9 THE RENAL TRACT AND UROLOGY

THE DIAGNOSTIC PROCESS IN NEPHROLOGY AND UROLOGY

These systems are more dependent than most on laboratory, histopathology and imaging techniques for completion of the diagnostic process. However, the basic principles and requirements of clinical assessment still apply—appropriate and careful history-taking and physical examination are essential, and can often lead to a diagnosis. Even if they do not, they serve the important function of directing subsequent laboratory and other technically orientated investigation.

The kidney and urinary tract, when diseased, manifest a somewhat restricted array of symptoms and signs. It is therefore helpful to adopt a syndrome-based approach—almost all patients can be categorized into one or other well defined renal and urological syndromes; keeping these in mind serves to inform the clinical diagnostic process.

In these patients there are many areas of overlap between clinical and pathological processes within a single syndrome and it is not generally helpful to create artificial distinctions between the two. Once the correct syndrome has been established, further details of assessment and management objectives become a great deal clearer. Finally, it is important to emphasize that a number of these syndromes were first described many years ago. They have stood the test of time principally because of their pragmatic value and relative ease of recognition on the basis of clinical assessment and quite simple tests.

SYMPTOMS OF RENAL AND UROLOGICAL DISEASE

PAIN

Pain arising from the urinary tract is one of the commonest symptoms and is most often due to obstruction, infection or tumour. Renal pain is usually felt in the flank region or in the loin. When renal pain arises from ureteric obstruction (e.g. a stone) discomfort may additionally radiate to the iliac fossa, the testicle or the labia, the pattern depending to a certain extent on the level of the obstruction.

Pain in the suprapubic region and the perineum usually arises from lower urinary tract infection—cystitis or urethritis. Such pain is frequently accompanied by *dysuria*, *frequency* or *strangury*. This constellation of symptoms constitutes the syndrome of *cystitis*. It is nearly always associated with urinary abnormalities on stick testing (protein, blood and leucocytes). In men the pain may be associated with extreme perineal or rectal discomfort, in which case prostatitis is suggested.

In young children with urinary tract infection and cystitis the symptoms may be much less obvious—cystitis should be suspected in any child who cries on micturition. Pain from the kidneys, if resulting from acute infection or abscess, may occasionally reflect tracking of pus upwards to the diaphragm or in the retroperitoneal space to the psoas muscle with, respectively, diaphragmatic pain or impairment of hip extension. Glomerulonephritis is usually painless. Large cystic kidneys or kidneys bearing a tumour may cause a dull persistent flank pain.

HAEMATURIA

This can be present with or without pain and may be continuous or intermittent. If visible to the naked eye it is termed *macroscopic or gross haematuria*; if only detected by stick tests or microscopy it is called *microscopic haematuria*. Haematuria as a result of parenchymal renal disease is usually:

- continuous
- painless
- microscopic (occasionally macroscopic)

Haematina arising from renal tumours is likely to be:

- intermittent
- associated with renal pain
- macroscopic.

Bleeding from bladder tumours is often intermittent, often with associated local symptoms suggesting cystitis.

It is important to decide early in the diagnostic process whether the haematuria originates from the kidneys or elsewhere in the urinary tract (see Box 9.1). This decision affects the order with which investigations should be conducted. For example, continuous painless microscopic haematuria with associated proteinuria in a young man or woman is most likely to be the result of glomerulonephritis or other renal pathology. However, haematuria in an older person with risk factors for urothelial malignancy (smoking) is more likely to be caused by a bladder or ureteric tumour and merits a cystoscopy early in the investigative process. It is important to remember that the commonest cause of dipstick haematuria in women is contamination from menstruation.

BOX 9.1 Causes of haematuria.

Systemic
- purpura
- sickle cell trait
- bleeding disorders, including anticoagulant drugs

Renal
- infarct/papillary necrosis
- trauma
- tuberculosis
- stones
- renal pelvis TCC, and other renal tumours
- Wilms' tumour (in children)
- acute glomerulonephritis

Post-renal
- ureteric stones
- ureteric neoplasms
- bladder tumours (transitional cell carcinoma)
- bladder tuberculosis and bilharziasis
- radiation cystitis
- drug-induced cystitis, eg cylcophosphamide
- prostatic ennlargement
- urethral neoplasms
- bacterial cystiti

OLIGURIA/ANURIA

Oliguria is the passage of < 500 ml urine per day. Anuria is the complete absence of urine flow. A reduction of urine flow rate to the point of oliguria may be physiological, as in a patient whose fluid intake is low. Physiological reduction of urine flow rate implies that the glomerular filtration rate (GFR) remains normal, and that the kidney is avidly retaining sodium and water. If inadequate fluid intake leads to significant reduction in the extracellular fluid compartment (ECF), the resulting decrease in renal blood flow leads to oliguria and reduction of the GFR. Oliguria arising in this fashion is termed *prerenal* and is clearly pathological. *Renal oliguria* implies the presence of intrinsic renal disease, whereas *postrenal oliguria* results from mechanical obstruction at any level from the collecting system in the kidney to the urethra. Anuria and oliguria may be signs of renal failure.

POLYURIA

Polyuria implies no more than a high urine flow rate. There will always be an associated increase in the frequency of micturition (*frequency*) and often *nocturia* as well. Polyuria results from excessive water intake (psychogenic polydipsia or beer drinking for example), from an osmotic diuresis (glucose as in diabetes mellitus, urea as in chronic renal failure and sodium chloride as in diuretic use), and finally from abnormal renal tubular water handling as seen in pituitary diabetes insipidus or renal resistance to antidiuretic hormone—nephrogenic diabetes insipidus.

FREQUENCY

Increased frequency of micturition results from polyuria or from a decrease in the functional bladder capacity. The commonest cause of the former is excessive fluid intake whereas a decreased functional bladder capacity is seen most frequently in patients with lower urinary tract infection (cystitis) and in older men with prostatic hypertrophy and bladder outlet obstruction. Some patients with neurological diseases, in particular multiple sclerosis, also have frequency of micturition. The detrusor muscle of the bladder contracts at an inappropriately low bladder volume resulting in a low functional bladder capacity.

NOCTURIA

The term implies the need to rise during the hours of sleep to empty the bladder. In health there is a substantial diurnal variation in urine flow rate: night-time reduction in urine flow and an adequate functional bladder capacity together serve to obviate the need for night-time micturition. Thus polyuria of any cause, or any cause of reduction of functional bladder capacity, may lead to nocturia.

DYSURIA

This is a specific form of discomfort arising from the urinary tract in which there is pain immediately before, during or immediately after micturition. The urine is often described as 'burning' or 'scalding' and there is usually an association with frequency of micturition and a decreased functional bladder capacity. Infection and neoplasia in the bladder or urethra are the most important causes. An extreme form of dysuria, *strangury*, implies an unpleasant and painful desire to void urine when the bladder is empty or nearly so.

URGENCY OF MICTURITION, INCONTINENCE AND ENURESIS

Urgency is the loss of the normal ability to postpone micturition beyond the time when the desire to pass urine is initially perceived. In extreme cases it may lead to *urge incontinence*, in which the perceived desire to void is followed immediately by voiding. In a more general sense, incontinence implies the involuntary passage of urine and almost always results from local disorders of the bladder or of its nerve supply.

SLOW STREAM, HESITANCY AND TERMINAL DRIBBLING

This triad of symptoms is most frequently seen in elderly men with prostatic hypertrophy. Here the bladder outlet is partially obstructed by the enlarging prostate gland with the result that the maximum achievable urine flow rate during micturition is reduced. Such patients often experience difficulty in initiating the process of micturition (*hesitancy*) and of completing micturition in a 'clean stop' fashion (*terminal dribbling*). The symptoms are nearly always associated with frequency of micturition and nocturia, the result of a low functional bladder capacity. In more advanced cases there may be progressive bladder enlargement with eventual *overflow incontinence* and continuous or intermittent dribbling of urine.

URETHRAL DISCHARGE

This is usually only noticed by men and always requires further investigation. There may be associated symptoms of urethral irritation and the underlying pathology is likely to be urethritis which is often infective and sexually transmitted.

PHYSICAL SIGNS IN RENAL AND UROLOGICAL DISEASE

These physical signs fall into three principal groups:

- Local signs related to the specific pathology, for example an enlarged palpable tender kidney containing a large tumour, or a palpably enlarged bladder in a patient with acute or chronic retention
- Symptoms may arise from disturbance of renal salt and water handling with resulting ECF volume expansion or contraction—to ellicit the appropriate physical signs in this category requires careful assessment of the patient's volume status
- Those signs resulting from a failure of the kidney's normal excretory and metabolic functions.

In many renal patients, particularly those with advanced chronic renal failure and uraemia, signs from all three of the above categories may be present.

GENERAL INSPECTION

Patients with chronic renal failure always look unwell. The skin is pallid, the complexion sallow and a slightly yellowish hue is often evident. The mucous membranes are pale, reflecting the normochromic, normocytic anaemia that is associated with chronic renal failure. There may be *bruises, purpura* and *scratch marks* due to uraemic pruritis and also an underlying disorder of platelet function and capillary fragility. The nails often appear pale and some times opaque (*leuconychia*) in patients with the nephrotic syndrome and in some patients with chronic renal failure. Intercurrent episodes of severe illness in the past may have led to the appearance of *Beau's lines* which appear as transverse ridges across the nails. *Splinter haemorrhages* in the nail beds point to underlying vasculitis which may be the cause of the renal failure or be indicative of endocarditis or other vasculitic illness; there may be an associated *purpuric rash* (Fig. 9.1). *Uraemic frost* may be seen on any part of the body and appears as a white powder which is made up of crystalline urea appearing on the skin via the sweat. The onset of chronic renal failure in childhood almost

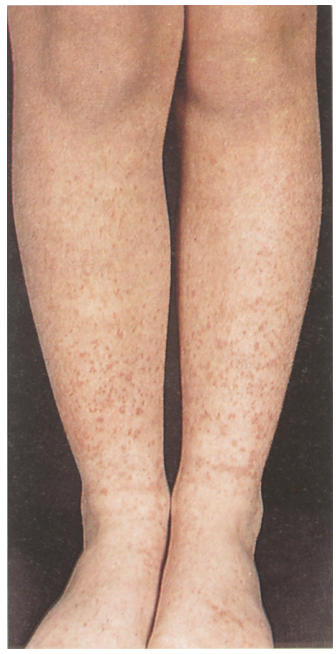


Fig. 9.1 Purpura in Henoch–Schönlein disease.

invariably results in impaired growth with resulting *short stature* in adult life. More severe bony deformity may be evident in some cases, particularly in children who may develop rickets (Fig. 9.2). Advanced uraemia is also associated with *uraemic metabolic flap*, a coarse tremor which is best seen at the wrists when in the dorsiflexed position. It is very similar to the metabolic flap seen in patients with advanced hepatic disease or respiratory failure. Metabolic acidosis, if present, leads to increased ventilation with an increased tidal volume—*Kussmaul respiration*.

THE CIRCULATION IN THE RENAL PATIENT

Of crucial importance here is the correct assessment of the patient's volume status. It is important to be able to define the patient as *euvolaemic*, *hypovolaemic* or *hypervolaemic*. This is a bedside diagnosis that, with practice, can be made correctly in the vast majority of patients.

Hypervolaemia is associated with some or all of the following:

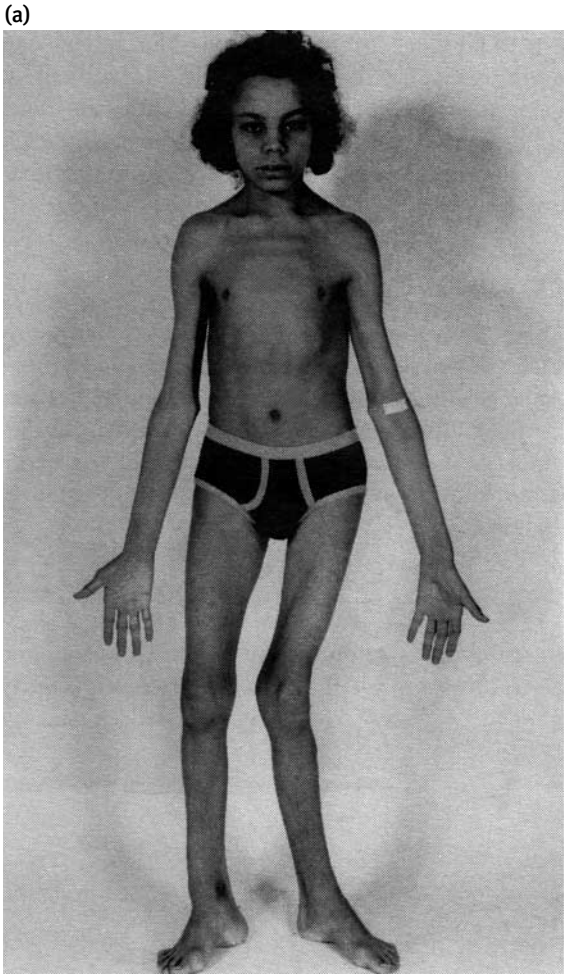
- hypertension
- elevation of the jugular venous pressure
- peripheral oedema at the ankles or sacrum
- basal crackles on lung auscultation
- ascites
- pleural effusion.

In patients with *nephrotic syndrome* (see below) the oedema and salt and water retention are driven by the reduced plasma oncotic pressure. In some cases both these mechanisms are operative simultaneously. Oedema with expansion of the extracellular fluid (ECF) is often accompanied by hypertension and, particularly if the cardiac reserve is poor, may progress to pulmonary oedema and other manifestations of heart failure.

The diagnosis of *hypovolaemia* requires the absence of any signs of *hypervolaemia*. The hypovolaemic patient may have the following:

- low blood pressure, often exaggerated in the upright position—*postural hypotension*
- sinus tachycardia (exaggerated in the upright position)
- low pulse pressure (exaggerated in the upright position)
- flat neck veins even when almost supine
- poor skin turgor.

(a)



(b)

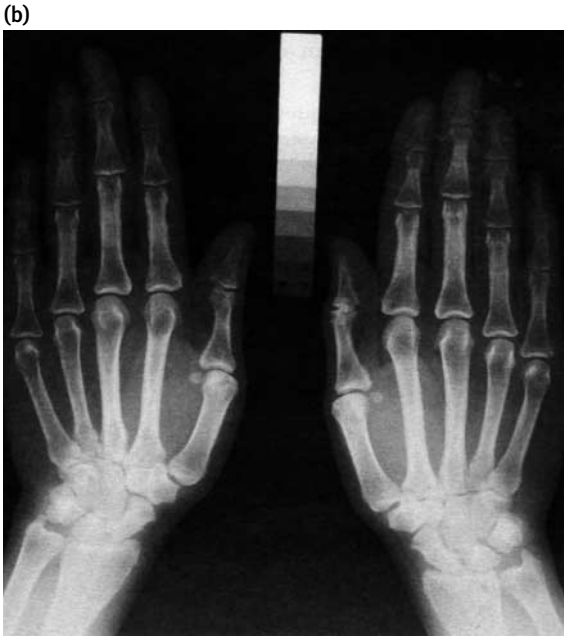


Fig. 9.2 **(a)** Knock knees and varus deformity of the ankles due to renal osteodystrophy. **(b)** X-ray of the hands of a patient with chronic renal failure and secondary hyperparathyroidism showing renal osteodystrophy. There is a loss of density of the tips of the digits (acro-osteolysis) with loss of density on either side of the interphalangeal joints and subperiosteal bone resorption. The latter is best seen in the middle phalynx of the index and middle fingers.

In the elderly, however, in whom the elastic recoil of the skin is physiologically impaired, poor skin turgor is an unreliable sign. Dry mouth and mucous membranes—though these may also result from general illness, mouth breathing and hyperventilation—are often present.

ABDOMINAL PALPATION

In slim people with relaxed abdominal muscles it is sometimes possible to feel a normal right kidney (the right kidney is situated slightly lower than the left at the level of T12–L3). More often a palpable kidney can only be felt because it is abnormally enlarged, as with hydronephrosis, multiple cysts (as in polycystic kidney disease), tumour (generally unilateral). A *distended bladder* is identified in the lower abdomen by a combination of palpation and percussion. *Rectal examination* is an important part of the clinical assessment of the renal patient; bimanual palpation of the bladder is a more reliable way of assessing bladder enlargement than is simple per abdominal examination. Rectal examination also allows evaluation of the *prostate gland*, both for benign enlargement and for the possibility of malignant change suggested by hard irregularity of the gland.

AUSCULTATION

Uraemic pericarditis and pleurisy may be suggested by pericardial and pleural friction rubs respectively. Their presence points to either advanced uraemia or a multisystem inflammatory disorder such as systemic lupus erythematosus (SLE) which may have both renal and extrarenal manifestations. Added heart sounds (S3 and S4) suggest, respectively, volume expansion and incipient heart failure, and ventricular hypertrophy, often as a consequence of hypertension. The presence of vascular bruits and/or impairment of the major arterial pulses is an important finding, raising the possibility of renal vascular disease which may underlie hypertension and/or renal failure if bilateral.

THE EYE IN URAEMIA

External inspection may reveal *corneal calcification* (*limbic calcification*), particularly in patients with long-standing hyperparathyroidism or elevation of blood calcium and phosphorous concentrations. The presence of limbic calcification should not be confused with a *corneal arcus* (*arcus senilis*)—the latter is a broader band at the edge of the cornea and merges with the sclera. Corneal arcus is usually most marked in the superior and inferior position whereas limbic calcification is seen medially and laterally or circumferentially. *Retinal changes* are extremely important in uraemic patients, many of whom have hypertension and/or diabetes. Patients with renal disease as part of systemic vasculitis may have manifestations of the latter in the retinae with haemorrhages and exudates. As a group, patients with chronic renal failure are at greatly increased risk of a range of vascular complications affecting both the macro- and the microvasculature. In the retinae, thrombosis of the central retinal artery or its branches, or of the central retinal vein and its branches, is an important manifestation of this.

THE RENAL AND UROLOGICAL SYNDROMES

These syndromes are listed in Table 9.1. Some are exclusively nephrological, others exclusively urological, while some fall into both areas. The effects of renal faliure on other organ systems are listed in Table 9.2.

THE SYNDROME OF ACUTE RENAL FAILURE

This is the abrupt onset of declining renal function occurring over a period of hours or days, usually but not always accompanied by a marked reduction of the urine flow rate—*anuria* or *oliguria*. Central to the diagnosis, however, is a rapid decline in the GFR leading to nitrogen retention and usually to sodium and water retention as well. An exception is the patient in whom the decline of GFR is not accompanied by reduction of urine flow—so called *non-oliguric acute renal failure*. The outlook depends on the cause. Many are reversible spontaneously (repair of ischaemic injury as in tubular necrosis) or as a result of therapy (removal of stone or other cause of obstruction).

THE SYNDROME OF CHRONIC RENAL FAILURE

Chronic renal failure implies that GFR has been reduced for a considerable period of time and that the reduction is largely or completely irreversible. It can

TABLE 9.1 Renal and urological syndromes.

Renal	Renal and urological	Urological
Chronic renal failure	Acute renal failure	Urinary tract infection
Acute nephritic syndrome	Asymptomatic urinary abnormality	Urinary tract obstruction
Nephrotic syndrome	Recurrent gross haematuria	Renal and urinary tract stone
Renal hypertension		
Tubular syndromes		

BOX 9.2 Effects of renal failure on other organ systems.

Disturbances of water and electrolyte balance
- Breathlessness due to salt and water overload
- Deep sighing breathing (Kussmaul respiration) due to acidosis
- Weakness and postural fainting due to hypotension caused by salt and water depletion
- Lethargy and weakness from hypokalaemia

Disturbances of the haematological system
- Lethargy and breathlessness associated with anaemia due to impaired production of erythropoietin by the kidneys
- Defective coagulation and excessive bruising (advanced renal failure)
- Haemorrhage from the gastrointestinal tract or lungs

Disturbances of the cardiovascular system
- Cardiac failure or angina associated with fluid overload, hypertension, anaemia, and impaired ventricular function (uraemic cardiomyopathy)
- Precordial chest pain due to pericarditis
- Cardiac arrhythmias associated with hyperkalaemia/hypokalaemia

Disturbances of the respiratory system
- Breathlessness and haemoptysis from fluid overload
- Chest pain due to pleurisy

Disturbances of the musculoskeletal system
- Muscular weakness and bone pain due to impairment of vitamin D activation and to excessive parathyroid gland activity
- Acute pain due to gout

Disturbances of the nervous system
- Hypertensive stroke and encephalopathy
- Clouding of consciousness, fits and coma in advanced renal failure
- Impaired sensation or paraesthesiae in the feet, due to peripheral neuropathy in long-standing uraemia
- Impaired higher mental/intellectual function

Disturbances of the eyes
- Pain from conjunctivitis caused by local deposits of calcium
- Visual blurring from hypertensive retinal damage or retinal vascular disease

result from almost any form of renal parenchymal disease, chronic renal ischaemia or unrelieved obstruction. If renal impairment is severe, there may be clinical manifestations of *uraemia*. These are usually evident when the GFR has fallen to one-third or less of normal. The implication of the term *chronic renal failure* is that the time-scale of onset and progression is rarely shorter than a few months and often much longer. A further and crucial implication is an irreversible reduction in the number of functioning nephrons with no prospect of significant recovery. These patients manifest a number of symptoms that are not attributable to specific pathophysiological changes. Lethargy, poor concentration, irritability and failure of higher mental functions and ability to handle tasks are all commonly reported. In advanced cases there may be confusion, fits and stupor. These are preterminal but also reversible if steps are taken to remove the excess amounts of uraemic toxins by dialysis. Nausea, vomiting and diarrhoea are also common in advanced uraemia and likewise improve following restoration of normal kidney function or treatment with dialysis or transplantation.

THE ACUTE NEPHRITIC SYNDROME

As in acute renal failure, the acute nephritic syndrome implies a fairly brisk onset (days, weeks or months) of reduction of GFR and retention of nitrogenous waste and usually salt and water also. *Oliguria* is, therefore, common. The underlying pathology is an acute glomerulonephritis which, as well as causing the functional abnormalities described above, also results in florid abnormalities of the urine. *Haematuria* (macroscopic or microscopic), *proteinuria* and *tubular casts* are often present. Many of the causes of acute nephritis are associated with functional abnormalities of the immune system which may be detected by laboratory tests and which may also manifest with disease in other organs, for example the skin, joints or eyes, as in systemic lupus erythematosus, Henoch–Schönlein purpura and systemic vasculitis.

THE NEPHROTIC SYNDROME

This is defined somewhat imprecisely as the presence of *heavy proteinuria* (usually >3 g/day compared with normal of <150 mg/day), *hypoalbuminaemia*, *hypercholesterolaemia* and *oedema*. It is not generally very helpful to attempt a more precise definition because the clinical response to a given level of proteinuria shows considerable variability from patient to patient. It is, however, unusual for nephrotic syndrome to occur when the proteinuria is <2 g/24 h, and conversely some patients are able to maintain a normal or near normal serum albumin concentration despite very heavy proteinuria in excess of 6 g/24 h.

Proteinuria of this magnitude implies glomerular pathology and may coexist with significant reduction of GFR. Thus a number of the pathological entities capable of causing nephrotic syndrome may also present as acute nephritic syndrome or the syndrome of chronic renal failure in other patients.

THE SYNDROME OF ASYMPTOMATIC URINARY ABNORMALITY

This is the presentation that arises in the patient who presents for a routine medical examination, often in the context of employment or life insurance. Urine

testing leads to the unexpected finding of *proteinuria*, *haematuria* or *pyuria* in an otherwise healthy patient. Further assessment may reveal the coexistence of other renal syndromes, but nevertheless it is worth maintaining the above operational definition of the syndrome of asymptomatic urinary abnormality because this is such a frequent presentation in clinical practice. It should not be forgotten that this syndrome may not only reflect disease of the kidneys in that it can also be a manifestation of malignancy anywhere in the urinary tract, infection or stone (if asymptomatic).

THE SYNDROME OF RECURRENT GROSS HAEMATURIA

This implies intermittent, or in some cases continuous, bleeding into the urinary tract to a degree sufficient to alter the macroscopic appearance of the urine. Depending on the circumstances of the bleeding, the urine may be a rusty-brown colour, lightly tinged with red blood or more heavily bloodstained. The blood may be derived from anywhere in the urinary tract from the glomeruli at the top to the urethra at the bottom. Important causes are certain types of glomerulonephritis, renal tumours and infections (particularly tuberculosis), and tumours of the urinary tract transitional cell epithelium (urothelium) anywhere from the renal pelves to the bladder and urethra.

THE SYNDROME OF URINARY TRACT INFECTION

The normal urinary tract is sterile except at its extreme distal end. Infection in the urinary tract leads to a range of symptoms and signs that reflect the location and severity of the infection. By far the most frequent site is the bladder and the local symptoms reflect bladder irritation with *frequency of micturition, low functional bladder capacity* and pain on passing urine—*dysuria*. The presence of the syndrome of urinary tract infection is defined importantly by the presence of a significant number of infecting organisms in the urine—a working definition would be more than 10^5 colony forming units/ml urine in a carefully collected mid-stream specimen (MSU). For less common infections this definition may not be appropriate. For example, in tuberculosis of the urinary tract the number of organisms being excreted may be extremely low and formal identification on the basis of urine culture is sometimes difficult or impossible.

THE SYNDROME OF URINARY TRACT OBSTRUCTION

This syndrome may conveniently be divided into, respectively, lower and upper urinary tract obstruction. Lower urinary tract obstruction is defined by residual urine in the bladder after micturition, or in more extreme forms by urinary retention with inability to empty the bladder at all. The most common causes relate to prostatic hypertrophy (benign hyperplasia or carcinoma) and a characteristic array of symptoms and signs arises (*frequency, nocturia, poor stream, hesitancy, terminal dribbling*). All of these are a consequence of a low functional bladder capacity, inability to empty the bladder completely and impairment of the urine flow rate.

The presence of upper urinary tract obstruction is established in most cases by the demonstration of a dilated renal collecting system (renal pelvis and/or calyces), often seen to be proximal to a specific obstructing lesion. These features may be demonstrated by a number of imaging techniques, including ultrasound and intravenous urography (IVU). Both upper and lower urinary tract obstruction may coexist, most frequently when the lower urinary tract obstruction is severe and/or of long standing and leading to progressive dilatation of the upper urinary tract with consequent renal damage.

THE SYNDROME OF RENAL AND URINARY TRACT STONE

The operational definition is largely a pathological one, centering around the demonstration of one or more stones in any part of the urinary tract. Resulting symptoms and signs depend much on the location of the stone(s) and on size. For example, small stones in the kidneys are frequently asymptomatic, or they may lead to subtle urinary abnormalities with initial presentation as the syndrome of *asymptomatic urinary abnormality*. Larger stones in the kidneys frequently lead to renal pain whereas stone in the ureter is particularly likely to cause acute obstruction with very severe ureteric and renal pain. Bladder stones are usually associated with symptoms suggestive of cystitis—frequency, haematuria and pain are all common and urinary tract infection is often associated.

THE SYNDROME OF RENAL HYPERTENSION

By far the commonest cause of sustained elevation of blood pressure is essential hypertension. However, in a minority of patients with raised blood pressure renal disease will be found to be the cause and the likelihood of this is greatly increased in patients with coexisting renal disease of any kind. Hypertension may be one of the presenting features of virtually any disease of the renal parenchyma, including all forms of glomerulonephritis, many forms of tubulointerstitial disease, renal vascular disease, renal stone disease and obstruction. Renal tumours and renal infections may occasionally present with hypertension which in some cases can be the only presenting feature. Thus in any patient with newly identified hypertension the possibility of underlying renal disease as a cause should be considered. Conversely, the exclusion of renal disease as a cause of hypertension is generally straightforward, comprising the absence of symptoms and signs of renal disease, the absence of urinary abnormalities on simple stick testing and the presence of normal

glomerular filtration rate as judged by serum creatinine concentration or other surrogate for GFR.

RENAL TUBULAR SYNDROMES

The majority of patients with parenchymal renal disease or obstructive renal damage manifest disordered tubular function, although in only a few of these are the tubular defects responsible for specific clinical manifestations. Tubular syndromes arising in this context are generally unobtrusive and are certainly common. Much less common is the patient in whom the tubular defect dominates the clinical picture. These defects may be inherited or acquired and are seen mainly in children. They usually require careful laboratory testing to characterize them fully. Proximal tubular abnormalities include renal phosphate wasting, aminoaciduria (of these, cystinuria with cystine stone formation is the most important) and renal tubular acidosis leading to chronic metabolic acidosis. Distal tubular defects are also associated with metabolic acidosis and with disturbances of potassium metabolism, sodium-losing nephropathy and nephrogenic diabetes insipidus with resulting failure, respectively, of salt and water conservation.

LABORATORY ASSESSMENT AND IMAGING OF THE KIDNEYS AND URINARY TRACT: ASSESSMENT OF STRUCTURE AND FUNCTION

THE URINE

The urine should be tested as part of any general medical examination—this should not be confined to patients with known renal or urinary tract disease. Not only may the testing lead to the discovery of hitherto unsuspected diseases such as diabetes or renal disease, but also documentation of normal urine often provides a very useful historical yardstick in the event of the later development of renal disease or urinary abnormalities. The urine specimen should be passed into a clean container without additives. Testing should normally be conducted as soon as possible and if delayed more than 2 hours the urine should be refrigerated (not frozen) and returned to room temperature before testing. A mid-stream urine specimen is essential for microbiological assessment and desirable for microscopic examination.

QUANTITY

Normal adults in temperate climates usually pass between 750 and 2500 ml of urine every 24 hours. The minimum daily urine output compatible with normal renal excretory function varies from person to person and also with other factors such as diet. Abnormally low urine output (oliguria or anuria) implies that the flow rate is below the minimum required to allow excretion of the daily solute load (usually < 500 ml/day in an adult). Polyuria is an imprecise term implying no more than passage of a large urine volume but not implying anything about the reasons for this.

COLOUR

Urochrome and uro-erythrin are pigments which contribute to the natural yellow tinge of urine. Darkening occurs on staining as a result of oxidation of urobilinogen to coloured urobilin. The colour of urine is also heavily influenced by the urine flow rate—high flow leads to dilute urine and hence pale colour. Bile pigments in excess colour the urine brown with a characteristic yellow froth on shaking. Small to moderate quantities of blood inpart a smoky appearance, with larger amounts leading to progressive brown or, in the case of brisk bleeding, bright red discolouration. Free haemoglobin from intravascular haemolysis (e.g. in severe malaria—blackwater fever) produces a darker red colour verging on black in severe cases. Myoglobin may appear in the urine after acute muscle necrosis (rhabdomyolysis), causing a brown-red discoloration. Certain drugs discolour the urine—examples include rifampicin (red), anthraquinone purgatives such as senna (orange), nitrofurantoin (brown) and methyldopa (grey). Urine is normally transparent when freshly passed and still warm but may be cloudy if there are large numbers of red blood cells or leucocytes, or if phosphates have precipitated in significant amounts.

SPECIFIC GRAVITY OSMOLALITY

These measurements yield similar information and, in the absence of significant glycosuria, are functions of the urinary concentrations of sodium, chloride and urea. The range of specific gravity is 1.001 to 1.035 which is equivalent to 50–1350 mosmol/kg water (Fig. 9.3). The presence of renal insufficiency

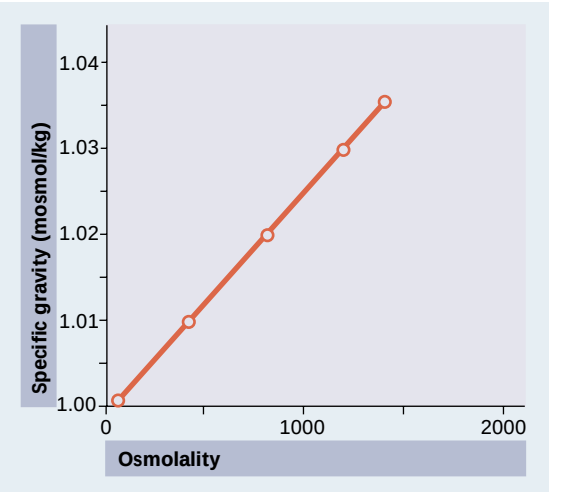


Fig. 9.3 Relationship between specific gravity and osmolality.

leads to reduction of the range of osmolality that the kidneys can generate and in advanced renal disease the osmolality becomes relatively fixed at about 300 mosmol/kg water—close to that of the glomerular filtrate (Fig. 9.4). This is termed *isosthenuria*, and predisposes the patient to sodium and water overload if intake is high, and to salt and water depletion if intake is low.

pH

This varies from pH 4–8 and can be measured crudely using paper strips impregnated with an indicator. If more accurate measurements are needed, as with suspected renal tubular acidosis, a pH electrode is used. Most people pass acid urine most of the time, exceptions being some vegetarians, certain types of renal tubular acidosis, rapid water diuresis, metabolic alkalosis and urine infection with urea-splitting organisms.

GLUCOSE

Glucose oxidase impregnated dipsticks provide a quick and semi-quantitative test for glucose in urine.

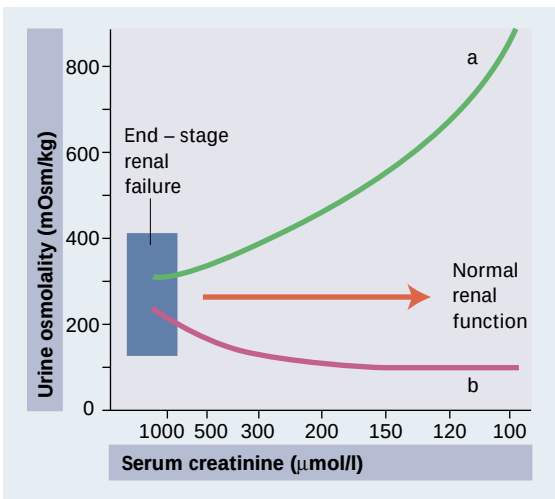


Fig. 9.4 Relationship between renal concentration and diluting capacity, and serum creatinine concentration. The serum creatinine is plotted on a logarithmic scale. This therefore represents linear changes in glomerular filtration rate, such as might occur in progressive renal failure. End in stage renal failure is shown on the left of the figure, and normal renal function on the right. Curve **(a)** represents maximum concentrating capacity, e.g. in water deprivation, when the normal kidney can maintain the serum creatinine in the normal range by increasing urine osmolality. In renal failure the urine cannot be concentrated and the serum creatinine rises. Curve **(b)** represents the maximum diluting capacity, e.g. after ingestion of large volumes of water. The normal kidney excretes urine of low osmolality. In end-stage renal failure urine osmolality cannot be reduced and the water load is not adequately handled. In end-stage renal function there is isosthenuria, i.e. the urine tends toward an iso-osmolar state (specific gravity 1.010).

By far the commonest causes of abnormal glycosuria are elevation of the plasma glucose to a point where the tubular reabsorbative capacity for glucose is exceeded (usually seen in people with diabetes) and during pregnancy, in which glycosuria occurs with normal plasma glucose concentration. Very rarely, tubular transport defects may be associated with glycosuria at normal plasma glucose concentrations and more frequently, but less predictably, patients with acquired chronic renal diseases may exhibit glycosuria at normal plasma glucose concentrations. Collectively these disorders are termed *renal glycosuria*.

PROTEIN

The normal daily urine protein output is <150 mg. Dipsticks reactive to urine albumin provide a simple semi-quantitative test. They are sensitive to 200–300 mg protein/litre and have almost completely superseded the more cumbersome sulphosalicylic acid test. The urinary protein excretion rate generally rises in the upright posture and with activity, and in some normal individuals this may lead to apparently abnormal proteinuria on spot urine specimens in ambulant patients and even in 24-hour urine collections (*orthostatic proteinuria*). Measurement of protein in an early morning urine, however reveals no protein reveals and this serves to distinguish abnormal proteinuria from orthostatic proteinuria. A further refinement is the specific measurement of urine albumin which is increasingly employed and should be < 20 mg/day. Albumin excretion in the range 20–200 mg/day is termed *microalbuminuria*. Although this range is frequently too low to be detectable by stick testing, it is an important finding, particularly in diabetics in whom it predicts the later onset of overt diabetic nephropathy.

The diagnostic implications of proteinuria depend greatly on its magnitude (Table 9.2). Heavy proteinuria (in excess of 1.5 g/24 h) is nearly always of glomerular origin and albumin predominates over larger proteins such as globulins. Other proteins, rarely measured, arise from the renal tubules and include Tamm–Horsfall protein, retinol binding protein and nephrocalcin, the latter helping to prevent the formation of urinary stones.

MICROSCOPY (Figs 9.5–9.8)

This is performed after slow spinning (not more than 1000 g) of a fresh urine specimen for approximately 2 minutes. The pellet is re-suspended in 0.5 ml of urine and examined unstained on a microscope slide under a cover slip. Important findings include leucocytes (suggestive of infection), *red blood cells* and various types of *tubular casts*. The presence of tubular casts is indicative of parenchymal renal disease. They may be red cell casts or white cell casts in which Tamm–Horsfall protein matrix has solidified and is studded with red or white blood cells. Granular casts probably represent degenerate

TABLE 9.2 Proteinuria.

Mild (<500 mg/day)	**Moderate** (up to 3 g/day)	**Heavy** (>3 g/day)
Benign hypertensive nephrosclerosis	Chronic pyelonephritis	Acute glomerulonephritis
Obstructive nephropathy	Acute tubular necrosis	Chronic glomerulonephritis
Prerenal uraemia	Acute glomerulonephritis	Diabetic nephropathy
Renal tumour	Chronic glomerulonephritis	Pre-eclampsia
Fever	Obstructive nephropathy	Myeloma
Tubulointerstitial nephropathy	Accelerated phase hypertension	All causes of nephrotic syndrome
Chronic pyelonephritis	Orthostatic proteinuria	
Early diabetic nephropathy	Urinary tract infection	
Orthostatic proteinuria		

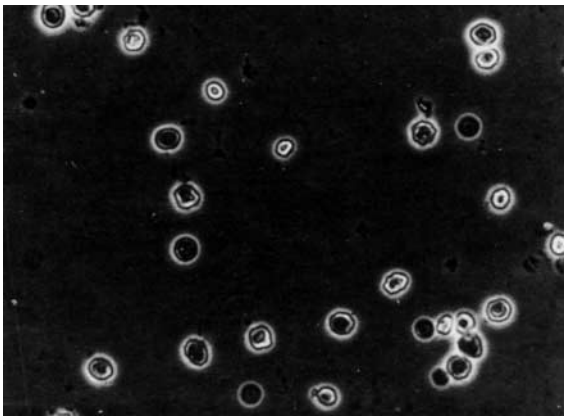


Fig. 9.5 Erythrocytes in urinary sediment.

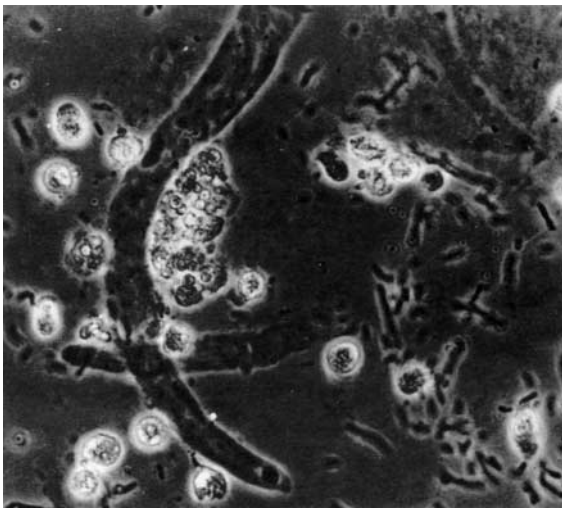


Fig. 9.7 Hyaline casts, leucocytes and bacteria in urinary sediment. Reproduced with permission from Hand Atlas of the Urinary Sediment (1971) by E.S. Spencer and I. Petersen, published by Munksgaard, Copenhagen.

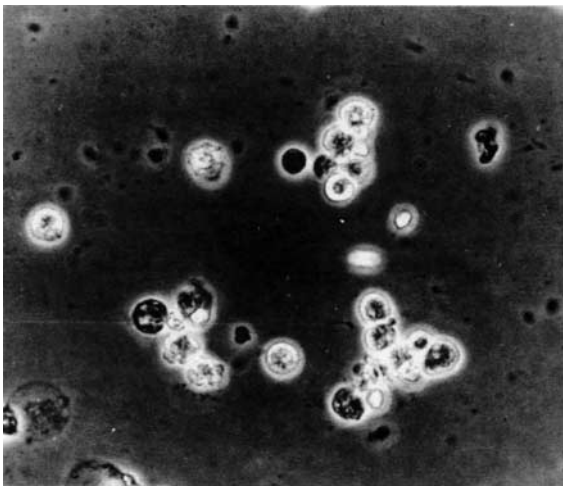


Fig. 9.6 Leucocytes in urinary sediment.

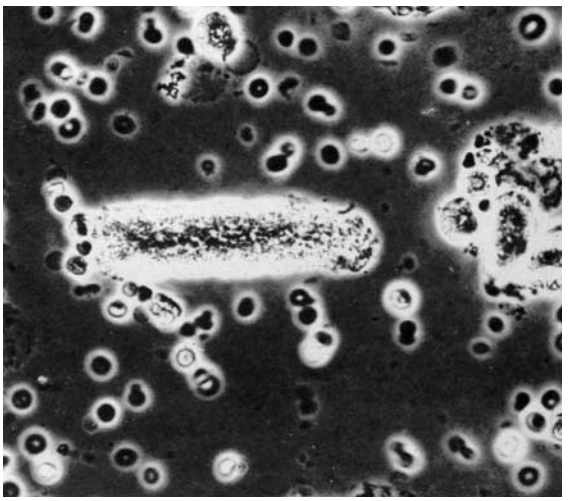


Fig. 9.8 Granular casts in urinary sediment.

cellular casts and have a grainy appearance. Haline casts contain no elements or debris and may be seen in small numbers in normal urine. It is usual to express the number of cells or casts seen per high power field. Red cell morphology may be a useful indicator to the source of bleeding. Red cells with a normal outline usually, though not always, arise from the renal collecting system or from a point

downstream of that, whereas red cells arising from the glomeruli are often distorted and dysmorphic, probably as a result of movement through the glomeruli or osmotic insults during passage down the renal tubule.

MICROBIOLOGICAL EXAMINATION OF THE URINE

Mid-stream urine specimens are normally satisfactory, but are always contaminated to a certain extent during passage to the exterior. Extensive studies have shown that the finding of more than 10^5 bacteria per ml in a mid-stream specimen is usually associated with active urinary infection, especially when accompanied by leucocytes. Occasionally urine is taken directly from the bladder for diagnostic purposes. It should be sterile.

MEASUREMENT OF THE GLOMERULAR FILTRATION RATE

Accurate assessment of the glomerular filtration rate (GFR) requires measurement in blood and urine of a compound that is filtered freely at the glomerulus and neither reabsorbed nor secreted by the tubules (Table 9.3). Inulin is the best agent, but involves a continuous infusion of inulin and measurements of inulin concentration in plasma and urine—a laborious and not routinely available investigation that is generally confined to research. A number of surrogates for the inulin clearance method exist, however, and details of these are given in Table 9.3. The most frequently used surrogates, and also the crudest ones, are the plasma urea and plasma creatinine concentrations. Both compounds are produced endogenously (at an inconstant rate in the case of urea) and excreted by glomerular filtration. Neither is particularly accurate when used to establish the absolute level of glomerular filtration in an individual patient, although the plasma creatinine concentration is certainly very useful when used to follow changes in an individual patient's renal function, especially when the GFR is significantly reduced (Fig. 9.9). Creatinine clearance is more precise but requires a 24-hour urine collection with measurements of plasma creatinine concentration and urine creatinine excretion rate. The clearance is then calculated using the simple formula: UV/P, where U equals the urinary concentration of creatinine, V the urine flow rate (usually expressed in ml/min) and P equals the plasma creatinine concentration. This formula can be applied to urea or to any other compound subject to renal excretion. Only those compounds that are freely filtered at the glomerulus and neither secreted nor reabsorbed by the renal tubules are suitable for GFR measurement. It should be remembered that the GFR peaks at 20–25 years of age and at about 120 ml/min and declines steadily thereafter at a rate of approximately 1 ml/min/year. Appreciation of this age-related change in GFR is important in clinical practice, particularly when prescribing drugs to the elderly. The most precise measures of GFR used in clinical practice depend on measurement of the excretion of radiolabelled compounds. The most commonly used is ^{51}Cr-EDTA which gives a relatively easy and reproducible measure of GFR.

TABLE 9.3 Measurement of the glomerular filtration rate.

Method	Comments
Plasma	Poor surrogate — variable production rate — variable excretion rate
Plasma creatinine	Better than urea Poor discrimination at near-normal GFR
Creatinine clearance	Reasonable surrogate but depends on accurate timed urine collection (usually 24 hours)
^{51}Cr-EDTA practice	The best surrogate in clinical Expensive
Inulin clearance	Near perfect measurement of GFR but — needs continuous infusion — difficult urine and plasma assays — research studies only—not suited to clinical practice

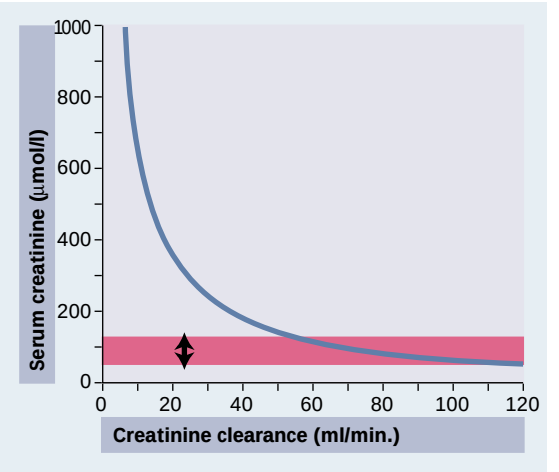


Fig. 9.9 Relationship between creatinine clearance and plasma creatinine concentrations. The normal range of serum creatinine concentration can be maintained only when the renal creatinine clearance is greater than about 60 ml/min. The red area represents the normal range of creatinine concentration.

MEASUREMENT OF RENAL TUBULAR FUNCTION

The two tests most frequently utilized are:

- tests of renal concentrating ability when probing possible causes of polyuria
- tests of renal acidification in patients with metabolic acidosis and possible underlying renal tubular acidosis.

Renal concentrating ability involves perturbing the patient in a way that should lead to the production of a concentrated urine. Water deprivation is the most common provocation and after 12 hours the urine osmolality should be at least 750 mosmol/kg (specific gravity 1.020). Failure to concentrate the urine in these circumstances indicates either impairment of vasopressin output (pituitary diabetes insipidus) or resistance of the renal tubules to the action of vasopressin (nephrogenic diabetes insipidus). These two possibilities may be distinguished by measuring the urine osmolality after an injection of vasopressin or an analogue thereof—again the urine osmolality should increase to at least 750 mosmol/kg.

Renal tubular acidification can be assumed to be adequate if the pH of a random specimen of urine is below 5.5. Urine pH >5.5 in the presence of metabolic acidosis usually indicates renal tubular acidosis. If the patient is only minimally acidotic and the urine pH is >5.5 a provocative test in which ammonium chloride is given at a dose of 0.1 g/kg body weight to provide an acid load and an acute mild metabolic acidosis can be performed. The pH should fall to <5.4 if acidification is normal.

ASSESSMENT OF THE URINE IN THE STONE FORMING PATIENT

This involves measurement of the important constituents of stone whose outputs may be abnormally increased, and also measurement of at least one of the natural inhibitors of stone formation. Ideally this should be combined with analysis of the stone itself. The tests that should be undertaken in all patients are:

- plasma calcium, phosphate, alkaline phosphatase, urea, urate, creatinine and electrolytes
- 24-hour urine collection for simultaneous measurement of
  - — calcium
  - — uric acid
  - — oxalate
  - — citrate
  - — creatinine
  - — sodium
- nitroprusside test for cystine.

The identification of increased excretion rates of calcium, uric acid, oxalate or cystine indicates a strong predisposition to recurrent stone formation. Conversely, citrate is a natural inhibitor of stone formation and a low urine citrate is associated with increased stone risk. All patients who make radiopaque stones should be screened for cystinuria using the nitroprusside test.

KIDNEY BIOPSY

This investigation, in which one or two small cores of renal cortex are removed using a needle biopsy technique, is performed in patients in whom diffuse renal parenchymal disease is suspected. However, not everyone with renal parenchymal disease requires a biopsy. The test is invasive and carries small but definite risks of serious complication. It is important, therefore, to define the indications and contraindications carefully. The risk of the procedure can be minimized by the following preconditions:

- A cooperative patient
- Prior knowledge of the position, size and function of both kidneys (this is usually provided by a combination of ultrasound and IVU or isotope renography; a solitary functioning kidney should not be biopsied unless the diagnostic yield is deemed to be crucial)
- Absence of bleeding disorder
- Availability of blood for transfusion in the event of haemorrhage
- An appropriate indication.

Kidney biopsy is often the only way to distinguish the various forms of glomerulonephritis from one another and from tubulointerstitial diseases of the kidney.

IMAGING OF THE URINARY TRACT

PLAIN RADIOGRAPHS

In many people one or both of the kidneys can be seen outlined by perirenal fat on plain abdominal films or nephrotomograms. The information gleaned is limited, although certain types of renal stone or other calcifications may be identified.

ULTRASOUND

Ultrasound provides good images of the renal parenchyma and collecting system and in nearly all patients gives a reliable estimate of renal size as well as identifying discrete lesions within the parenchyma, hydronephrosis and stone. Doppler studies often permit assessment of blood flow in the main renal arteries and in the larger intrarenal branches. Although the upper ureter can be seen quite well in most patients, the lower ureter is not visualized adequately. Ultrasound examination of the bladder is also extremely useful, allowing calculation of the bladder capacity when full and also after micturition (empty-

ing should be virtually complete), as well as visualization of the bladder wall and lesions projecting into the bladder itself (e.g. bladder tumours). It is sometimes combined with measurement of micturation flow rate.

INTRAVENOUS UROGRAPHY

Intravenous urography involves the injection of organic iodine compounds which are excreted and concentrated radiographically. It is an extremely good technique for examining the renal collecting system, the ureters and the bladder but gives less information than ultrasound about the renal parenchyma (Fig. 9.10). Imaging by IVU depends on renal function. This is useful in that it gives a crude measure of the symmetry or otherwise of excretory capacity but it also means that the image quality is poor in patients with renal insufficiency in whom the GFR is low (Fig. 9.11).

ANTEGRADE AND RETROGRADE UROGRAPHY

Here X-ray contrast material is instilled directly into the urinary tract via a percutaneous needle (*antegrade*) or a ureteric catheter inserted via a cystoscope (*retrograde*). These tests are invasive and are most often used in the evaluation of patients with obstruction of the urinary tract.

CYSTOGRAPHY

In cystography the bladder is filled with contrast medium via a urethral catheter and X-rays are taken before, during and after micturition. The test indicates the completeness of bladder emptying and also whether or not urine refluxes up the ureters during micturition. This also is an invasive test, the principal risk being the introduction of infection. Pressure and flow measurements may be included in more detailed studies of bladder function—urodynamics.

RADIONUCLIIDE STUDIES

^{99}Tc-DTPA (diethylenetriamine penta-acetic acid) is used to investigate the excretory function of each kidney selectively (Fig. 9.12). The test is very useful for the assessment of symmetry of function, delayed onset of excretion (as may happen in renal artery stenosis) and retention of excreted isotope (as seen in the presence of obstruction). ^{99}Tc-DMSA (dimercaptosuccinic acid) is a similar technique used to show the gross renal morphology.

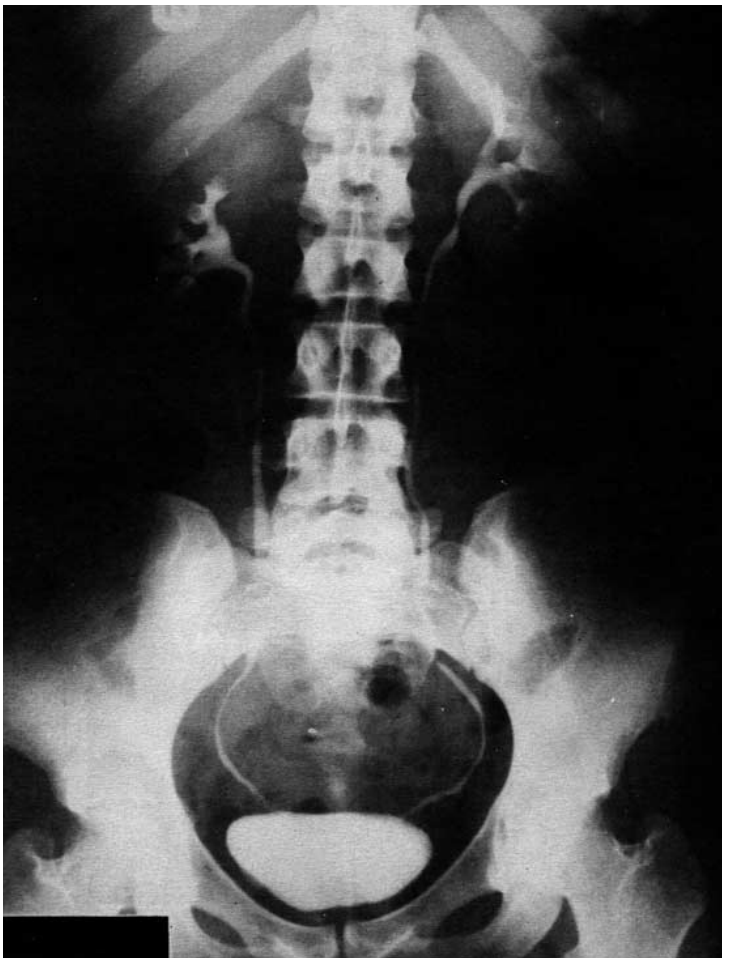


Fig. 9.10 Normal excretion urogram. In this film, taken 15 min after intravenous injection of the iodine-based contrast medium, the calyces of both kidneys, the ureters and the bladder can be seen.

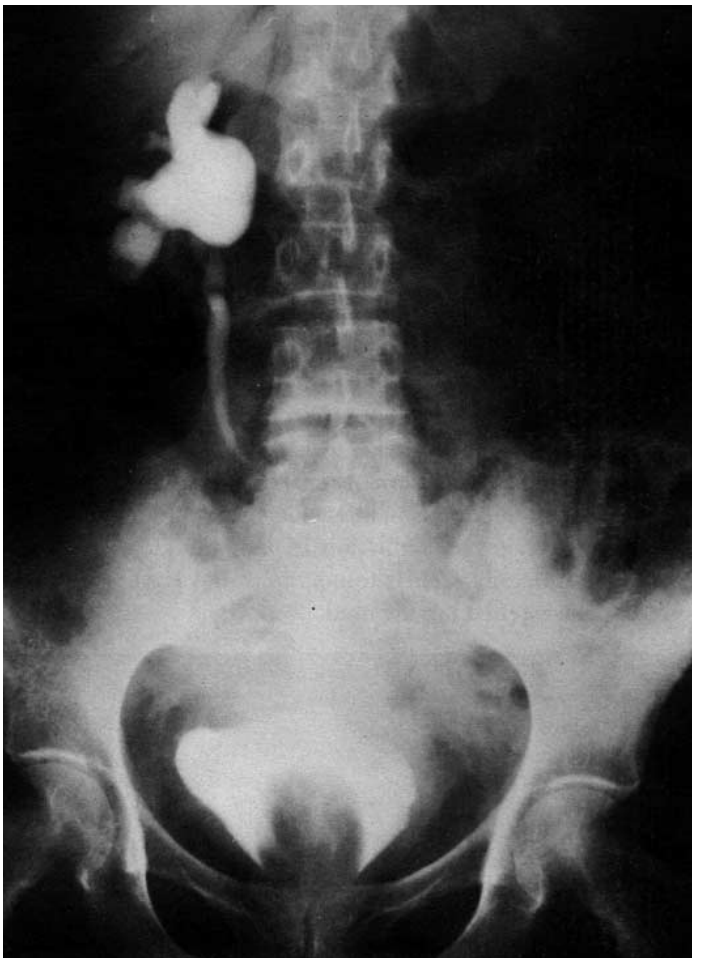


Fig. 9.11 Excretion urogram. In this film, made 30 min after injection of contrast, the left kidney fails to excrete a detectable concentration of contrast (non-functioning left kidney) and the right kidney shows dilated, hydronephrotic calyces. The right ureter is partially obstructed at the level of the body of the fifth, lumbar vertebra. The circular lucency in the bladder is the dilated balloon of a foley catheter.

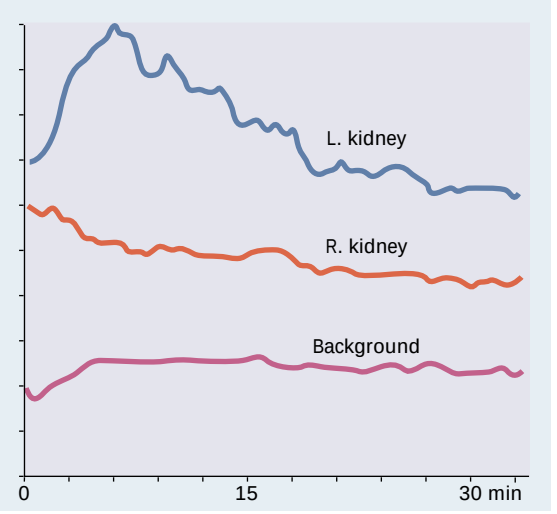


Fig. 9.12 Radioisotope excretion (ordinate) during the 30 min after intravenous injection in a patient with right renal artery stenosis and hypertension. The left kidney achieves more rapid excretion of isotope. The malfunctioning right kidney was the cause of the patient's hypertension.

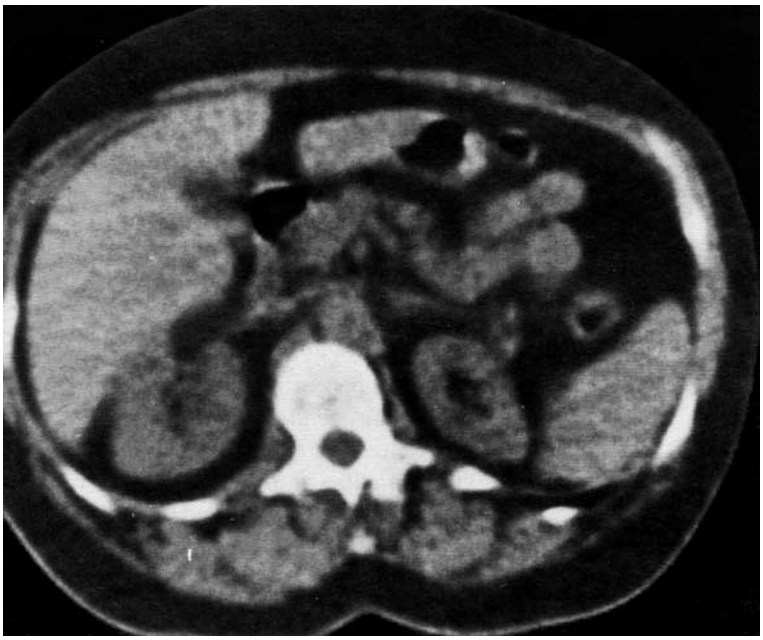
COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

Computed tomography (CT) scanning of the kidneys sometimes complements the information gained from ultrasound and certainly yields important information about the surrounding structures in the retroperitoneum (Fig. 9.13). It is particularly useful in patients with ureteric obstruction from, for example, retroperitoneal malignancy or retroperitoneal fibrosis. In some cases, more information is obtained using magnetic resonance imaging (MRI).

ARTERIOGRAPHY AND VENOGRAPHY

These are both invasive and used in selected patients in whom detailed evaluation of the renal blood supply (arterial or venous) is required. The commonest indication is in the patient with hypertension and/or renal insufficiency in whom renal artery stenosis is suspected. *Magnetic resonance imaging* generates images of the major renal vasculature—magnetic resonance angiography (*MRA*). Although the images are generally not as good as those from conventional arteriography, the technique has the

(a)



(b)

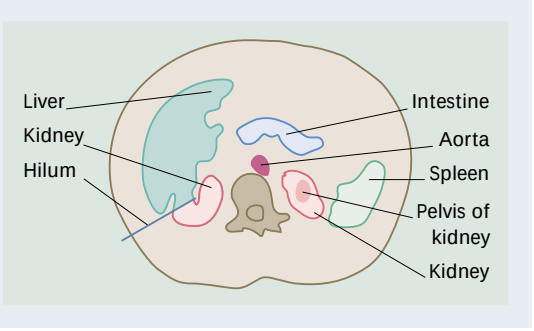


Fig. 9.13 **(a)** Computerized tomographic scan with **(b)** drawing showing normal kidneys.

advantage of being non invasive. CT imaging may also be used in this way (see p. 191).

CONCLUSIONS

From the forgoing it is evident that the detailed assessment of the patient with renal disease can be a complex and challenging process. In the vast majority of patients, however, the assessment is relatively straightforward, particularly if the major syndromes of renal and urological disease are kept in mind. In most cases the number of syndromes that have to be considered can be narrowed down quite quickly, and usually to one or two by the end of the physical examination. Armed with this information the doctor is then much better placed to devise an effective and efficient strategy for the laboratory investigation and imaging, and in turn make the correct diagnosis.