Urology and Renal Medicine

J.E. Newsam

M.B., Ch.B., F.R.C.S. (Edin.),
Consultant Urological Surgeon,
Western General Hospital, Edinburgh.

J.J.B. Petrie

M.D., B.Sc., F.R.C.P. (Edin.),
Director, Renal Unit, Princess Alexandra Hospital,
Brisbane, Australia.

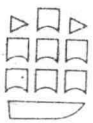
THIRD EDITION

Urology and Renal Medicine

J.E. Newsam
M.B., Ch.B., F.R.C.S. (Edin.),
Consultant Urological Surgeon,
Western General Hospital, Edinburgh.

J.J.B. Petrie
M.D., B.Sc., F.R.C.P. (Edin.),
Director, Renal Unit, Princess Alexandra Hospital,
Brisbane, Australia.

THIRD EDITION



CHURCHILL LIVINGSTONE
EDINBURGH LONDON MELBOURNE AND NEW YORK 1981

CHURCHILL LIVINGSTONE
Medical Division of Longman Group Limited

Distributed in the United States of America by Churchill Livingstone Inc., 19 West 44th Street, New York, N.Y. 10036, and by associated companies, branches and representatives throughout the world.

First edition 1971
Second edition 1975
Third edition 1981

ISBN 0 443 02391 3

British Library Cataloguing in Publication Data
Newsam, J.E.
Urology and renal medicine. — 3rd ed.
1. Genito-urinary organs — Diseases
I. Title II. Petrie, J.J.B.
616.6 RC871
Library of Congress Catalog Card Number 81–9924

Printed in Singapore by Huntsmen Offset Printing Pte Ltd

Preface

This book provides a brief account of the medical and surgical disorders of the kidneys and of the urinary and male genital tracts. A combined text of this kind has many advantages and avoids the duplication of some topics and the neglect of others.

In this third edition most of the chapters have been re-written to incorporate the advances and changes made in the diagnosis, assessment and treatment of disease since the second edition was published six years ago in 1975. Many new illustrations have been added and the references, which appear at the end of each chapter, have been brought up to date.

1981

J.E.N.
J.J.B.P.

Contents

1

The structure and function of the kidneys

The excretion of waste products is the most obvious function of the kidneys, but to regard them solely, or even primarily, as organs of excretion is a mistake. If cells are to function normally they must have a constant internal environment. The kidneys are largely responsible for controlling the volume, osmotic concentration and electrolyte content of this environment. They also have an important role in vitamin D metabolism and endocrine functions which are concerned with the regulation of blood pressure and the control of red cell production. It is not surprising that disordered renal function can affect almost every system in the body.

A clear understanding of the structure and function of the kidneys is essential for the diagnosis and management of renal disorders.

THE STRUCTURE OF THE KIDNEYS

The kidneys are paired organs which lie on the posterior abdominal wall behind the peritoneum. Each kidney is about 12 cm in length and weighs about 150 g. The centre of the medial aspect of the kidney is concave and occupied by a deep fissure called the hilum, which transmits the renal vessels and nerves and which contains the renal pelvis. The kidney is composed of an internal medulla and an external cortex. The medulla consists of the renal pyramids, the bases of which are directed towards the cortex, while the apices converge and project into the calices as the renal papillae (Fig. 1.1).

The functional unit of the kidney is the nephron, which consists of a glomerulus and a renal tubule. The glomerulus is a network of capillaries fed by a relatively wide-bore afferent arteriole, and drained by a somewhat narrower efferent arteriole. The two arterioles are in close proximity to each other and form what is sometimes called the 'stalk' of the glomerulus.

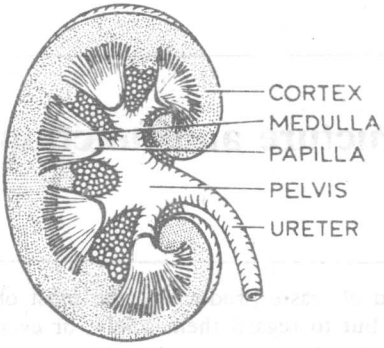


Fig. 1.1 Gross structure of the kidney

The entire glomerulus apart from the stalk is invested in a capsule, called Bowman's capsule, which is the invaginated blind proximal end of the renal tubule, and which has two layers, a visceral and a parietal. The glomerular filter is made up of three layers. The innermost consists of the cells of the capillary itself and is called the endothelial cell layer. The outer is the visceral layer of Bowman's capsule, and is called the epithelial cell layer. The third layer lies between the endothelial and epithelial cells and is called the basement membrane (Fig. 1.2).

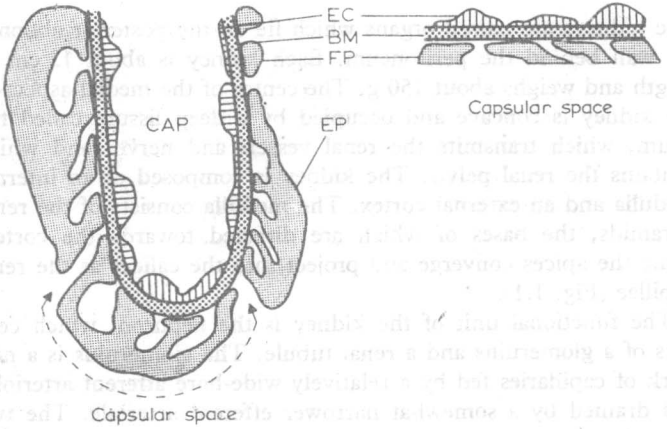


Fig. 1.2 The glomerular filter as seen on electron microscopy. CAP — capillary lumen; EC — endothelial cell layer; BM — capillary basement membrane; EP — epithelial cell layer; FP — foot processes of the epithelial cells

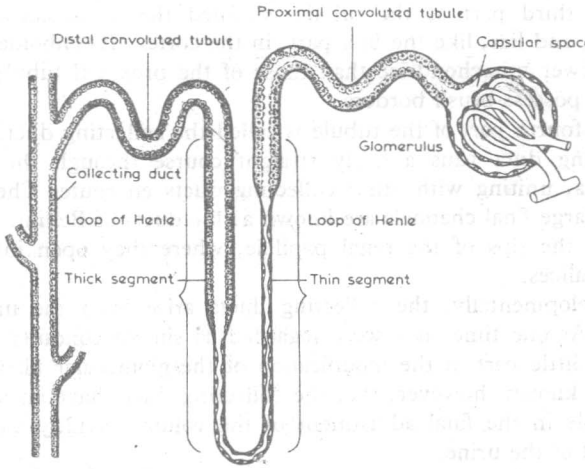


Fig. 1.3 The nephron

Spaces known as slit pores exist in both the endothelial and the epithelial cell layers. These have a diameter of 100 to 200 nm and are closed by a slit pore membrane.

For descriptive purposes the renal tubule is divided into four parts (Fig. 1.3). The first part is tortuous and is known as the proximal convoluted tubule. Its luminal border is called a 'brush border' because it has numerous narrow and deep indentations which provide a large surface area. The cells are cuboidal, and contain many mitochondriae — a fact that suggests intense enzymatic activity. Structurally the proximal convoluted tubule is well suited to active reabsorption and reabsorbs no less than four-fifths of the glomerular filtrate.

The second part of the tubule is called the loop of Henle. It decends into the renal medulla, bends sharply and ascends to re-enter the cortex. The descending limb of the loop, the bend, and the proximal part of the ascending limb are all lined by flat epithelium, whereas the distal part of the ascending limb is lined by cuboidal cells. The loop of Henle plays an essential part in the concentration of urine and the longer it is the more concentrated can urine be made. The kangaroo rat, which lives in the desert and which is able to survive for months on the water derived from the metabolism of dry grain, has the longest loops of Henle in proportion to its size in the animal kingdom, and produces urine which is three times as concentrated as that which man can produce even in his most dehydrated state.

The third part of the tubule is called the distal convoluted tubule, and lies, like the first part, in the cortex. Its cuboidal cells have fewer mitochondriae than those of the proximal tubule, and do not possess brush borders.

The fourth part of the tubule is called the collecting duct. Each collecting duct runs a fairly straight course through the renal medulla, uniting with other collecting ducts en route. The relatively large final channels are known as the ducts of Bellini. These run to the tips of the renal papillae, where they open into the renal calices.

Developmentally, the collecting ducts arise from the ureteric buds. At one time they were regarded as simple conduits which played little part in the modification of the glomerular filtrate. It is now known, however, that the collecting ducts have an important role in the final adjustment of the volume, acidity and salt content of the urine.

In mammals the tubules receive their blood supply through a peritubular complex of capillaries which arises from the efferent arteriole. The blood reaching the tubular capillaries has already passed through the glomerular capillaries of the same nephron. Thus the kidneys, like the liver and the pituitary, have a portal circulation.

In addition to a peritubular capillary plexus, the efferent arterioles draining the glomeruli situated nearest to the medulla give rise to capillary sized vessels known as the vasa recta. These descend into the medulla, bend sharply and re-ascend into the cortex, where they drain into venules. The vasa recta are concerned, along with the loops of Henle and the collecting ducts, with the concentration of the urine.

THE FUNCTION OF THE KIDNEYS

Production of the glomerular filtrate

Man and most other animals produce urine primarily by glomerular filtration. The volume and the composition of the glomerular filtrate, however, is considerably modified by the tubules (see Fig. 1.8).

Since there is little vascular resistance between the aorta and the wide-bore afferent arterioles, the pressure in the glomerular capillaries is high. The efferent arterioles are narrower than the afferent vessels. The glomerular capillaries are thin-walled, and have a large surface area. All these factors combine to produce a system ideally suited to high pressure ultrafiltration.

The amount of glomerular filtrate is determined by the filtration force at the glomeruli and by the number of functioning glomeruli. The filtration force is the hydrostatic pressure at the glomerulus (about 60 mmHg) minus the osmotic pressure of the plasma proteins (25 mmHg) and the back pressure in the capsular space (about 10 mmHg). The glomerular filtration rate is normally about 120 ml/minute, or 170 litres/24 hours.

Complex nervous and humoral mechanisms control renal blood flow but, in general, lowering the renal artery pressure reduces the filtration rate. Reducing the concentration of plasma proteins or the back pressure in the capsular space increases the glomerular filtration rate, while increasing them reduces it.

In 1924 Richards and his colleagues introduced a technique for sampling the fluid in the capsular space and tubules of the frog with micropipettes; later the technique was used on mammalian kidneys. Analysis of fluid obtained from Bowman's capsule has shown it to be an ultrafiltrate of plasma. Its composition with respect to small molecular weight substances is almost identical to that of plasma, but it contains only about 20 mg per cent of protein — a concentration less than 0·5 per cent of the 7 g protein/100 ml which is present in plasma.

Renal clearance

The renal clearance of a substance can be defined as the number of millilitres of plasma which contain the amount of the substance excreted in the urine in 1 minute.

Renal clearances can be used to measure glomerular filtration rate and renal blood flow, and also to study the behaviour of substances as they pass through the renal tubules. The renal clearance of any substance can be determined as follows. A timed specimen of urine is collected and a sample of blood is taken near the midpoint of the collection period. The volume of urine is measured, and the concentration of the substance concerned is determined in both plasma and urine. (Confusion is avoided if both concentrations are expressed as mmol/ml).

If U is the concentration of the substance in the urine, in mmol/ml

V is the volume of the urine collection (in ml),

T is the duration of the collection period (in minutes),

then the amount of the substance excreted in the urine in 1 minute is

$$\frac{UV}{T} \ mmol$$

If the plasma concentration of the substance is P, the *volume of plasma* which *contains the amount of the substance excreted in 1 minute* is

$$\frac{UV}{PT} \text{ ml}$$

This is the renal clearance expressed in millilitres/minute. If the term T is expressed in *seconds*, the clearance value obtained will be millilitres/second.

Determination of glomerular filtration rate

Homer Smith found in dogs that inulin, creatinine, ferrocyanide, thiosulphate and mannitol all had the same renal clearance. This clearance was unaltered by varying the plasma concentrations of the substances concerned. He thought it unlikely that the chemical processes of tubular reabsorption and tubular secretion could proceed at precisely the same rate for such different substances, and postulated that they were all excreted solely by glomerular filtration, and were neither secreted nor reabsorbed in the tubules. It follows that the volume of plasma 'cleared' of inulin or endogenous creatinine is the volume of plasma filtered at the glomeruli, and that the clearance of inulin or endogenous creatinine measures the glomerular filtration rate. (In man some endogenous creatinine is secreted by the renal tubules, and the clearance of creatinine is slightly higher than the glomerular filtration rate.)

Tubular reabsorption and tubular secretion

Some substances are reabsorbed from the tubular lumen. Others are secreted into it by the tubular cells. Figures 1.4 and 1.5 show the relationship which exists between plasma concentration and urinary excretion, and between plasma concentration and renal clearance, for substances handled by the tubules in different ways.

In Figure 1.4, line 1 represents a substance, such as inulin, which is filtered at the glomeruli but neither reabsorbed nor secreted by the tubules. What is filtered is excreted, and excretion is therefore directly proportional to plasma concentration. Line 2 represents a substance which (like glucose) is filtered and reabsorbed, but which is not secreted. At low plasma concentrations all that is filtered is reabsorbed, and none of the substance appears in the urine. Active reabsorption proceeds at a finite rate, however, and there is a limit to its extent. When the amount of the substance filtered at the glomeruli becomes greater than the tubular reabsorptive capacity, the substance appears in the urine. The plasma level

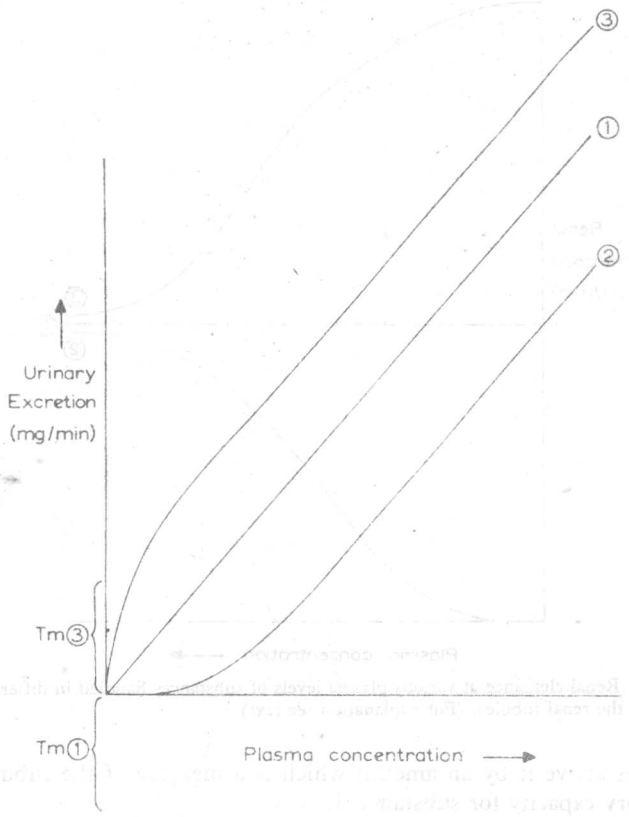


Fig. 1.4 Urinary excretion at various plasma levels of substances handled in different ways by the renal tubules. (For explanation see text)

at which this occurs is known as the renal threshold for the substance concerned. Once reabsorption is fully saturated, any further increase in plasma concentration results in a corresponding increase in urinary excretion. Line 2 becomes parallel to line 1, and the vertical distance between the two lines is a measure of the tubular reabsorptive capacity of the kidneys for substance 2. Line 3 represents a substance which is filtered and secreted, but which is not reabsorbed. At low plasma levels, excretion rises steeply with plasma concentration. Once the tubular secretory capacity has been saturated, however, any further increase in excretion with rising plasma levels is due entirely to the increase in the amount of substance 3 filtered at the glomeruli. Line 3 becomes parallel to line 1,

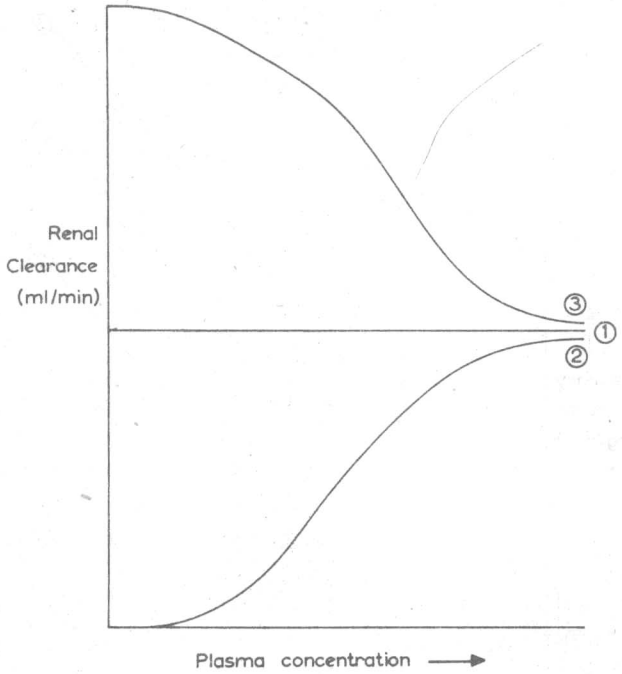


Fig. 1.5 Renal clearance at various plasma levels of substances handled in different ways by the renal tubules. (For explanation see text)

and lies above it by an amount which is a measure of the tubular secretory capacity for substance 3.

From Figure 1.5 it can be seen that the renal clearance of a substance which is neither reabsorbed nor secreted (line 1) is constant, regardless of plasma levels. This clearance is equal to the glomerular filtration rate. For substances which are reabsorbed by the tubules, but not secreted (line 2), the clearance is zero at low plasma levels, but rises to approach the glomerular filtration rate at high plasma concentrations. For substances which are secreted but not reabsorbed (line 3) the clearance at low plasma concentrations is higher than the glomerular filtration rate, but at high plasma concentrations, the clearance falls, and line 3 approaches line 1.

Para-amino hippuric acid (PAH) and the measurement of renal plasma flow

Para-amino hippuric acid is actively secreted by the renal tubular cells. At low plasma levels of PAH, blood samples taken from the

renal artery and renal vein show that only 5 per cent of the PAH which enters the kidney leaves in the renal venous blood. The remaining 95 per cent is excreted in the urine.

PAH can be used to measure renal plasma flow, using the Fick principle; that is to say, if we know how much PAH leaves the kidney in the urine per minute, and the fall in PAH concentration between renal arterial plasma and renal venous plasma, we can calculate the amount of plasma which has flowed through the kidney.

If U is the concentration of PAH in the urine (mmol/ml),
V the volume of urine collected (ml), and
T the duration of the collection period (min),

the amount of PAH excreted in 1 minute in the urine is $\frac{UV}{T}$ (mmol). If Pa is the concentration of PAH in the renal artery, Pv the concentration in the vein, both in mmol/ml, $(Pa - Pv)$ represents the amount of PAH lost in the urine by 1 ml of plasma. The amount in the urine, $\frac{UV}{T}$, must therefore have been lost by $\frac{UV}{T(Pa-Pv)}$ ml of plasma, which is the amount of plasma flowing through the kidney in 1 minute. If we ignore the small amount of PAH which remains in the renal vein, this becomes $\frac{UV}{PaT}$. With a constant slow infusion of PAH the concentration of PAH in the renal artery (Pa) is the same as that in a *peripheral* vein, and renal plasma flow can then be regarded as $\frac{UV}{PT}$ which is the clearance value of PAH. The renal clearance of PAH is thus a measure of renal plasma flow, provided the plasma concentration of PAH is sufficiently low.

The renal handling of sodium

Sodium is freely filtered at the glomeruli and actively reabsorbed by the tubules. About 20 000 mmol of sodium are filtered daily, but in subjects taking an average diet, only 100 to 200 mmol are excreted in 24 hours. Thus 99 per cent or more of the filtered load of sodium is reabsorbed.

The bulk of sodium reabsorption takes place in the *proximal convoluted tubule*. This region of the nephron is accessible to micropuncture and has been intensively studied in animals.

Sodium is actively transported from the tubular lumen across the tubular cell to the interstitial space outside the tubule. As positively

charged sodium ions leave the tubular fluid, negatively charged chloride ions follow, for reasons of electrical neutrality. (The fact that the tubular lumen has a negative charge with respect to the surrounding interstitium tells us that events occur in this order.) The loss of sodium and chloride ions from the filtrate lowers its osmotic concentration and leads to the diffusion of water out of the tubular lumen. This occurs rapidly, as the proximal tubular cells and the spaces between them are highly permeable to water. The filtrate in this region of the nephron remains isotonic with respect to plasma.

There is also rapid movement of the reabsorbed filtrate from the peritubular interstitium to the neighbouring capillaries. The blood in the peritubular capillaries comes from the efferent arteriole. It has already passed through the glomerular filter, and has lost 20 per cent of its plasma water to the renal tubule. Its protein concentration and its colloid osmotic pressure have increased by 20 per cent as a result. This high oncotic pressure leads to rapid and efficient transfer of the reabsorbed filtrate to the blood.

The proximal convoluted tubule is an important site of active bicarbonate reabsorption. This process contributes to sodium reabsorption.

Between 60 and 70 per cent of the filtered sodium, chloride, bicarbonate and water is reabsorbed in the proximal convoluted tubule. This segment also reabsorbs all the filtered glucose, all the filtered amino acids, and 70 to 90 per cent of the filtered phosphate.

The *loop of Henle* is less accessible to micropuncture than the proximal tubule, and the mechanisms operating in this segment are less fully understood. The thin descending limb serves as a site for passive diffusion. Active reabsorption of electrolytes occurs in the thick ascending limb. It has recently been found that the tubular fluid in the ascending limb carries a positive charge; in all other areas of the nephron the tubular lumen is negatively charged. This positive charge indicates that the active process in the ascending limb of Henle's loop is one of *chloride* reabsorption, with sodium following passively along an electrical gradient.

Under normal circumstances about 10 per cent of the filtered load of sodium and chloride is reabsorbed in the loop of Henle. If, however, the amount of sodium and chloride reaching this segment is increased, the loop shows an amazing ability to cope with the additional load by markedly increased reabsorption. A diuretic which blocks sodium reabsorption in only the proximal tubule has a relatively slight effect on salt and water excretion; reabsorption in the loop simply increases. On the other hand a diuretic such as

frusemide, which blocks reabsorption in the loop of Henle, is capable of increasing salt and water excretion to 30 per cent of the filtered load.

The *distal convoluted tubule* and *collecting ducts* are presented with 20 to 30 per cent of the filtered sodium. At this site in the nephron, relatively little chloride and bicarbonate remain in the filtrate. Much of the sodium is associated with anions such as sulphate and phosphate which cannot be reabsorbed in the distal nephron. At the proximal end of the distal tubule, the lumen has a negative charge of about −5 mV. Continued active reabsorption of sodium in excess of anion leads to an increase in negative charge to −50 mV towards the distal end of this segment.

As sodium is positively charged, this strong negative force opposes its reabsorption. As a result, sodium reabsorption in the distal nephron is largely dependent on *ion exchange*. Positively charged hydrogen, ammonium, or potassium ions enter the tubular lumen as positively charged sodium ions leave it. This ion exchange mechanism occurs throughout the nephron, but is particularly important in its distal part, where the intratubular negative charge is greatest.

The ion exchange mechanism is potentiated by the hormone aldosterone, derived from the adrenal cortex. In the absence of aldosterone, a little over 2 per cent of the filtered sodium escapes into the urine. In the presence of maximal aldosterone activity, the urine becomes almost sodium-free. Because of the large amount of sodium filtered in 24 hours (the total amount of sodium present in the body passes into the glomerular filtrate about five times a day) very small adjustments to sodium in terms of the percentage reabsorbed have large effects in terms of the body's content of sodium.

The *osmotic concentration* of the body fluids is determined by the antidiuretic hormone of the posterior pituitary. Provided that there is free access to water, the *volume of the extracellular fluid* is determined by the sodium content of the body, and this is regulated by the kidneys. Salt depletion has profound effects on plasma volume, cardiac output and blood pressure. It is perhaps hardly surprising that among the many homeostatic functions of the kidneys, preservation of sodium balance appears to take precedence. An example of this is seen in the protracted vomiting of pyloric stenosis. The vomitus contains a considerable amount of hydrogen ions, and a moderate amount of sodium and potassium. There is a stimulus to conserve sodium, potassium and hydrogen ions, but in severe cases the drive to conserve sodium over-rides other considerations. Under the influence of aldosterone, sodium is avariciously reab-

sorbed in exchange for potassium and hydrogen ions, and we get the paradox of a severely alkalotic, potassium-depleted patient passing an acid urine which is rich in potassium.

The renal handling of potassium

Potassium is freely filtered at the glomeruli. Under normal circumstances about 5 per cent of the fitered load is excreted — a fact which indicates considerable tubular reabsorption. In some patients with renal failure, however, the clearance of potassium is greater than the clearance of inulin. In this situation, since the amount excreted is more than the amount filtered, tubular secretion of potassium is obviously present.

From experiments involving micropuncture of the nephron at various sites, we now know that practically all the filtered potassium is reabsorbed in the promixal part of the nephron. The potassium which appears in the urine is derived from tubular secretion in the distal tubule and collecting ducts. This secretion is by way of the ion exchange mechanism for sodium reabsorption.

When diuretics block sodium reabsorption in the proximal tubule and the loop of Henle, there is a considerable increase in the amount of sodium delivered to the distal nephron. Much of this is reabsorbed by the ion exchange mechanism, and as a result there is an increase in urinary potassium excretion. It is often necessary to give potassium supplements to patients taking diuretics of this type.

Some diuretics such as spironolactone (an aldosterone antagonist) and amiloride act in the distal nephron to block the ion exchange mechanism. These diuretics *reduce* potassium excretion. If potassium supplements are given along with spironolactone a dangerously high plasma potassium concentration may result.

The renal regulation of acid-base balance

If cells are to function normally, the pH of the extracellular fluid must be maintained between 7·35 and 7·45.

The first line of defence against a change in pH is the blood buffering system. The principal buffer in the blood is the bicarbonate/carbonic acid system. The blood pH is given by the Henderson-Hasselbach equation

$$\text{pH} = \text{pK} + \log \frac{\text{Bicarbonate}}{\text{Carbonic acid}}$$

where pK is the dissociation constant of carbonic acid.