in a specimen from an attempted needle biopsy of kidney in a man of 49

unlikely to be detectable, and in this case, a surgeon would not know which part of the kidney to resect. Surveillance by imaging at intervals may be considered, but whether this is necessary is unknown. The pathologist should be included in discussions about management, the aim of which is to avoid unnecessary surgery for a trivial lesion and to ensure that a potentially lethal neoplasm is adequately treated.

## Summary: Other Indications for Biopsy of Kidneys

Renal biopsy is hardly ever done other than for the nephrotic syndrome, acute renal failure, chronic renal failure, hematuria, and proteinuria, and in renal allografts.

Renal biopsy may be used in investigation of the clinically normal kidney in systemic disease, such as vasculitis.

Some unusual metabolic or other familial or tubular disorders may be investigated by renal biopsy.

Renal biopsy may be used to investigate a renal mass. The commonest finding is renal cell carcinoma. A neoplasm may be found by chance in any biopsy specimen.

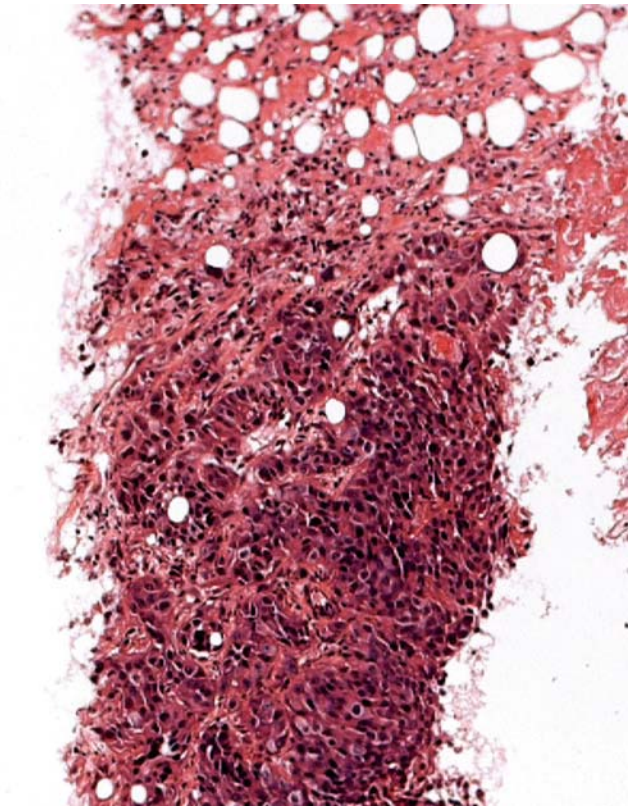

**Fig. 12.4** Needle biopsy specimen of a mass found in the kidney of a man of 68, during follow up of transitional cell carcinoma of the bladder. There is a transitional cell carcinoma

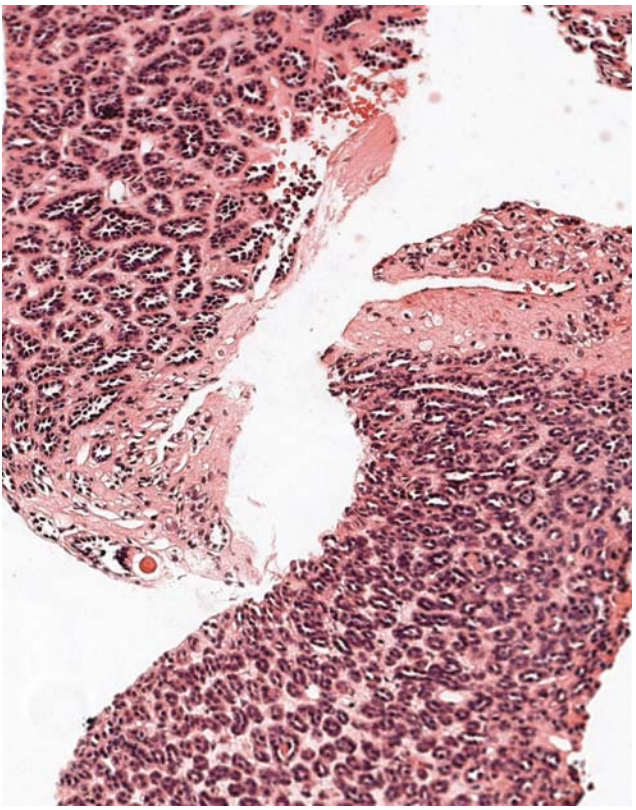

**Fig. 12.5** Needle biopsy specimen of a mass found incidentally by computed tomography in the kidney of a woman of 69. There is a basophilic tubular neoplasm of metanephric type. Distinction between basophilic renal cell carcinoma, metanephric neoplasms, and nephroblastoma may be difficult in a needle biopsy specimen

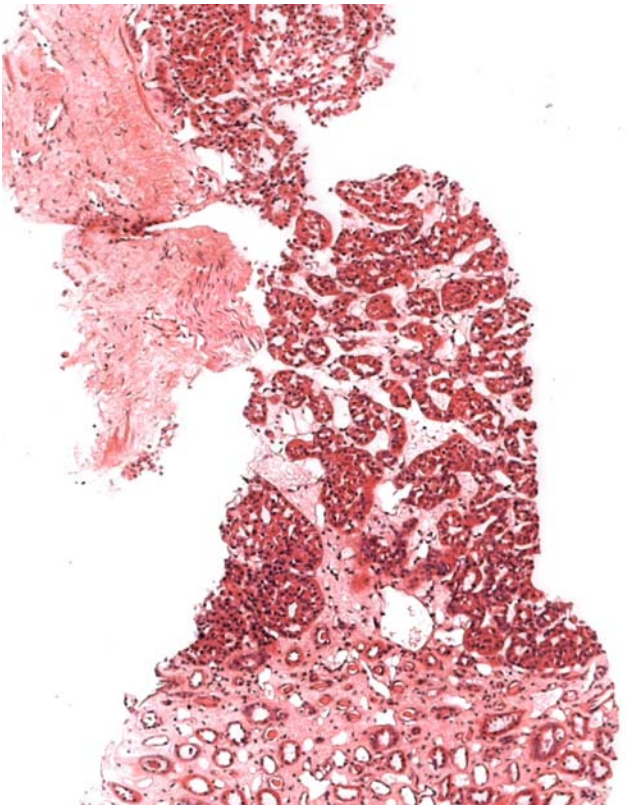

**Fig. 12.6** Needle biopsy specimen of a mass found incidentally in the kidney of a woman of 60, during follow up after treatment of fibromatosis. There is a neoplasm consisting of small groups of uniform eosinophilic cells consistent with an oncocytoma

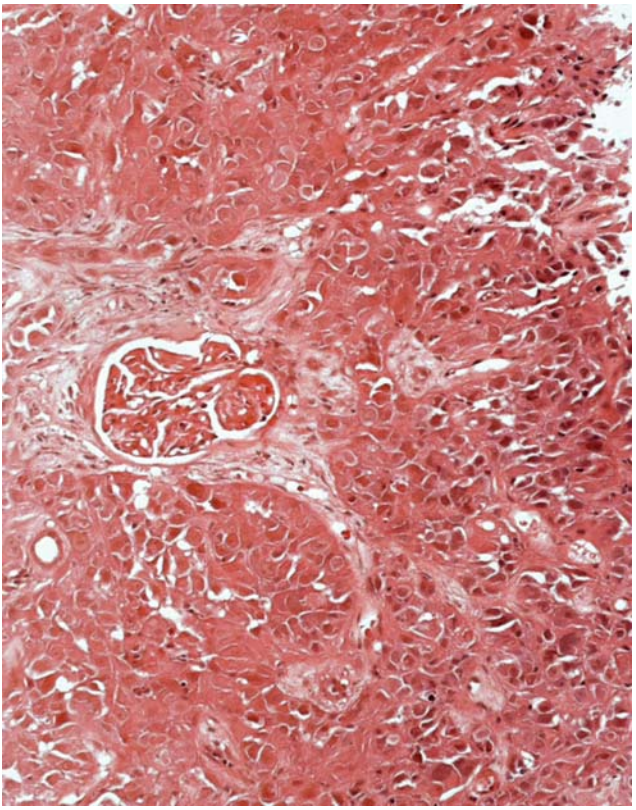

**Fig. 12.7** Needle biopsy specimen of a mass found in the kidney of a man of 51 during investigation of a lung mass. There is a squamous carcinoma, partly necrotic, consistent with a metastasis from carcinoma of the bronchus

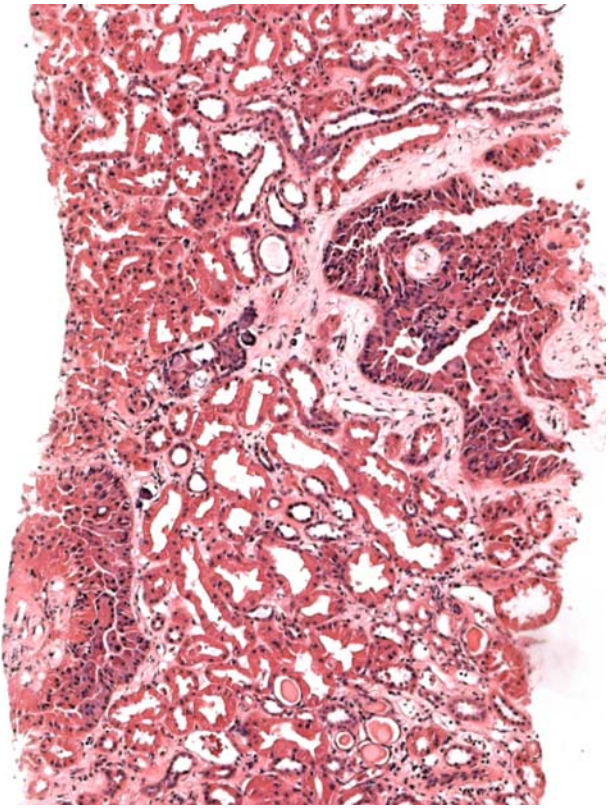

**Fig. 12.8** Needle biopsy specimen of kidney from a man of 83 with chronic renal failure, hematuria, proteinuria, and normal kidneys on ultrasonography. As a chance finding, there are a couple of areas of neoplastic tissue, probably part of one lesion, consistent with an eosinophilic renal cell neoplasm. No mass was detected on detailed imaging, and no action was taken to treat the renal cell neoplasm. The man died 3 years after the biopsy with no evidence of carcinoma of the kidney

# Further Reading: Other Indications for Biopsy of Kidneys

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