

The renal system

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Our cells are surrounded by a watery environment that is probably similar in composition to the primordial sea in which life originated. The constancy of this 'internal environment' of extracellular fluid is a requirement of life, and the process of maintaining this constancy is called homeostasis. The kidneys, together with the lungs, are the most important organs ensuring a constant chemical composition of our extracellular fluid.

The kidneys' importance can be gauged from the fact that they receive one-fifth of the cardiac output of blood, i.e. 1 litre per minute.

The major role of the kidneys is to 'purify' blood by extracting waste products of metabolism; they must also help to control the osmolality, volume, acid–base status and ionic composition of the extracellular environment by modifying the composition of that part of the extracellular fluid (the blood plasma) that passes through them. The waste products extracted by the kidneys must be ejected from the body and, of course, this is done in the urine, a watery solution. However, the kidneys have a limited water budget with which to do this. We can not afford to use unlimited amounts of water, even to carry out this important task, and the wastes are concentrated by reabsorbing 99% of the water that enters the millions of functional units (nephrons) which make up our kidneys.

As if this were not enough, our kidneys play important roles in controlling the

production of red blood corpuscles and regulating blood-pressure.

The importance of our kidneys is seen in those unfortunate people whose kidneys have ceased to function, and who depend on dialysis machines to maintain the composition of their blood; they can only live normally for a few days while their bodies accumulate wastes before having to make use of an 'artificial kidney'.

Section overview

This section outlines:

- The kidney's regulation of volume and composition of extracellular fluid by the processes of filtration, reabsorption and secretion
- The gross structure of the kidney, which is a cortex surrounding a medulla containing an inner cavity, the pelvis
- The functional unit of the kidney – the microscopic nephron (1 million in each kidney)
- How about 180 litres of plasma filters into the nephrons each day and how most of it is reabsorbed
- Autoregulation of renal blood flow which, along with renal nerves and the renin–angiotensin system, influences the rate of filtration
- Active reabsorption of substances from the nephrons, and how water follows passively
- Regulation of absorption by endocrine factors including prostaglandins, the renin–angiotensin–aldosterone system, atrial natriuretic peptide and antidiuretic hormone
- The effect of the shape of the loop of Henle enabling countercurrent multiplication to produce hyperosmotic extracellular fluid in the medulla. This effect is reinforced by movement of urea
- The excretion of fixed acids formed and absorbed by the body
- The control of acid–base balance by the kidneys in conjunction with the lungs
- Passage of urine from the kidney to the bladder and micturition.

General functions of the kidney

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Introduction

The main function of the kidneys is to regulate the volume and composition of the extracellular fluid. This they do by filtering large volumes of plasma, retaining only plasma proteins, and then selectively reabsorbing from or secreting into the filtrate. The urine therefore contains ‘unwanted’ solutes in water. The processes of filtration, absorption and secretion are regulated homeostatically so as to minimize changes in extracellular fluid composition; in achieving this, urine of appropriate volume and composition is produced.

The kidneys also:

- excrete metabolic waste products including creatinine, urea, uric acid and some end products of haemoglobin breakdown
- excrete foreign substances and their derivatives, including drugs, and food additives – such substances are therefore excreted less efficiently when kidney function is impaired
- synthesize prostaglandins and kinins that act within the kidney
- function as endocrine organs, producing the hormones renin, erythropoietin and calcitriol, the active form of vitamin D.



Basic Science 8.1.1

Filtration and osmosis

Filtration

At a molecular level, filtration is the bulk flow of fluid through a membrane or other barrier that selectively impedes the movement of some molecules, the largest being impeded most. This process is sometimes called **ultrafiltration**. The movement is driven by a hydrostatic pressure difference across the barrier. The volume of fluid filtered per unit time is proportional to the hydrostatic pressure difference, the surface area of the barrier and its permeability. Those molecules that are too large to pass through the pores of the membrane are concentrated on the high-pressure side of the barrier. The concentration of freely filtered solutes in the filtrate is the same as in the filtered fluid.

Osmosis

When two aqueous solutions are separated by a semipermeable membrane that is permeable to the solvent (water), but not to the solute, and if the concentration of solute is higher on one side of the membrane than on the other, then solvent will move from the less concentrated solution to the greater. Thus, water will move across a semipermeable membrane down its own concentration gradient. This process is known as **osmosis**. Any solutes to which the membrane is permeable will move with the osmotic flow of water. Their concentrations will not be changed by osmosis.

The tendency for water to move to the region of high solute concentration can be prevented by applying a pressure to the concentrated solution (Fig. BS8.1.1). The pressure needed to completely prevent movement is termed the osmotic

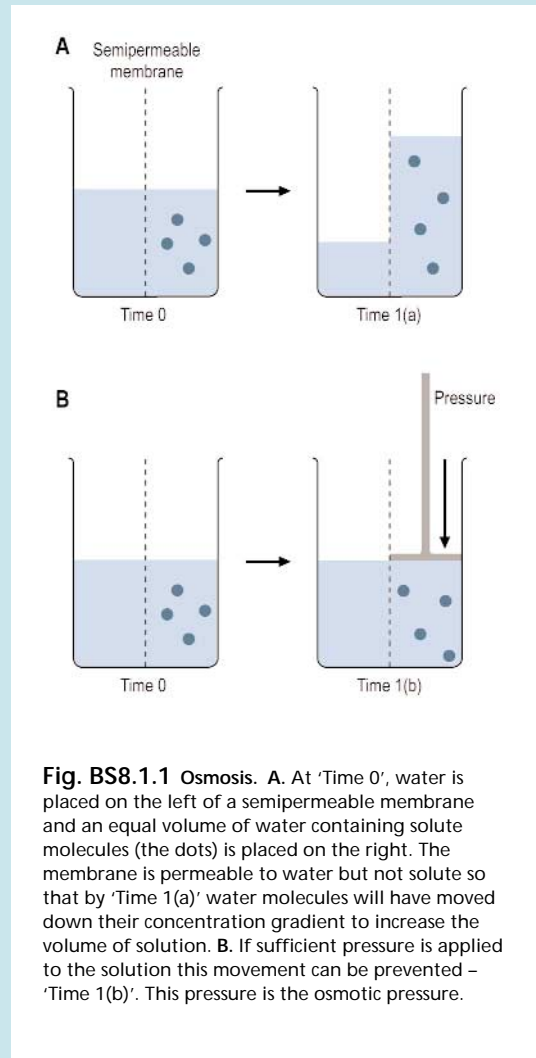


Fig. BS8.1.1 Osmosis. A. At 'Time 0', water is placed on the left of a semipermeable membrane and an equal volume of water containing solute molecules (the dots) is placed on the right. The membrane is permeable to water but not solute so that by 'Time 1(a)' water molecules will have moved down their concentration gradient to increase the volume of solution. B. If sufficient pressure is applied to the solution this movement can be prevented – 'Time 1(b)'. This pressure is the osmotic pressure.

pressure of the fluid. Osmotic pressure is expressed in the same units as hydrostatic pressure. You should note that the solution can only exert an osmotic pressure when it is in contact with another solution via a membrane that is permeable to the solvent and not to the solute.

Structure of the kidneys

The kidneys are paired, bean-shaped organs that lie behind the peritoneal lining of the abdominal cavity (Fig. 8.1.1). Each kidney is surrounded by a thin capsule, which is usually removed when the kidney is used for culinary purposes. The capsule resists stretch and limits swelling. This has important consequences for the renal circulation. The renal artery and the renal vein, renal lymphatics and ureter enter and leave the kidney through its concave surface, at the **hilum**.

When the kidney is cut in half longitudinally, an outer layer, the **cortex**, can be seen surrounding the **medulla**, which is made up of a series of conically shaped **pyramids**. The apical end of each pyramid, the **papilla**, opens into a space,

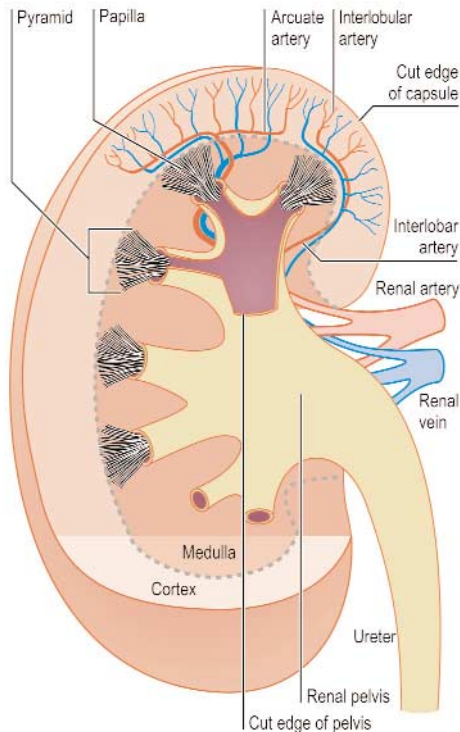


Fig. 8.1.1 Structure of the kidney. The kidney is shown cut across so that the hollow pelvis, which empties into the ureter, is partially opened. Into the pelvis project the papillae which are made up of the apices of two or more pyramids. The pyramids make up most of the medulla of the kidney.

the renal **pelvis**, which is continuous with the **ureter**. The ureter drains into the bladder.

Structure of the nephron

The basic unit of the kidney is the nephron (Fig. 8.1.2), which is a blind-ended tubule running from **Bowman's capsule** into the ureter at the renal pelvis. There are about one million of them in each human kidney.

Each nephron begins at the **glomerulus**, which comprises a tuft of glomerular capillaries contained within Bowman's capsule, which is the blind end of the nephron. The capillaries are derived from an afferent arteriole and drain into an efferent arteriole. The many branches of the capillaries form a cluster that invaginates

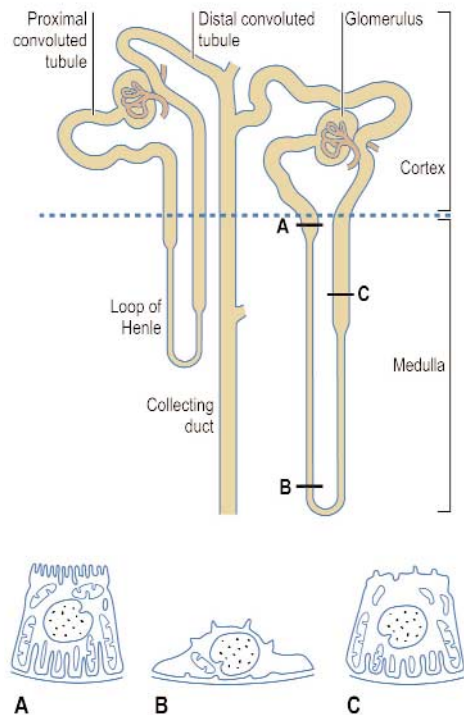


Fig. 8.1.2 Structure of the nephron. There are two types of nephron (see text) in which the proportions of their parts are different. The structure of the epithelium of the tube in these parts is shown.

into Bowman's capsule, like a fist pushed into a partially inflated balloon. All glomeruli are found in the cortex. The glomerulus produces a more or less protein-free filtrate of plasma.

Fluid from Bowman's capsule flows into a coiled segment, the **proximal convoluted tubule**, and then into the **loop of Henle**, which courses down into the medulla forming a hairpin shape. Two different populations of nephrons exist:

- **cortical nephrons** that have glomeruli in the outer two-thirds of the cortex and short loops of Henle that just dip into the outer medulla
- **juxtamedullary nephrons** that have glomeruli in the inner cortex and long loops of Henle that plunge deep into the medulla, as far as the tips of the papillae.

The terms descending and ascending are used to describe the two limbs of the loop of Henle. The nephron first descends into the medulla and then ascends back into the cortex. The ascending limb of the loop of Henle leads into a second coiled section, the **distal convoluted tubule**. The distal convoluted tubule begins at a specialized structure known as the juxtaglomerular apparatus (Fig. 8.1.3). Here the tubule passes between the afferent and efferent

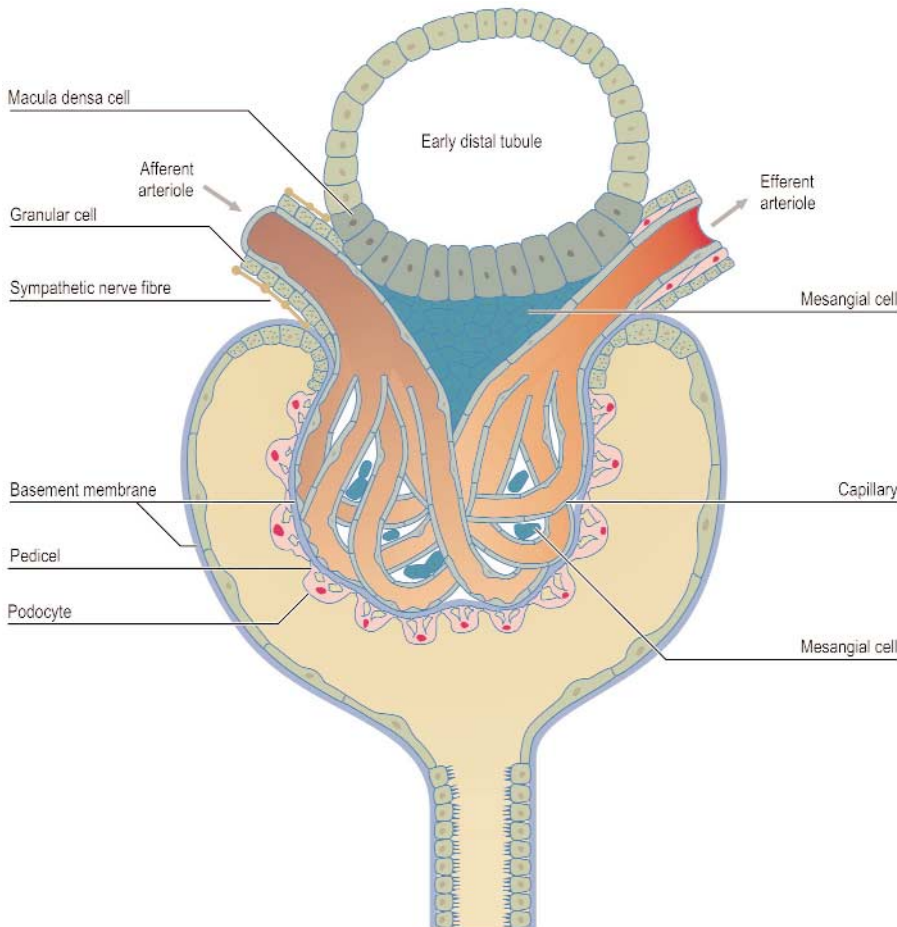


Fig. 8.1.3 The glomerulus and juxtaglomerular apparatus. The early distal tubule lies very close to the afferent and efferent arterioles of the glomerulus. Cells of all three structures are modified as described in the text and there is a rich supply of sympathetic nerves.

arterioles that supply the tubule's own glomerulus. This short section of tubule is known as the **macula densa** and senses the flow and composition of tubular fluid. It abuts onto a specialized region of the afferent arteriole whose granular cells secrete renin.

The distal tubules of several different nephrons join to form a **collecting duct** that passes through the medulla to the papilla.

Throughout its length, the nephron is composed of a single layer of epithelial cells resting on a basement membrane. There are characteristic differences in the structure of the cells along the length, which reflect their different functions (see below). The cells form a selectively permeable barrier to diffusion into or out of the tubule; they are joined together to form the barrier by specialized tight junctions that limit diffusion between the cells.

Structure of the glomerulus

In the glomerulus, the filtrate of plasma has to pass through three layers:

- The fenestrated (perforated; from the Latin *fenestra* – a window) endothelium of the capillary which is the filtering membrane.
- The basement membrane of the Bowman's capsule (Fig. 8.1.4) which is mainly composed of connective tissue, but also contains mesangial cells that are both phagocytic and contractile. By contracting they are thought to be able to actively reduce glomerular filtration by reducing the area available for filtration.
- The epithelial cells of the capsule. These are known as podocytes because they have numerous foot-like projections (pedicels) that clasp the tubes of capillary endothelium. Substances that pass through the filtration



Summary

Structure of the kidney

- The kidney is composed of an outer cortex and an inner medulla, which reflect the position and arrangement of the renal tubules (nephrons).
- Each tubule consists of a glomerulus, proximal convoluted tubule, loop of Henle and distal convoluted tubule.
- Distal convoluted tubules join to form collecting ducts which drain into the renal pelvis and ureter.
- All glomeruli are found in the cortex; cortical nephrons have short loops of Henle which just dip into the outer medulla, whereas juxtamedullary nephrons have long loops of Henle that reach deep into the medulla.
- The renal artery and vein, renal lymphatics and ureter enter and leave the kidney via its concave surface – the hilum.

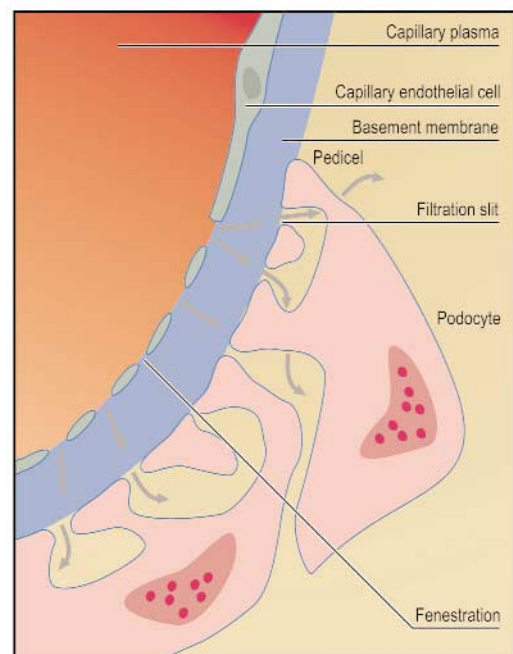


Fig. 8.1.4 Glomerular filtration. The structures that renal filtrate passes through from the glomerular capillary to the lumen of the Bowman's capsule.

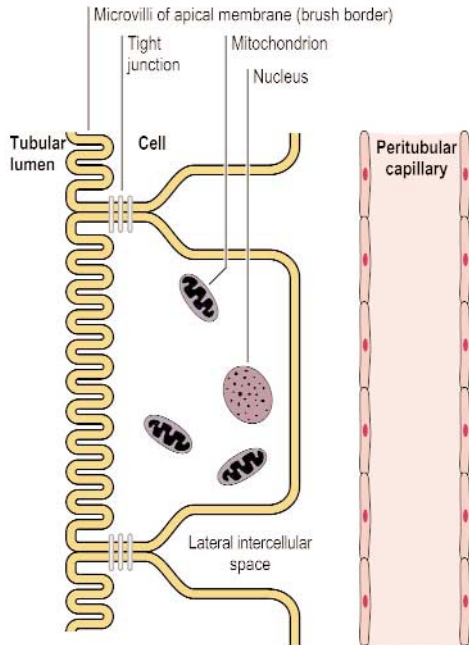


Fig. 8.1.5 Tubular cells and peritubular capillaries. The microvilli, tight junctions and intercellular spaces provide the anatomical basis for the absorptive mechanisms of the tubule described in the text.

slits (or pores) between the pedicels therefore pass close to the cell surface of the podocytes (see Fig. 8.1.4).

Structure of the tubule

The epithelial cells of the proximal tubules contain many mitochondria and have many microvilli at their luminal surface, called a **brush border**, which increase the surface area (Fig. 8.1.5). Adjacent cells are joined together at their luminal (apical) ends by tight junctions (see p. 60). At their basal ends, there are gaps between them, known as lateral intercellular spaces.

The descending limb of the loop of Henle and the first part of the ascending limb are thin walled: the epithelial cells contain relatively few mitochondria and are flattened with few



Summary

The nephron

- Each nephron begins at Bowman's capsule – the blind end of the tubule.
- Bowman's capsule contains a knot of capillaries which is supplied by an afferent arteriole and drained by an efferent arteriole. This whole structure is known as a glomerulus and it filters plasma.
- Fluid passes from Bowman's capsule to the proximal tubule, to the descending and ascending limbs of the loop of Henle and thence to the distal convoluted tubule which begins at a specialized structure known as the juxtaglomerular apparatus.
- In the juxtaglomerular apparatus, the tubule passes between the afferent and efferent arteriole of its own glomerulus. This section of the tubule is known as the macula densa and it abuts onto a specialized region of the afferent arteriole which secretes renin.

microvilli. The ascending limb becomes thick walled as it enters the cortex; there are many mitochondria and microvilli, but fewer than in the proximal tubule. Along the length of the distal tubule and collecting ducts, the numbers of mitochondria and microvilli decrease. In the late part of the distal tubule and collecting duct there are two specialized types of cells (**principal** and **intercalated**) that are involved in Na^+ - K^+ balance and H^+ balance (see Ch. 8.4).

Renal blood supply

As it enters the kidney, at its hilum, the renal artery branches to form interlobar arteries which radiate out towards the cortex (Fig. 8.1.6).

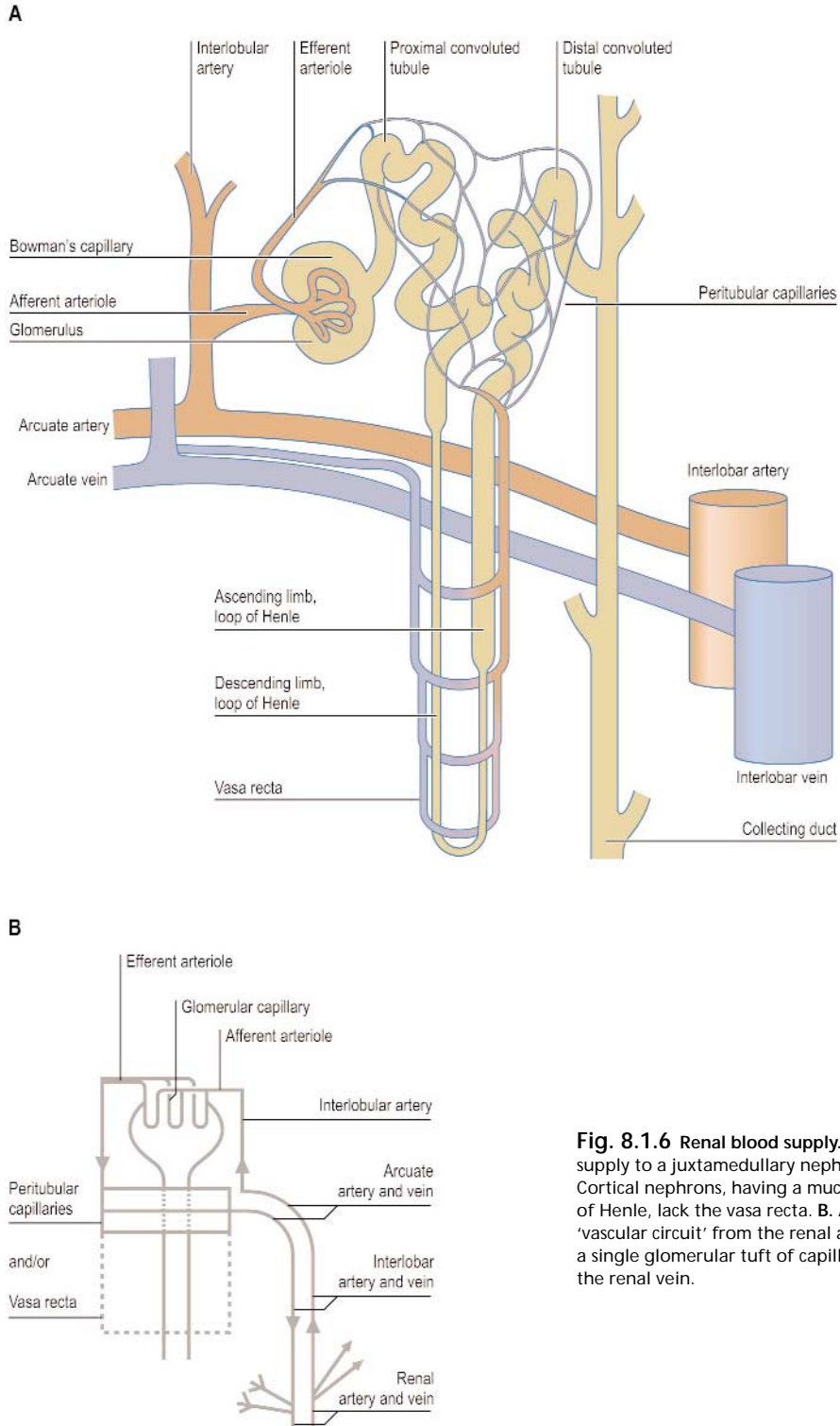


Fig. 8.1.6 Renal blood supply. A. The blood supply to a juxtamedullary nephron is shown. Cortical nephrons, having a much shorter loop of Henle, lack the vasa recta. B. A generalized 'vascular circuit' from the renal artery through a single glomerular tuft of capillaries back to the renal vein.

At the boundary between the cortex and medulla, arcuate arteries branch off at right angles and from these arise the interlobular and afferent arterioles that supply the glomeruli. The efferent arterioles that drain the glomeruli branch to form a secondary capillary, or a portal system. Those from the cortical glomeruli give rise to a peritubular capillary network that supplies the renal tubules. Those from the juxtamedullary glomeruli give rise either to similar peritubular capillaries, or to capillaries which plunge deep into the medulla and form hairpin loops parallel with the loops of Henle. These vascular loops are called the **vasa recta**.

All the capillaries drain into a cortical venous system and then into the renal vein.

Renal nerve supply

The kidney is richly innervated. Postganglionic **sympathetic** noradrenergic nerve fibres supply the renal artery and its branches. The afferent and efferent arterioles of the glomeruli and the juxtaglomerular renin-secreting cells are particularly densely innervated. Sympathetic noradrenergic fibres also supply the proximal tubules, the thick ascending limb of the loop of Henle and the distal tubule.



Summary

Renal blood and nerve supply

- The renal artery branches to form interlobar arteries that radiate out to the cortex.
- At the corticomedullary boundary, arcuate arteries branch off at right angles, giving rise to interlobular arteries. These in turn give rise to the afferent arterioles that supply the glomerular capillaries.
- Efferent arterioles which drain the glomerular capillaries, branch to form a second, or portal, capillary system.
- Efferent arterioles from cortical glomeruli give rise to the peritubular capillaries. Those from juxtamedullary glomeruli form either peritubular capillaries or the vasa recta, which are capillary loops that run parallel with the loops of Henle.
- The kidney has a rich sympathetic noradrenergic innervation, which supplies the renal artery and its branches, the juxtaglomerular renin-secreting cells and the renal tubules, particularly the proximal tubule.

Glomerular function



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Introduction

By the process of ultrafiltration (filtration at a molecular level) of blood plasma, the glomerulus produces enormous amounts of tubular fluid, the volume and composition of which is modified by absorption, or secretion, according to the requirements of the body to retain, or excrete, specific substances. The process of filtration is so intimately associated with renal blood flow and pressure that they can all be considered together.

Glomerular filtration

In the glomeruli, blood is exposed to a filtering membrane of about 1 m^2 in area, equal to over half of the external surface of the body. As described in Chapter 8.1, the filtering membrane is composed of three layers. The capillary endothelium, being fenestrated, is about 50 times more permeable than, for example, the capillary endothelium of skeletal muscle. The filtration barrier only allows substances of up to a molecular weight of 10 000 to pass freely. Larger molecules are increasingly restricted, those of molecular weight of 100 000 and above usually being unable to pass through at all. An additional barrier is formed by fixed negative charges, probably on the basement membrane but possibly on the podocyte cell membrane as well, which repel negatively charged anions.

Thus, haemoglobin from lysed red blood cells passes into the tubule far more easily than albumin, even though they both have a molecular

weight of about 70 000, simply because albumin has more negative charges.

The fluid that filters into Bowman's capsule is therefore more or less protein-free and contains all other substances that are present in plasma in virtually the same concentrations as they are found free in the plasma. The exceptions that are not immediately obvious are low molecular weight substances that bind to plasma proteins and are therefore not filtered. These include some hormones (e.g. thyroxine), much of the plasma calcium and almost all plasma fatty acids.



Summary

Glomerular filtration

- Fluid passes into Bowman's capsule by a process known as ultrafiltration through three layers:
 - the fenestrated endothelium of the glomerular capillary
 - the basement membrane of Bowman's capsule
 - the epithelial cells (podocytes) of Bowman's capsule.
- This filtration barrier generally allows substances of <10 000 molecular weight to pass. However, negatively charged ions are restricted more because the barrier has a negative charge which repels anions.
- Low molecular weight substances (e.g. thyroxine) and ions (e.g. Ca^{2+}) that are bound to plasma proteins do not pass.

Glomerular filtration rate

Glomerular filtration rate is determined by the difference between the hydrostatic pressure and osmotic pressures in the glomerular capillaries and in the lumen of the Bowman's capsule (Fig. 8.2.1).

The hydrostatic pressure in the glomerular capillary is higher than in other capillaries in the body because:

- renal **afferent arterioles** are usually wider than most other arterioles and offer less resistance
- renal **efferent arterioles** offer a substantial postcapillary resistance.

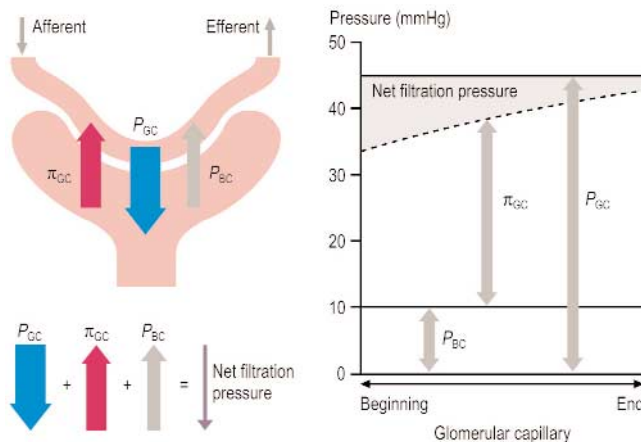


Fig. 8.2.1 Glomerular filtration. The pressures involved in glomerular filtration are shown on the left, and plotted against position in the glomerular capillary on the right. The glomerular capillary hydrostatic pressure (P_{GC}), the back pressure built up in the Bowman's capsule (P_{BC}) and the colloid osmotic pressure of the glomerular capillary plasma (π_{GC}) result in a net filtration pressure – the shaded area of the graph. The situation when there is a vigorous capillary blood flow is shown. At low flow rates there may be insufficient net pressure to bring about filtration at the end of the capillary but whether that is so is still open to debate.

The presence of efferent arterioles (unique to the renal circulation) and the fact that the glomerular capillaries are relatively short and wide explains another difference between glomerular and other capillaries; that is, the hydrostatic pressure does not fall significantly along the length of the glomerular capillary and is about 45 mmHg.

The hydrostatic pressure of the tubular fluid in Bowman's capsule is about 10 mmHg. Therefore, there is a hydrostatic difference of 45 – 10 mmHg (35 mmHg) between the capillary and the fluid in Bowman's capsule. This is the net **hydrostatic filtration pressure**. Because the barrier between the glomerular capillary and Bowman's capsule acts as a semipermeable membrane that is impermeable to protein, the protein in the plasma exerts an osmotic pressure that tends to draw water back into the capillary (see Ch. 8.1). An osmotic pressure that is due to protein is known as **oncotic pressure**. It is about 25 mmHg at the arteriolar end of the capillary. By contrast, the oncotic pressure in Bowman's capsule is negligible and can be regarded as zero. Therefore, there is an osmotic pressure difference between the capillary and Bowman's capsule which by itself would cause an osmotic flow of water into the capillary. The hydrostatic pressure difference is greater than, and opposed to, the osmotic pressure difference so there is a net outward filtration of fluid into Bowman's capsule.

The net outward movement of water from the capillary leads to a gradual increase in the plasma protein concentration as the blood passes along the capillary. Because fenestrated capillaries are so much more permeable to water than, for example, continuous capillaries in skeletal muscle, outward movement of water has a much greater effect on the plasma protein concentration in glomerular capillaries than in muscle capillaries. When the plasma oncotic pressure in the glomerular capillary reaches 35 mmHg, the hydrostatic and osmotic forces are in equilibrium and filtration ceases. (This equilibrium is reached towards the end of the capillary in the rat, but in man it may not be reached at all.)

Summarizing, we can write:

Hydrostatic pressure difference across filtration barrier = $P_{GC} - P_{BC}$

and

Osmotic pressure difference across filtration barrier = $\pi_{GC} - \pi_{BC}$

where P_{GC} and P_{BC} are hydrostatic pressures in the glomerular capillary and Bowman's capsule respectively and π_{GC} and π_{BC} are mean oncotic pressures in the glomerular capillary and Bowman's capsule respectively. (π_{BC} is included for completeness but is usually zero, as noted above.)

Therefore,

$$\text{GFR} \propto (P_{GC} - P_{BC}) - (\pi_{GC} - \pi_{BC})$$

where GFR (glomerular filtration rate) is the filtration volume per unit time.

GFR is also dependent on the permeability of the filtration barrier and on the surface area available for filtration. If K_F (the **filtration coefficient**) is the product of these two factors we can write:

$$\text{GFR} = K_F(P_{GC} - P_{BC}) - (\pi_{GC} - \pi_{BC}).$$

Clearly, if any of the factors that determine GFR change, then the GFR would be expected to change. Pathologically, GFR can be reduced by disease processes that reduce the number of functioning nephrons. Measurement of GFR is therefore important in renal physiology and in assessment of renal function in patients.

Measurement of GFR

GFR is not measured directly, but by measurement of the excretion of a marker substance.

If a substance has the same concentration in the glomerular filtrate as in plasma and if that substance is neither added to the urine nor taken away from it by the tubules, then the amount of that substance filtered per minute must equal the amount excreted per minute:

$$P_x \times \text{GFR} = U_x \times V$$

where P_x and U_x are the concentrations of the substance, X, in plasma and urine respectively and V is urine flow as a volume per unit time.

Therefore

$$\text{GFR} = \frac{U_x \times V}{P_x} .$$

GFR can be measured by using **inulin**, a polymer of fructose, which is freely filtered and neither secreted nor reabsorbed by the nephron. Inulin does not occur naturally in the body and must be given as a continuous intravenous infusion to achieve a constant plasma concentration.

In an average human adult, GFR is approximately 125 ml/min (180 l/24 h). As the total volume of plasma is about 3 litres, the entire plasma volume is filtered about 60 times every 24 hours.

Clinically, **creatinine** is often used for the measurement of GFR. It is naturally occurring and is released into plasma at a fairly constant rate by skeletal muscle. Therefore there is no need to give an infusion. Although it is freely filtered, some additional creatinine is secreted by the nephron. However, the methods available for measuring creatine concentration tend to overestimate its concentration in plasma. Thus, the errors tend to cancel out and GFR values estimated with creatinine agree well with those measured with inulin.

Renal clearance

The method just described for measuring GFR is one of several 'clearance methods'. Clearance is a concept, rather than an actual physiological process. The clearance of a substance is the rate at which plasma would have to be completely cleared of that substance in order to yield the substance at the rate at which it appears in the urine:

$$\text{Clearance} = \frac{U \times V}{P} .$$

Because inulin is neither secreted nor reabsorbed, its clearance is equivalent to the volume of filtrate produced in the glomerulus per unit

time (GFR). If a substance has a clearance greater than that of inulin, then it must have been secreted into the tubular fluid by the nephron epithelium. If it has a clearance lower than that of inulin, either it was not filtered freely at the glomerulus, or it must have been reabsorbed from the tubular fluid.



Summary

Glomerular filtration rate (GFR)

- GFR is the filtration volume per unit time.
- It is determined by the difference between the hydrostatic pressures in the glomerular capillaries and Bowman's capsule (P_{GC} and P_{BC}) and the osmotic pressures in the glomerular capillaries and Bowman's capsule (π_{GC} and π_{BC}):

$$\text{GFR} \propto (P_{GC} - P_{BC}) - (\pi_{GC} - \pi_{BC}) .$$

- It is also dependent on the permeability of the filtration barrier and the filtration surface area – the filtration coefficient (K_f):

$$\text{GFR} = K_f (P_{GC} - P_{BC}) - (\pi_{GC} - \pi_{BC}) .$$

- It can be measured indirectly via the 'clearance method' by administering a marker substance (e.g. inulin) which is neither reabsorbed nor added to the urine.
- For such a substance (X) the amount filtered must equal the amount excreted, i.e.:

$$P_x \times \text{GFR} = U_x \times V$$

or

$$\text{GFR} = \frac{U_x \times V}{P_x}$$

where P_x and U_x are the concentrations of X in plasma and urine and V is urine volume per unit time.

- GFR can be measured clinically, but with a small error, by using the naturally occurring substance, creatinine.

Regulation of GFR

A change in any of the hydrostatic or osmotic forces within the glomerulus can produce a change in GFR.

It might be expected that changes in capillary hydrostatic pressure, GFR and renal blood flow would be produced by changes in systemic arterial pressure. However, capillary pressure, GFR and renal blood flow (see below) are held nearly constant over the systemic mean arterial pressure range 90–200 mmHg (Fig. 8.2.2). This is known as **autoregulation**. Autoregulation of blood flow and GFR can occur in denervated kidneys (e.g. transplanted kidneys) and in isolated, perfused kidneys. Thus, it is not dependent on the nerve supply, nor on blood-borne substances. Autoregulation can be explained in part by an intrinsic or myogenic property of vascular smooth muscle; when pressure within the afferent arteriole increases, it stretches the vessel wall and triggers contraction of its smooth muscle, so leading to arteriolar constriction. This increase in afferent arteriolar resistance prevents an increase in systemic arterial pressure from reaching the capillaries.

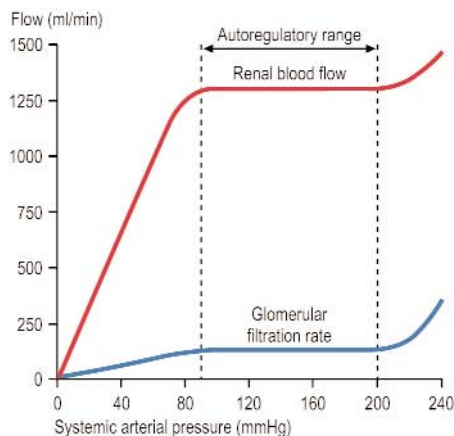


Fig. 8.2.2 Autoregulation. The effects of changing arterial blood pressure on total renal blood flow and glomerular filtration rate in the absence of any extrinsic influences on the kidney.

The opposite happens when systemic arterial pressure falls.

Another process that plays a part in autoregulation of GFR is **tubular glomerular feedback**; within each individual nephron, the rate at which filtered fluid arrives at the distal tubule regulates the GFR of that nephron. It seems that the sensors controlling this process are the cells of the macula densa, but the mechanisms are still controversial.

One explanation is that the macula densa cells are sensitive to sodium chloride concentration. When flow rate in the tubule increases, more NaCl arrives at the macula densa. This causes release of substances at the glomerulus that reduce GFR. Recent evidence suggests that one of these substances is **adenosine**, which constricts afferent arterioles and dilates efferent arterioles, so reducing glomerular capillary hydrostatic pressure. Adenosine may also inhibit renin secretion and thereby reduce the concentration of angiotensin II, whose preferential constrictor action is on efferent arterioles (see Ch. 8.5).

A decrease in the flow rate at the macula densa would produce opposite effects, so tending to increase GFR.

GFR is also maintained constant when there is a moderate increase in sympathetic noradrenergic activity to the kidney. This causes balanced constriction of both afferent and efferent arterioles, so that hydrostatic pressure in the glomerular capillaries does not change, even though renal blood flow is reduced (see below).

Circumstances in which GFR does not remain constant

A large increase in sympathetic activity, as occurs after a major haemorrhage, causes greater constriction of the afferent than of the efferent arteriole and GFR falls. On the other hand, an increase in GFR can be produced by a decrease in plasma oncotic pressure. This can happen when plasma protein concentration is reduced, for example in liver disease or malnutrition.

Although it is not immediately obvious from looking at the hydrostatic and osmotic forces that determine GFR, GFR can be decreased by a decrease in renal blood flow and increased by an increase in renal blood flow. The reason for this is that, if renal blood flow is reduced, plasma spends longer traversing the glomerular capillary. This allows a greater time for filtration of solvent out of any given volume of plasma. Thus, the capillary oncotic pressure will rise more for a given distance along the capillary and the point at which equilibrium is reached between the outwardly directed filtration force and the inwardly directed osmotic force occurs earlier. Therefore, less of the length of the glomerular capillary takes part in filtration (Fig. 8.2.1). The opposite occurs when blood flow is increased.

If the filtration coefficient (K_f) is reduced, this can also reduce GFR. This can be brought about by contraction of the mesangial cells, which probably reduces the capillary surface area available for filtration by causing twisting and occlusion of some capillary loops. Mesangial cells can be contracted by a number of substances including angiotensin II, vasopressin and noradrenaline. Pathologically, K_f is most often reduced by a loss of filtration surface area as a result of disease or damage of the glomeruli.



Summary

Regulation of GFR

- GFR can be held constant over the systemic mean arterial pressure range (90–200 mmHg) because glomerular capillary pressure (P_{GC}) is kept constant. This is known as autoregulation.
- Autoregulation is achieved by:
 - the myogenic response of the afferent arteriole, which constricts when systemic arterial pressure rises, so stretching the blood vessel wall
 - tubular glomerular feedback, such that an increase in the flow rate of fluid in the distal tubule causes constriction of the afferent arteriole of that tubule.
- GFR can be changed. For example:
 - a large increase in renal sympathetic activity constricts the afferent arteriole and thereby reduces P_{GC} and GFR
 - a decrease in plasma oncotic pressure reduces π_{GC} and thereby increases GFR
 - a decrease in K_f produced by a decrease in the permeability or surface area of the filtration barrier can decrease GFR.



Clinical Example

Glomerulonephritis

As the name implies, this is a condition where there is inflammation of the glomeruli of the kidneys. A complex condition which has been recognized for some two centuries, it takes many possible forms with varied effects. Some of these illustrate glomerular function by demonstrating

what happens when normal function is lost. Inflammation, swelling and subsequent damage interfere with the normal functions of the glomerulus. In the early stages, swelling of tissues in the glomeruli can cause a reduced glomerular filtration rate. In the later stages, damage can lead to serious loss of protein in the urine, which is normally protein-free.

Clinical Example (Continued)

The *reduced glomerular filtration rate* leads to scanty urine (oliguria) and an accumulation of extracellular fluid (oedema). The accumulated fluid leads to a puffy appearance and to circulatory overload with venous congestion in both the systemic and pulmonary circulations. In the systemic circulation this is manifested by venous engorgement, with the back pressure transmitted to the hepatic sinusoids causing enlargement of the liver. In the pulmonary circulation there is increased fluid in the lungs, leading to an uncomfortable awareness of breathing (dyspnoea). The heart is also enlarged.

When the acute stage has passed, some patients develop *loss of protein* as a result of damage to the glomerular membrane (nephrotic syndrome). Although protein is normally absent from the urine, a small amount is filtered at the glomeruli, and completely reabsorbed by cells in the proximal convoluted tubules. With damage to the glomerular membrane, protein, largely albumin, can be lost in large amounts, e.g. 10 g or more per day (*proteinuria*, or more precisely, *albuminuria*). This steady loss of protein eventually leads to a serious fall in the albumin level in the blood (*hypoalbuminaemia*).

The balance sheet of protein handling by the glomeruli in normal circumstances and in someone with severe albuminuria (20 g per day lost in the urine) illustrates the precision of normal renal retention of plasma albumin and the effect of a relatively small derangement of function. If we assume a glomerular filtrate of 125 ml/min, this equals 7.5 litres per hour or 180 litres per day. If each litre of plasma contains 45 g of albumin, then the plasma filtered per day originally contained some 8100 g of albumin. Since the retention of albumin within the glomerular capillaries is not 100% complete, some passes through the glomerular membrane

with the filtrate. Of some 45 g of albumin per litre, only about 0.2 g is filtered and this is completely reabsorbed by a mechanism which is nearly saturated by this amount. Thus about 36 g/day are filtered and reabsorbed, the tubular maximum for albumin being about 45 g/day. The balance sheet of renal protein handling in health and in a severe case of the nephrotic syndrome would then be approximately as shown in Table 8.2.1.

This albuminuria and consequent hypoalbuminaemia cause an appreciable drop in the plasma colloid osmotic pressure which is normally a major force retaining fluid in the capillaries throughout the body, opposing the outward hydrostatic pressure gradient. As a result, fluid leaks from the circulation into the interstitial spaces and results in oedema in the dependent parts of the body, usually the ankles, or over the sacrum in someone spending much of the time lying flat.

As with oedema due to raised capillary hydrostatic pressure in heart failure, a vicious circle of positive feedback tends to develop. Fluid loss from the circulation leads to a fall in circulating blood volume. The body responds to this by increasing aldosterone secretion which causes salt retention in the kidney (see p. 755).

Table 8.2.1 Renal protein handling in health and disease

	Normal	Nephrotic syndrome
Albumin in plasma to be filtered (g)	8000	8000
Albumin actually filtered (g)	36	65
Albumin reabsorbed (g)	36	45
Albumin lost in urine (g)	0	20

Clinical Example (Continued)

This retained salt is accompanied by water to maintain the normal osmolality. The retained sodium chloride does not enter the cells, so it and the associated water add to the volume of the extracellular fluid. This additional extracellular

fluid passes into the interstitial space and adds to the oedema. The vicious circle of inappropriate salt and water retention can be broken by the use of diuretics (see Clinical Example, p. 766) which increase the salt lost in the urine.

Renal blood flow

Measurement of renal blood flow

Renal blood flow can be measured directly by placing an electromagnetic or ultrasonic flow probe around the renal artery. Renal plasma flow (RPF) can be measured indirectly using the clearance technique (see above). Thus, if a substance is completely removed from the plasma passing through the kidney, leaving none in the plasma in the renal vein, then the clearance of that substance is equal to renal plasma flow. **Para-aminohippuric acid (PAH)** is a substance that approaches this ideal. PAH is not normally present in the blood, but can be infused intravenously to achieve a low stable plasma concentration. Almost all PAH is extracted in one passage through the kidney; some is filtered at the glomerulus and the remainder is secreted into the lumen by the proximal tubules (see Transport mechanisms, p. 734). However, remember that not all renal artery blood flow passes through vessels supplying the proximal tubule, some passes from the efferent arterioles into the vasa recta (see Ch. 8.1). This means that some PAH (less than 10% of the total) in the renal artery escapes excretion and appears in renal venous blood. It is possible to correct for this. However, usually the uncorrected value obtained from the clearance of PAH is taken as the **effective renal plasma flow (ERPF)**.

$$\text{ERPF} = \frac{U_{\text{PAH}} \times V}{P_{\text{PAH}}}$$

where U_{PAH} and P_{PAH} are urine and plasma concentration of PAH respectively, and V is urine flow in ml/min. P_{PAH} is usually measured in a sample taken from a limb vein where the concentration of PAH is equal to that in arteries supplying the limb and the kidney.

In a normal adult man, ERPF averages 630 ml/min. Assuming the extraction of PAH from arterial blood is 90%, then actual RPF could be estimated as:

$$\text{RPF} = \frac{\text{ERPF}}{0.9} = \frac{630}{0.9} = 700 \text{ ml/min.}$$

If the packed cell volume (PCV), the fraction of whole blood occupied by red blood cells, is 0.44, then the fraction occupied by plasma is:

$$1 - 0.44 = 0.56.$$

Therefore:

$$\text{Total renal blood flow (RBF)} = \frac{700}{0.56} = 1250 \text{ ml/min.}$$

Thus, the two kidneys, which represent about 0.5% of body weight, receive about 20% of the resting cardiac output.

Regulation of renal blood flow

Renal blood flow, like GFR (see above), shows autoregulation in response to changes in systemic arterial pressure (Fig. 8.2.2). Since blood flow and GFR are autoregulated simultaneously, it seems that the myogenic behaviour of the afferent arteriole must be more important than the myogenic behaviour of the efferent arteriole. For example, myogenic constriction of the afferent arteriole would reduce both renal blood flow and GFR, whereas myogenic constriction of the efferent arteriole would reduce renal blood flow, but increase GFR, by increasing capillary hydrostatic pressure.

The function of autoregulation of renal blood flow is that it tends to stabilize renal function. However, changes in renal blood flow and renal vascular resistance do occur in many circumstances in which renal blood perfusion is sacrificed to maintain systemic arterial blood pressure and to redistribute blood flow to other vital tissues.

Such changes are achieved mainly by the **sympathetic noradrenergic fibres**. Moderate increases in renal sympathetic activity in response to a change in body position from supine to standing, mild exercise or mild emotion, reduce renal blood flow and increase renal vascular resistance, but have no effect on GFR because there is balanced constriction of afferent and efferent arterioles. Larger increases in

renal sympathetic activity occurring in heavy exercise, strong emotion or severe haemorrhage, increase renal vascular resistance even more, but decrease both renal blood flow and GFR because the afferent arterioles are constricted more than the efferent arterioles.



Summary

Renal blood flow

- Renal plasma flow can be measured indirectly via the clearance method and by using a marker substance which is completely removed from plasma by one passage through the kidney. PAH is a suitable substance.
- Renal blood flow can be calculated from renal plasma flow and the fraction of whole blood that is occupied by plasma ($1 - \text{packed cell volume}$).
- Renal blood flow (like GFR) can show autoregulation over the mean arterial pressure range of 90–200 mmHg.
- Renal blood flow can be decreased by an increase in renal sympathetic activity.

Tubular function

8.3

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Introduction

Glomerular filtration rate (GFR) in the normal adult is relatively fixed, at about 120 ml/min. Urine production can vary from 0.5% of this during water deprivation to up to 10% during maximal diuresis, showing that water reabsorption is a major tubular function. Flexibility in the reabsorption of the components of the filtrate allows the kidney to rapidly adjust the body's fluid and salt balances.

Once a substance (X) has been filtered at the glomerulus into the tubule, the tubular epithelial cells progressively modify its concentration as the fluid flows through the nephron. They may remove some of it (**reabsorption**), or they may add to the tubular fluid (**secretion**). They may do both. Net reabsorption or secretion can be shown by measurement of clearance (see Ch. 8.2).

As indicated in Chapter 8.2, if the clearance of a substance is smaller than GFR, then there has been net reabsorption, and if it is greater than GFR, then there has been net secretion. This is the same as saying that the net amount of X that is transported by the tubule (T_x) is equal to the filtered load of X (which is the product of GFR and the plasma concentration of X (P_x)) minus the amount of X that appears in the urine (which is the product of urine concentration of X (U_x) and urine flow rate (V)), i.e.:

$$T_x = (P_x \times \text{GFR}) - (U_x \times V).$$

Table 8.3.1 Amounts of various substances filtered by the glomeruli and excreted in the urine by a healthy adult on an average diet

	Amount filtered (mmol/24 h)	Amount excreted (mmol/24 h)
Sodium	2550	150
Potassium	700	100
Calcium	550	10
Bicarbonate	4500	2
Chloride	18500	180
Glucose	1000	0.5
Urea	900	450
Water	180 litre/24 h	1.5 litre/24 h

If T_x is positive, then reabsorption exceeds secretion. If T_x is negative, then secretion exceeds reabsorption.

Table 8.3.1 shows filtered loads and excretion rates per day for a normal adult on an average diet. It is clear that the filtered loads are very large, that the reabsorption of some physiologically useful substances like water and sodium is very efficient and that reabsorption of waste products like urea is relatively incomplete. Some substances, like potassium, are both reabsorbed and secreted.

Transport mechanisms

Substances can be reabsorbed or secreted by passing either:

- across the tubular epithelial cells (**transcellular** route), or
- between the cells via the tight junctions and lateral intercellular spaces (**paracellular** route) (see Fig. 8.1.5, p. 720).

Substances move passively between the interstitial space and the blood in the peritubular capillaries. Most substances that are secreted come from the plasma of the peritubular capillaries. Ammonia is an important exception; it is synthesized and secreted by the tubular cells (see Ch. 8.7).

Transcellular transport usually involves active transport across either the luminal or basolateral membrane of the tubular epithelial

cell. Transport across the other membrane (i.e. the luminal membrane if active transport is across the basolateral membrane, and vice versa) and paracellular transport occur by diffusion. Transport from the interstitial space into the peritubular capillaries occurs by a combination of bulk flow, when water and solutes move together, and diffusion. The small amount of albumin and the small proteins that filter into the tubule at the glomerulus, including unbound hormones like angiotensin and insulin, are reabsorbed, mostly in the proximal tubule, by pinocytosis.

Active transport is transport of a substance up an electrochemical gradient. This transport requires energy and is often directly coupled to, and dependent on, ATP-hydrolysis. This is called **primary active transport** to distinguish it from **secondary active transport**, when the movement of a substance by primary active transport creates a gradient across a cell membrane that drives the movement of a second substance. If, during the linked movement, the second substance moves in the same direction as the first, the process is termed **cotransport** or a **symport**. If they move in opposite directions, the process is termed **countertransport** or an **antiport**.

Sodium is an example of a substance that is reabsorbed by primary active transport in the cells of walls of the proximal and distal tubules and collecting ducts. Other substances, including glucose, phosphate and amino acids, are cotransported with sodium into the cells.



Summary

Transport mechanisms

- Substances can be reabsorbed or secreted across tubular epithelial cells (transcellular) or between the cells via tight junctions and lateral intercellular spaces (paracellular).
- Transcellular transport usually involves active transport across either the luminal or basolateral membrane of the epithelial cells. Transport across the other membrane is by diffusion.
- Primary active transport is movement of a substance up an electrochemical gradient which is directly dependent on ATP hydrolysis.
- Primary active transport can create a gradient for the movement of a second substance by secondary active transport; this can be cotransport (symport) or countertransport (antiport).
- Most substances that are actively secreted come from the plasma of the peritubular capillaries. Ammonia is an exception; it is synthesized by the tubular cells.
- Substances move passively between the interstitial space and peritubular capillaries by bulk flow (of water and solutes), which is dependent on osmotic and hydrostatic pressure differences, and by diffusion (of solutes).

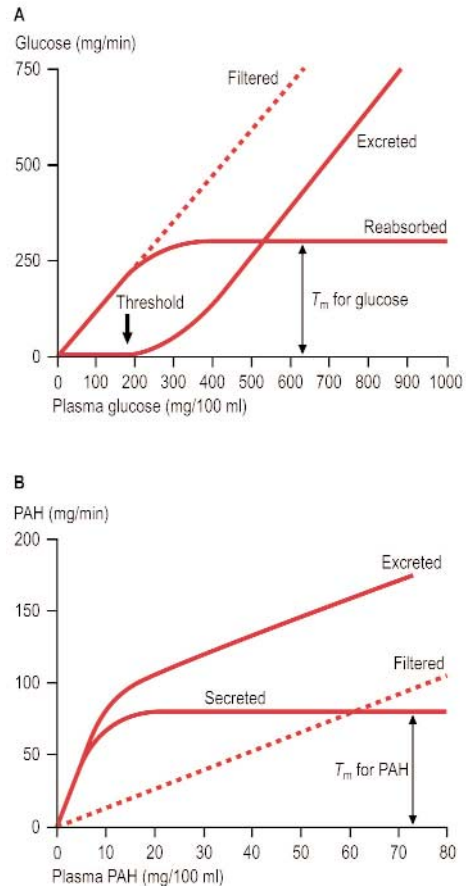


Fig. 8.3.1 Tubular transport maxima (T_m). Relationships between plasma concentration and excretion (urine concentration) for (A) glucose (filtered and reabsorbed) and (B) para-aminohippuric acid (PAH) (filtered and secreted), showing what happens as the T_m is exceeded in each case. Glucose does not appear in the urine until its *absorptive* T_m is exceeded. PAH is secreted at a rate which increases faster than its rate of filtration until its *secreting* mechanism is saturated. The gradual appearance of glucose is because there is a variety or 'splay' of transport maxima within the population of tubules.

Tubular transport maximum

All active transport systems have a **transport maximum** (T_m), i.e. a limit for the amount of the substance they can transport per unit time. This is because the membrane proteins responsible for transport become saturated. Glucose is normally entirely reabsorbed from the tubular fluid

so that none appears in the urine (Table 8.3.1). When the concentration of glucose in plasma is increased, glucose is presented to the tubule at increasing rates. Glucose is absent from urine until the transport process is saturated, i.e. the T_m for glucose reabsorption is reached (Fig. 8.3.1A). From then on glucose appears in urine at a rate which increases linearly with the filtered load.

The **renal threshold** for glucose is the plasma concentration at which glucose first appears in the urine. Note that the rate at which glucose appears in the urine increases slowly at first, while the absorption curve flattens off gradually. This deviation from the ideal curve is called **splay**. This reflects the fact that different tubules have different T_m values.

Active secretion shows similar characteristics to active reabsorption. Using PAH as an example, when the plasma concentration of


PAH increases, there is a linear increase in the filtered load of PAH, but there is a steeper increase in the rate of excretion of PAH, because it is secreted into the tubule until the T_m for PAH secretion is reached (Fig. 8.3.1B). From then on, PAH excretion increases at the same rate as the filtered load.

The proximal tubule

In the proximal tubule, about 60–70% of the filtered load of sodium, water and urea is reabsorbed. In addition, there is almost complete reabsorption of chloride, bicarbonate, phosphate, potassium, glucose, amino acids and protein. Hydrogen ions, ammonia and organic acids are secreted into the tubule.

Sodium reabsorption

Sodium reabsorption (Fig. 8.3.2) in the proximal tubule is important because it conserves total body sodium and because the reabsorption of many other substances (chloride, water, glucose, amino acids) depend upon it. The proximal tubular cells have an **Na^+/K^+ ATPase pump** on the basolateral membrane which pumps sodium out of the cell into the interstitial fluid.



Summary

Tubular transport maximum (T_m)

- All active transport systems have a T_m – an upper limit for the amount of the substance they can transport per unit time.
- A substance (e.g. glucose) that is actively reabsorbed appears in urine when the T_m is exceeded.
- The plasma concentration at which this occurs is called the renal threshold.

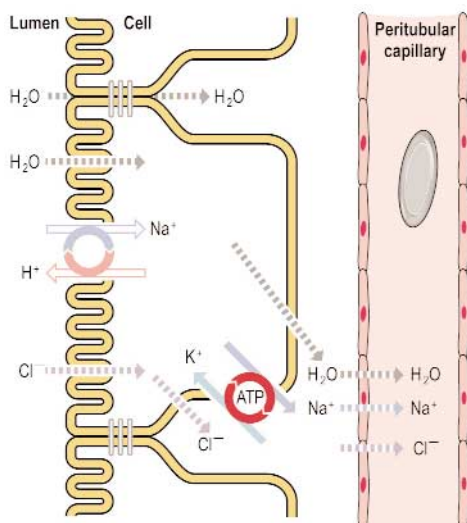


Fig. 8.3.2 Sodium, chloride and water reabsorption in the proximal tubule. This figure shows only an outline of mechanisms operating in the proximal tubule; these vary from the early to late tubule. The key element throughout is the ATP-driven Na^+/K^+ exchange mechanism on the basolateral membrane.

This keeps the intracellular concentration of sodium low relative to the lumen. The cell interior also has a membrane potential of -70 mV relative to the lumen. Thus, sodium ions move passively from the lumen into the cell, down concentration and electrical gradients and are actively pumped out of the cell, in exchange for potassium ions at the basolateral membrane (Fig. 8.3.2). Much of the sodium is pumped into the lateral spaces between the epithelial cells. Three Na^+ leave for every two K^+ that enter the cell. These K^+ can leave the cells passively via K^+ channels that are mainly on the basolateral, rather than the luminal membrane. Thus, the intracellular concentration of K^+ , which is high, as in the majority of cells in the body, is not changed by the Na^+/K^+ pump.

Chloride reabsorption

In the early part of the proximal tubule, sodium entry into the cells is accompanied by H^+ secretion (see Fig. 8.3.4) which maintains electrical neutrality within the cell and leads to bicarbonate reabsorption as CO_2 (see Fig. 8.3.4). Sodium reabsorption is, most importantly, accompanied by water (see below). This results in chloride concentration in the tubular lumen increasing along the length of the proximal tubule. In the final two-thirds of the proximal tubule the chloride gradient generated is so large that chloride moves passively into the cell and thence into the interstitial fluid (Fig. 8.3.2). This movement of chloride makes the interstitial fluid negative relative to the lumen and so, in turn, some sodium moves passively into the interstitial fluid from the lumen.

Water reabsorption

The movement of sodium, bicarbonate and chloride from the cells into the interstitial space, particularly the **lateral spaces**, reduces the osmolality of the tubular fluid and increases the osmolality in the lateral spaces. The lateral spaces are particularly affected because they are

long, tortuous and narrow and have restricted access to the rest of the interstitial space. This causes net osmotic flow of water from the lumen into the lateral space by transcellular and paracellular routes (Fig. 8.3.2).

Reabsorption into peritubular capillaries

The movement of water into the lateral spaces raises the interstitial fluid hydrostatic pressure and thus increases the hydrostatic pressure gradient both between the lateral space and the tubular lumen and between the lateral space and the peritubular capillaries. Since the tight junctions between the epithelial cells are very permeable to water and salts, some of the water and solutes leak back into the lumen. However, much of the water and solutes are driven into the peritubular capillaries by both the osmotic and hydrostatic pressure gradients. Thus, because the filtrate at the glomerulus is essentially protein-free, the fluid that remains in the glomerular capillaries and which then circulates to the peritubular capillaries has a high protein concentration and therefore a high oncotic pressure. Water and solute reabsorption in the peritubular capillaries is also facilitated by the low capillary hydrostatic pressure resulting from the resistance of the efferent arterioles.

The volume of water that is reabsorbed is dependent partly on the **filtration fraction**, i.e. the ratio of GFR to renal plasma flow. For example, if the filtration fraction increases, then more water and solutes will be filtered at the glomerulus leaving a higher concentration of protein in the glomerular capillary. This means that the oncotic pressure in the peritubular capillaries is also raised and, consequently, reabsorption from the lateral spaces is increased. The opposite happens if the filtration fraction decreases.

In this way proximal tubular reabsorption matches GFR very closely over a wide range of GFR values. This is known as **glomerular-tubular balance**. Since an increase in GFR leads to an increase in the amount of sodium filtered, glomerular tubular balance means that there is

an automatic, compensatory increase in sodium reabsorption. Thus, sodium is conserved. In fact, the percentage of filtrate and therefore sodium that is reabsorbed in the proximal tubule, is fixed over a wide range of GFR.

Glucose reabsorption

At normal levels of plasma glucose, all glucose in the filtrate is reabsorbed in the proximal tubule. It is **cotransported** with sodium at the luminal membrane, when sodium moves down its electrochemical gradient using the sodium gradient as a source of energy. Glucose then diffuses from the cell into the interstitial fluid and thence to the peritubular capillaries (Fig. 8.3.3).

The normal plasma concentration of glucose is between 0.6 and 1 mg/ml (3.3–5.5 mmol/litre). So, if we take 0.8 mg/ml as an example and assume GFR is 125 ml/min then glucose is filtered at 100 mg/min. The transport maximum for glucose is about 375 mg/min in men. (It is lower, 350 mg/min, in women and even

lower in pregnancy.) Thus, the renal threshold for glucose (the plasma concentration at which glucose first appears in urine) is about 375 mg/min divided by 125 ml/min (GFR), i.e. 0.3 mg/ml for men. In fact, the renal threshold is about 0.2 mg/ml (11 mmol/l). The difference is accounted for by the splay of individual transport maxima (see above). Glucose appears in the urine (glycosuria) in diabetes mellitus when plasma glucose concentration is characteristically high.

Bicarbonate reabsorption

In the proximal tubule, hydrogen ions that enter the lumen in exchange for sodium or are secreted by H^+ ATPase (see below), combine with the bicarbonate ions that were filtered at the glomerulus and form H_2CO_3 (Fig. 8.3.4). This leads to the formation of H_2O and CO_2 , so raising the luminal P_{CO_2} . This reaction is catalysed by **carbonic anhydrase** present in the luminal brush border. The CO_2 diffuses into the cell and, by the reverse reaction, forms H^+ and HCO_3^- . These hydrogen ions replace those that entered the lumen. HCO_3^- then diffuses across the basolateral cell membrane, in association with Na^+ , into the interstitial space, to be reabsorbed into the peritubular capillaries.

The normal plasma concentration of bicarbonate is about 25 mmol/litre and, as it is freely filtered at the glomerulus, the same concentration is present in the filtrate. Although there is no active transport of bicarbonate, the processes involved in reabsorption behave as if there were a T_m for bicarbonate, with a value very close to the amount filtered at normal GFR and normal plasma concentration. Not surprisingly, the T_m can be varied by changes in H^+ secretion and Na^+ reabsorption. However, the close correspondence of the T_m for bicarbonate to the normal filtered load means that if plasma bicarbonate concentration rises, then T_m tends to be exceeded and the excess excreted. This is considered further in the section on acid–base balance (Ch. 8.7).

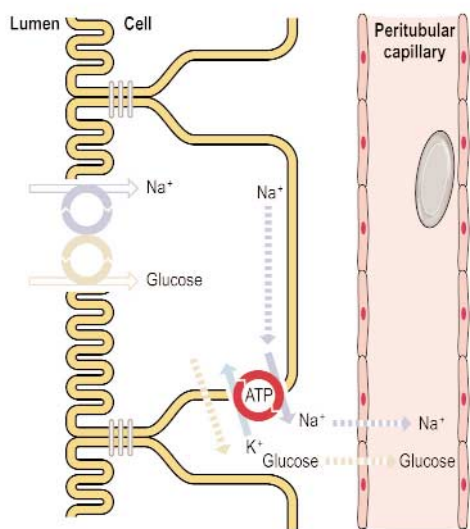


Fig. 8.3.3 Glucose reabsorption. Glucose, and many other metabolically useful substances, are reabsorbed by 'cotransport' with sodium. The movement of sodium down its concentration gradient into the cell powers the mechanism that absorbs glucose.

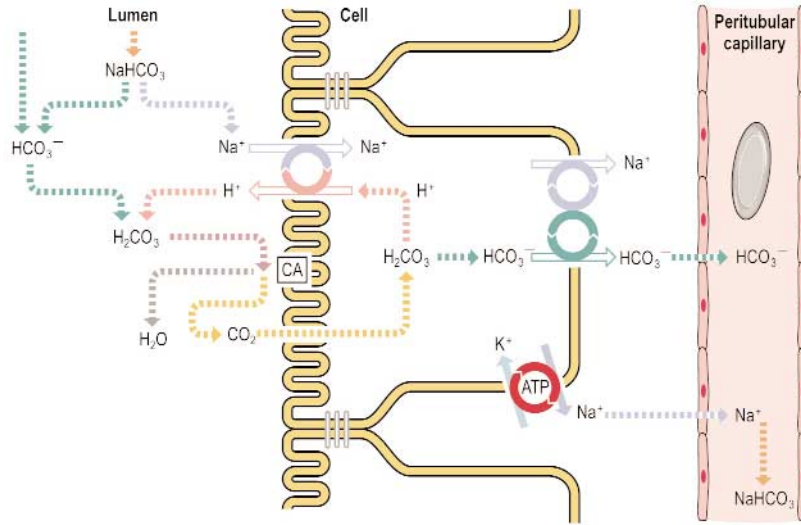


Fig. 8.3.4 Reabsorption of bicarbonate. Carbonic anhydrase (CA) on the brush border of tubular cells accelerates the equilibrium between carbon dioxide, water and carbonic acid. Carbonic acid within the cells dissociates to form bicarbonate which is largely removed via a symport with sodium on the basolateral margins of the cells.

Amino acids

Amino acids are freely filtered at the glomerulus and so occur in the filtrate at the same concentration as in plasma, approximately 3 mmol/litre. They are reabsorbed by **cotransport** with sodium at the luminal membrane, using the sodium gradient as the source of energy. Several carrier systems are involved, each with its own T_m . There is one each for the acidic (such as glutamic and aspartic acid), basic (such as cysteine, ornithine, arginine and lysine), and neutral amino acids, one for imino acids (e.g. proline) and a separate one for glycine.

Phosphate

Phosphate occurs in plasma at a concentration of 1 mmol/litre, as a breakdown product of protein metabolism. It is freely filtered at the glomerulus and is **cotransported** with sodium at the luminal border of the proximal tubules. The T_m for its reabsorption is very close to the

normal filtered load. Thus, any increase in plasma phosphate concentration can automatically lead to an increase in phosphate excretion. The rate of phosphate reabsorption is regulated hormonally; it is decreased by **parathyroid hormone** and increased by **calcitriol**, the active form of vitamin D.

Sulphate

Sulphate is also a breakdown product of protein metabolism. Like phosphate, it is reabsorbed by **cotransport** with sodium. The T_m for sulphate is normally exceeded, so that sulphate appears in the urine and the plasma concentration is held at 1–1.5 mmol/litre.

Urea

Urea is a product of protein metabolism. It is present in plasma at a concentration of 2.5–7.5 mmol/litre. It is freely filtered and

about 50% is reabsorbed by the end of the proximal tubule. This occurs because reabsorption of water and ions increases urea concentration in the tubule lumen. Thus, urea **diffuses** out of the tubule down its concentration gradient. The overall movement of these solutes and water results in the concentration of urea in the fluid that leaves the proximal tubule being approximately the same as in plasma.

Potassium

The proximal tubule reabsorbs about 80% of filtered potassium, but the mechanisms responsible are not fully understood. Potassium is freely filtered at the glomerulus and so is present in the filtrate at a concentration equal to that in plasma (4–5 mmol/litre). It appears to be reabsorbed **passively** into the cells of the proximal tubule. The reabsorption of sodium and water into the lateral spaces also tends to cause an increase in potassium concentration in the lumen so that some potassium probably diffuses passively through paracellular pathways. In addition, it seems that there is an active transport mechanism for potassium at the luminal border.

Calcium

Plasma normally has a calcium concentration of about 2.5 mmol/litre. 40–50% of plasma calcium is **bound** to protein and cannot be filtered by the glomerulus. The remainder is ionized Ca^{2+} , and is freely filtered by the glomerulus. Ca^{2+} is reabsorbed from the proximal tubule in parallel with sodium and water so that its concentration in the tubule stays more or less constant. Ca^{2+} enters tubule cells passively, down concentration and electrical gradients, but probably leaves the cell by a $\text{Ca}^{2+}/\text{Na}^{+}$ **countertransport** mechanism or via a Ca^{2+} ATPase mechanism.

Hydrogen

Hydrogen ions formed in the proximal tubule cells from the dissociation of H_2CO_3 (see Fig. 8.3.4) are secreted into the lumen. Most of this H^{+} secretion takes place late in the proximal tubule and is associated with Na^{+} reabsorption via a **countertransport** process, but some may be mediated by a H^{+} ATPase.

Organic cations and anions

The proximal tubule secretes organic cations and anions, some of which are end products of metabolism that circulate in plasma, e.g. bile salts, oxalate, urate, prostaglandins, creatinine, adrenaline, noradrenaline. The proximal tubule also secretes exogenous organic compounds, e.g. PAH which is used to determine renal plasma flow (see above) and drugs such as penicillin, aspirin, morphine and quinine. Because many of these substances are bound to plasma proteins, they are not freely filtered at the glomerulus. Therefore, secretion into the lumen provides an extremely important means of eliminating these potentially toxic substances from the body.

Taking PAH as an example, at plasma concentrations of up to 0.10–0.12 mg/ml the PAH-secreting process can completely remove PAH from the tubular capillaries, but at plasma concentrations above this level, significant concentrations of PAH begin to appear in the renal vein. In other words, there is a T_m for PAH, of about 80 mg/min. Therefore, if PAH is to be used to measure renal plasma flow (see Measurement of renal blood flow, p. 730), the plasma concentration of PAH must be below 0.12 mg/ml so that the T_m is not exceeded. There is competition for the secreting transport process between all organic anions so that at raised plasma levels, PAH can compete with, for example, secretion of penicillin. The organic cations use a different secreting process, but also compete with one another.



Summary

The proximal tubule

- 60–70% of filtered Na^+ is reabsorbed by primary active transport across the basolateral membrane into the lateral intercellular spaces.
 - The reabsorption of Cl^- is dependent on Na^+ transport, into the lateral intercellular spaces.
 - Transport of Na^+ and Cl^- into the lateral intercellular spaces causes an osmotic flow of water from the lumen into the same space.
 - Water and solutes are driven from the lateral intercellular spaces primarily into the peritubular capillaries by osmotic and hydrostatic pressure gradients.
- Some water and solutes may leak back into the tubular lumen.
- Glucose is cotransported with Na^+ up to a T_m of 350–375 mg/min, the renal threshold being ~2 mg/ml (11 mmol/litre).
 - H^+ is countertransported (secreted) with Na^+ into the lumen and combines with filtered HCO_3^- to form H_2CO_3 . This leads by a sequence of reactions to reabsorption of HCO_3^- .
 - Amino acids, urea, phosphate, calcium and sulphate ions are cotransported with Na^+ . K^+ reabsorption also seems to be dependent on Na^+ transport.

Loop of Henle, distal tubule and collecting duct

8.4

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Henle 745

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Introduction

The part of the nephron after the proximal tubule can be divided into the thin descending and ascending limbs of the loop of Henle, the thick ascending limb, the early and late parts of the distal tubule and the collecting duct (Fig. 8.1.2, p. 717). The functional characteristics of these sections are very different. However, it is convenient to consider them together since they have a common role: concentrating the urine. Briefly, the descending limb has a high water permeability and a low solute permeability, which means water moves across the descending limb into the interstitium until osmotic equilibrium is reached between the tubular fluid and interstitial fluid. By contrast, the thin and thick ascending limbs have a low permeability to water and the thick ascending limb actively reabsorbs sodium from the tubular fluid. Since the thick ascending limb has a large transport capacity, it plays a major role in diluting the tubular fluid and is often known as the diluting segment of the kidney.

The distal tubule and collecting duct also reabsorb sodium. In the absence of antidiuretic hormone (ADH), they are impermeable to water. However, in the presence of ADH, the later part of the distal tubule and the collecting duct become very permeable to water. This allows water to move out until the tubular fluid and interstitial fluid reach osmotic equilibrium.

Since urea also plays an important role in the concentrating process, as is discussed below, it is important to consider the urea permeability of individual parts of the nephron. The highest urea permeability is found in the inner, medullary part of the collecting duct and can be increased by ADH. The thick ascending limb, distal tubule and cortical parts of the collecting duct have very low, or no, permeability to urea, but the thin descending and ascending limbs of the loop of Henle are both permeable to urea. Urea moves passively down its concentration gradient and recycles from the medullary collecting duct to the medullary interstitium, where it raises the urea concentration of the interstitial fluid, and from there it passes to the thin limbs of the loop of Henle.

Finally, it should be noted that the late distal tubule and collecting duct are important in secreting K^+ and H^+ and in reabsorbing K^+ and HCO_3^- .

Transport processes

The active reabsorption of Na^+ that occurs in the thick ascending limb, the distal tubule and collecting duct is dependent on the **Na^+/K^+ ATPase pump** in the basolateral membrane, just as it is in the proximal tubule. This maintains a low concentration of Na^+ in the cell, so favouring movement of Na^+ into the cell from the tubular fluid. In the thick ascending limb, this mainly occurs via an $Na^+/Cl^-/K^+$ symporter, which couples the movement of these three ions in the ratios 1 : 2 : 1. In addition, some Na^+ also moves in via an Na^+/H^+ antiporter, thereby leading to **H^+ secretion** (Fig. 8.4.1) and HCO_3^- reabsorption (as shown in Fig. 8.3.4, p. 739). The Cl^- , HCO_3^- and some of the K^+ leave the cell via the basolateral membrane, but much of the K^+ that enters the cell leaves again via a K^+ channel in the luminal membrane. This K^+ is probably responsible for generating a positive charge in the lumen of the thick ascending limb which drives the movement of Na^+ , K^+ , Ca^{2+} and Mg^{2+} out of the tubule via the paracellular route.

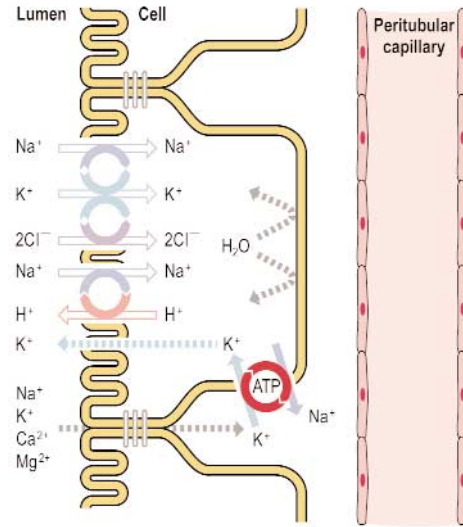


Fig. 8.4.1 Transport mechanisms in the thick ascending tubule. The positive charge within the tubule is probably due to the return of K^+ to the lumen via a K^+ channel. This charge is largely responsible for the paracellular reabsorption of cations, which accounts for 50% of total reabsorption in the thick ascending tubule.

In the early distal tubule, Na^+ moves into the cell via an Na^+/Cl^- symporter and the Cl^- leaves the cell again via the basolateral membrane.

In both the thick ascending limb and early distal tubule, water cannot follow the movement of solute from the lumen to the interstitium, so the luminal fluid is diluted.

In the collecting duct there are two types of cells:

- the **principal cells**, which actively reabsorb Na^+ and secrete K^+ and, in the presence of ADH, also absorb water
- the **intercalated cells** whose important function is to secrete H^+ (and reabsorb HCO_3^-).

In the principal cells, the Na^+/K^+ ATPase on the basolateral membrane is responsible for the reabsorption of Na^+ and for producing a high concentration of K^+ in the cell, which then causes K^+ to diffuse out of the cell, through K^+ channels, into the luminal fluid where the K^+

concentration is low (Fig. 8.5.1, p. 755). The fact that the permeability of the luminal membrane to K^+ is higher than that of the basolateral membrane favours the movement of K^+ into the lumen. Both the reabsorption of Na^+ and the secretion of K^+ in this segment of the tubule are affected by **aldosterone** (see Ch. 8.5).

In the presence of **ADH**, water channels are incorporated into the luminal membrane of the principal cells (see Ch. 8.5). The basolateral membrane is freely permeable to water. Therefore in the presence of ADH, water passes through the cell, from the lumen to the interstitial fluid down the osmotic gradient caused by the high osmotic concentration of the interstitial fluid.

In the intercalated cells, H^+ is generated from the dissociation of H_2CO_3 and, as in the proximal tubule, the formation of H_2CO_3 is facilitated by carbonic anhydrase. However, in contrast to the proximal tubule, it is thought that all of the H^+ leaves the intercalated cells via an H^+ ATPase

pump in the luminal membrane, rather than via countertransport with Na^+ . The HCO_3^- that is formed from the dissociation of H_2CO_3 diffuses out of the intercalated cells across the basolateral membrane. These cells also reabsorb K^+ from the tubule, but the mechanism is not known.

In the thick part of the ascending limb of the loop of Henle and in the distal tubule there is also reabsorption of Ca^{2+} and these are the major sites at which much excretion of Ca^{2+} is regulated. Entry of Ca^{2+} into the cells is passive, as in the proximal tubule. Exit from the cells at the basolateral membrane is by an Na^+/Ca^{2+} countertransport mechanism and, more importantly, by an active Ca^{2+} ATPase. The regulation of Ca^{2+} absorption is dealt with in Chapter 8.5.

Countercurrent multiplication by the loop of Henle

The kidney can excrete urine that is either hypo-osmotic or hyperosmotic relative to plasma. This requires that water be separated from solute. Hypo-osmotic urine can be formed simply by reabsorbing solute from the tubule without allowing water to follow. The formation of hyperosmotic urine is more difficult to understand because it means that water must be removed from the tubular fluid leaving solute behind and because water can only move **passively** from a region of low osmotic pressure to one of high osmotic pressure. Thus, in order to remove water from the tubular fluid, the kidney must create an area of high osmotic pressure *outside* of the nephron. This is done by the loop of Henle.

The loop of Henle consists of two parallel limbs arranged so that tubular fluid flows into the medulla in the descending limb and out of the medulla in the ascending limb, i.e. the flow in the two limbs is in opposite directions, or **countercurrent**. The fluid that enters the descending limb from the proximal tubule has an osmotic concentration approximately equal to that of plasma (300 mOsm/kg H_2O for numerical simplicity; Fig. 8.4.2). As indicated



Summary

Important features of the concentrating process

- The descending limb of the loop of Henle has a high permeability to water and a low permeability to solutes.
- The ascending limb of the loop of Henle has a low permeability to water, but actively reabsorbs Na^+ .
- The distal tubule and collecting duct also actively reabsorb Na^+ . In the presence of ADH they are permeable to water.
- The descending and thin ascending limbs of the loop of Henle are permeable to urea. The thick ascending limb and cortical part of the collecting duct have low permeability to urea. The medullary part of the collecting duct has a high permeability to urea that can be increased by ADH.

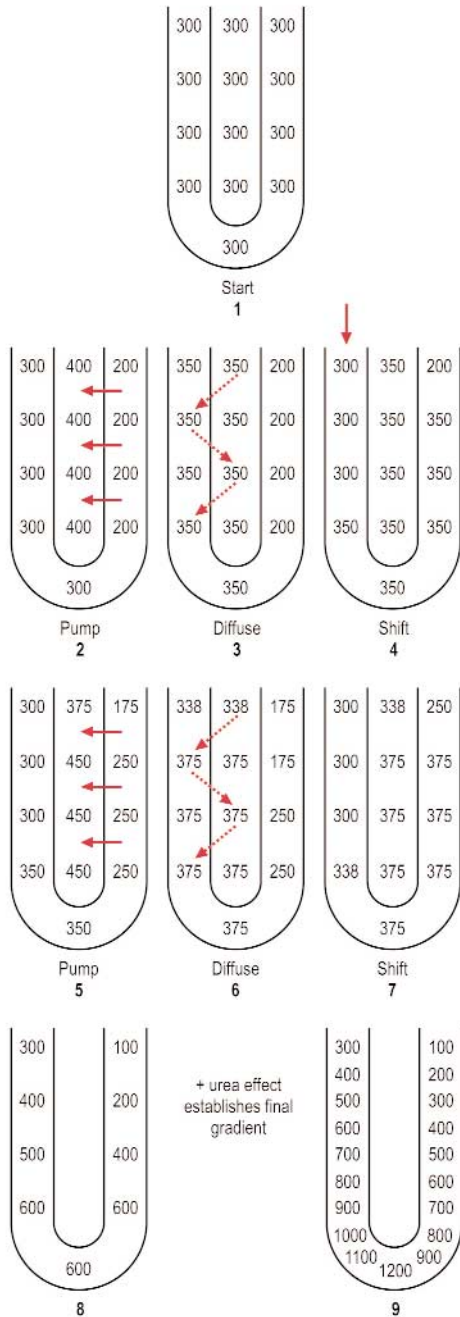


Fig. 8.4.2 Countercurrent multiplication. In steps 1–8 the effect of Na⁺ pumping is shown. The final osmolality can be as high as 1200–1400 mOsm/kg owing to the additional effects of urea, which is shown in the step from 8 to 9. Note that although the difference in osmolality between the incoming fluid and the tip is more than 1000 mOsm/kg, the difference between the two limbs is never more than 200.

above, the ascending limb is **impermeable** to water but reabsorbs solutes, principally NaCl, from the tubular fluid. Thus, the tubular fluid becomes more dilute as it passes up the ascending limb, while solute accumulates in the interstitial fluid around the loop, raising its osmolality. On the other hand, the descending limb is freely **permeable** to water. Thus, the hyperosmotic interstitial fluid causes water to move out of the descending limb into the interstitium. This ‘single effect’ of the countercurrent system creates an osmotic gradient between the tubular fluid in the ascending limb and descending limb, limited to 200 mOsm/kg H₂O because this is the maximum gradient that the cells of the ascending limb can sustain across their walls.

This ‘single effect’ is multiplied – the **countercurrent multiplication process** – because new fluid is continually entering the descending limb, pushing fluid from the descending limb around the loop to the ascending limb. This means that hyperosmotic fluid enters the bottom of the ascending limb, and hypo-osmotic fluid is pushed out of the ascending limb. Solute is again removed from the ascending limb and water again moves osmotically from the descending limb into the interstitial space until there is a gradient of 200 mOsm/kg H₂O between the two limbs at each point along their lengths. As seen in Figure 8.4.2, this has the effect of increasing the osmotic concentration of the interstitial fluid and luminal fluid at the tip of the loop and reducing the osmolality of the fluid that leaves the ascending limb, so creating an osmotic gradient from the junction of the medulla and cortex to the tip of the loop.

This countercurrent multiplication process continues with the help of **urea** (see below) until the osmolality of the tubular and interstitial fluid at the tip is 1200–1400 mOsm/kg H₂O which is four to five times that of plasma. This is very energy efficient since this considerable longitudinal osmotic gradient is achieved by using only the energy required to create an osmotic gradient between the two limbs of

200 mOsm/kg H₂O. About 15% of nephrons have long loops of Henle that dip down into the medulla. The osmotic gradient is produced by this 15%. Nephrons with short loops do not contribute significantly to the gradient, but their collecting ducts do pass through the medulla and therefore use the gradient to concentrate urine (see below).

Fluid that leaves the ascending limb of the loop of Henle is **hypo-osmotic** with respect to plasma and has an osmolality of only 100 mOsm/kg H₂O (Fig. 8.4.2). The distal tubule and cortical part of the collecting duct are impermeable to water except in the presence of ADH, which increases their water permeability (see Ch. 8.5). In the presence of ADH, water begins to diffuse out of the tubule into the interstitium where the osmotic concentration is higher; this begins the process of urine concentration. The maximum osmolality that the tubular fluid can reach by the end of the cortical collecting duct is 300 mOsm/kg H₂O. This is the same as the osmolality of the plasma and interstitium at this point and the same as the osmolality of the fluid that entered the descending limb of the loop of Henle, but the composition is very different. The fluid entering the medullary collecting duct contains much less NaCl, because NaCl has been actively reabsorbed, and it contains a higher concentration of urea, because urea has been added to the tubular fluid as it passes through the loop of Henle (see below).

In the medullary part of the collecting duct, water continues to diffuse out of the tubule into the interstitium along an osmotic gradient, particularly if ADH is present to increase the collecting duct's water permeability. This increases the osmotic concentration of the tubular fluid. The maximum osmotic concentration that can be reached in the tubule in the presence of ADH is therefore ~1200 mOsm/kg H₂O, equal to the osmolality of the interstitium at the tip of the loop of Henle. This process of concentrating the urine is facilitated by the fact that ADH also increases the permeability of the medullary

collecting duct to urea. Urea makes a major contribution to the total osmolality of the interstitium (see below).

In the absence of ADH, urine osmolality may be less than 100 mOsm/kg H₂O because solute is still reabsorbed from the distal tubule and collecting duct, but water cannot follow.

The role of urea

Although the countercurrent multiplication process is very important in establishing an osmotic gradient from the cortex to the tip of the loop of Henle (by actively transporting NaCl at the tip of the loop of Henle), NaCl only accounts for about *half* (600 mOsm/kg H₂O) of the total osmolality of the interstitial fluid. The remaining 600 mOsm/kg H₂O is due to urea.

Urea is freely filtered at the glomerulus; 50% of it is reabsorbed as the fluid passes through the proximal tubule. Since more than 50% of filtered water is reabsorbed in the proximal tubule, the concentration of urea in the fluid that enters the descending limb of the loop of Henle is slightly greater than in plasma. The loop of Henle and the cortical part of the collecting duct have relatively low permeability to urea. However, the medullary part of the collecting duct has a high permeability to urea, which can be further increased by ADH (see above). Thus, most of the urea remains trapped in the tubule until it reaches the medullary collecting duct.

By then, reabsorption of water has concentrated urea in the tubule. Urea diffuses out of the collecting duct into the interstitium, down its concentration gradient, so adding to the osmolality of the interstitium (Fig. 8.4.3). Urea tends to re-enter the loop of Henle. Thus, there is some **recycling of urea**, from the medullary collecting duct to the loop of Henle and through the tubule to the collecting duct. Since the permeability of the loop of Henle to urea is relatively low, the urea in the interstitial fluid around the loop acts as a very effective osmotic agent, playing a major role, with sodium

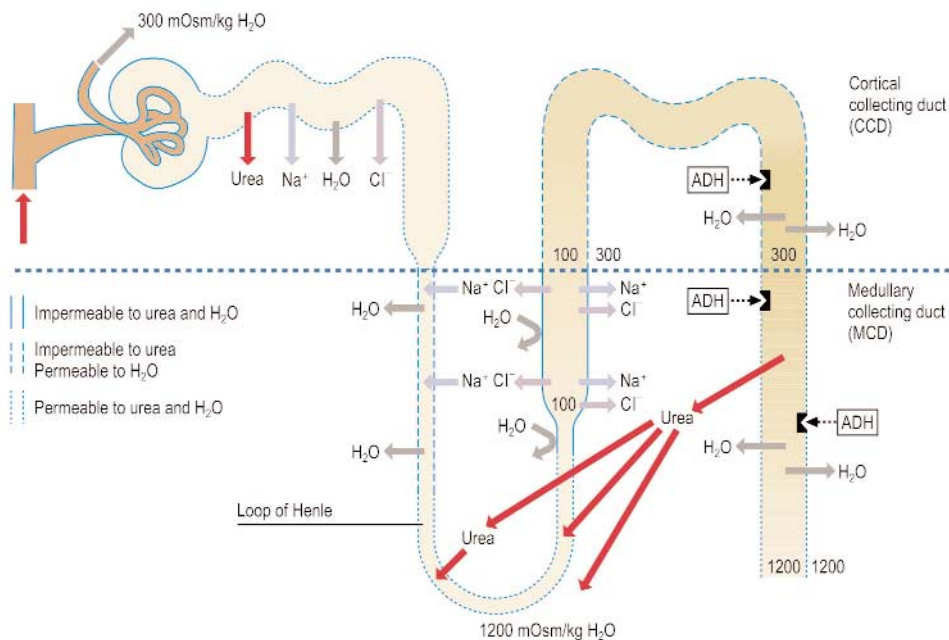


Fig. 8.4.3 Role of urea in concentration of urine. Because the loop of Henle has a relatively low permeability to urea, urea remains trapped in the interstitium of the medulla where it exerts about half of the kidney's concentrating effect on the tubular fluid.



Summary

Countercurrent multiplication; urea

- Fluid enters the loop of Henle at an osmotic concentration of ~ 300 mOsm/kg H_2O .
- At each level of the loop of Henle, the ascending limb actively reabsorbs solutes, mainly NaCl, from the tubular fluid into the interstitial fluid. Water cannot follow because the ascending limb is impermeable to water.
- The hyperosmotic solution in the interstitial fluid causes water to move from the descending limb to the interstitium.
- This process creates an osmolality gradient of 200 mOsm/kg H_2O between the ascending and descending limbs.
- The fluid in the ascending limb flows in the opposite direction (countercurrent) to that in the descending limb.
- Therefore the osmotic difference at a single level of the loop of Henle is multiplied (the countercurrent multiplication process) many times over as new fluid continually enters the descending limb.
- Urea that diffuses out of the collecting duct into the interstitium adds to the osmolality of the interstitium around the loop of Henle.
- The final outcome is that the osmotic concentration of the interstitium at the tip of the loop of Henle is 1200–1400 mOsm/kg H_2O . The fluid leaving the ascending limb has an osmolality of ~ 100 mOsm/kg H_2O .

chloride, in dragging water out of the descending limb of the loop of Henle along an osmotic gradient (see above).

ADH increases water permeability of the cortical and medullary collecting ducts and urea permeability of the medullary collecting duct.

The importance of urea in concentrating the urine is illustrated by the fact that people who are chronically malnourished and in whom there is a low rate of protein catabolism and therefore a low concentration of urea in plasma, do not concentrate urine as well as normal individuals.

The vasa recta

The vasa recta supply blood to the medulla. They are capillary loops in parallel with the loop of Henle. The fact that they are arranged in loops allows them to remove the water that is reabsorbed from the tubules without dissipating the longitudinal osmotic gradient from cortex to medulla that is built up by the loop of Henle. They act as **countercurrent exchangers**. Capillaries are freely permeable to solute and water and equilibrate with the surrounding interstitial fluid. Therefore, plasma flowing down the descending limb of the vasa recta, will be coming from a region of *lower* osmolality and it will be passing plasma in the ascending limb that is coming from a region of *higher* osmolality. It follows that, at any level, the osmolality of the ascending limb will be higher than that of the descending limb and water will pass from the descending to the ascending limb so bypassing the deeper medulla (Fig. 8.4.4). On the other hand, at any level, the solute concentration, including NaCl and urea, will be higher in the ascending limb than in the descending limb and solute will tend to diffuse from the ascending to the descending limb. This traps solute in the medulla. However, for these same reasons, the vasa recta are inefficient in supplying oxygen and removing carbon dioxide from the deeper regions of the medulla. Thus, oxygen tends to diffuse from the descending limb to the

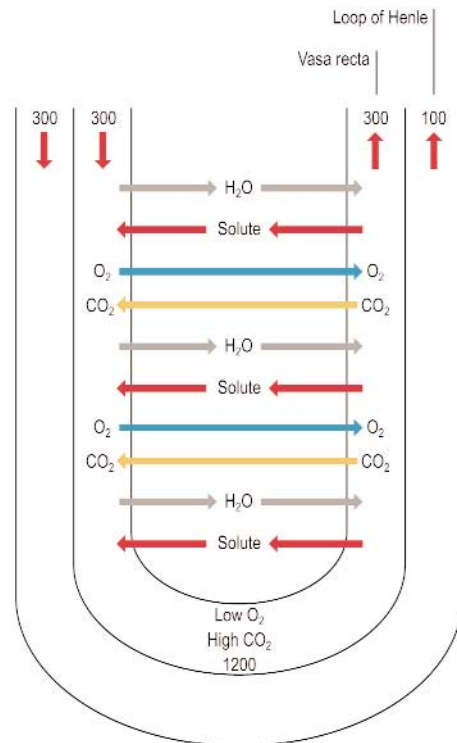


Fig. 8.4.4 Solute trapping by the vasa recta. Exchange of water and solutes between the two limbs of the vasa recta avoids dissipation of the osmotic concentration gradient, provided the blood flow in the vasa is not too great.

ascending limb down its concentration gradient so that less oxygen is available to be taken to the deeper medulla. On the other hand, carbon dioxide diffuses from the ascending limb to the descending limb so the blood that reaches the deeper medulla already has a high carbon dioxide concentration.

Although the anatomical arrangement of the vasa recta is effective in maintaining the osmotic gradient, changes in the blood flow can affect that gradient. If the blood flow in the vasa recta is increased, then solutes *are* washed out of the medulla and its interstitial osmolality *is* decreased. If blood flow is decreased, the opposite happens. The latter happens when ADH (also known as vasopressin because of its vasoconstrictor effect) constricts the renal arterioles



Summary

The vasa recta

- The anatomical arrangement of these blood vessels means that they do not dissipate the interstitial osmotic gradient created by the loop of Henle.
- However, they are inefficient in exchanging O_2 and CO_2 with the cells in the deeper medulla.
- Large changes in blood flow in the vasa recta can reduce or increase the medullary interstitial osmolality beyond its normal value.

and reduces blood flow. This helps to maintain the highest possible osmolality in the medullary interstitium and so allows maximal osmolalities to be reached in the tubular fluid.

Potassium excretion

Potassium is vital for the normal functioning of many cells, particularly excitable cells. Most K^+ is intracellular, its concentration being about 140 mmol/litre. The normal extracellular and plasma concentration of K^+ is 4 mmol/litre and this large concentration gradient between the extracellular and intracellular space is important in maintaining the potential difference across resting cell membranes. The normal diet contains 40–100 mmol K^+ /day which is far more than the body needs. In fact, 40–50 mmol of K^+ may be absorbed at a single meal which would increase plasma K^+ concentrations to a potentially lethal value of 7–8 mmol/litre if all of this K^+ were to remain in plasma. Such a rise in plasma K^+ is normally prevented in the short term (minutes) because K^+ is removed from the plasma under the influence of several

hormones (adrenaline, insulin and aldosterone) that promote K^+ uptake into liver, skeletal muscle, bone and red blood cells. However, in the longer term (over hours), the K^+ ingested must be excreted from the body by the kidneys to maintain K^+ balance. The kidneys excrete over 90% of the K^+ that is ingested; only 5–10% is lost in faeces and sweat.

The **proximal tubule** reabsorbs about 80% of the filtered K^+ . There is further reabsorption of K^+ in the thick ascending limb but much of this probably leaks back from the interstitium into the descending limb, i.e. it is recycled rather like urea. Thus, it is the process of K^+ secretion by the **distal tubule** and **collecting duct** that is predominantly responsible for the K^+ that appears in the urine. Alterations in the balance of K^+ reabsorption and K^+ secretion by the distal tubule and collecting duct are responsible for changes in the urinary excretion of K^+ . The rate of secretion of K^+ is determined by:

- the activity of Na^+/K^+ ATPase in the basolateral membrane of the principal cells (see Fig. 8.5.1, p. 755)
- the electrochemical gradient for K^+ efflux across the luminal membrane into the lumen
- the permeability of the luminal membrane to K^+ .

An increase in plasma K^+ stimulates Na^+/K^+ ATPase, so increasing K^+ uptake across the basolateral membrane and increasing the driving force for K^+ efflux into the lumen. This effect is facilitated because an increase in plasma K^+ stimulates aldosterone secretion by the adrenal cortex (see p. 434), which acts synergistically with K^+ . **Aldosterone** increases the activity of Na^+/K^+ ATPase and so increases the intracellular concentration of K^+ (as well as pumping Na^+ out of the cell). It also increases the permeability of the luminal membrane to K^+ . On the other hand, if plasma K^+ is decreased, then K^+ secretion is decreased by effects that are opposite to those just described. Indeed, if plasma K^+ becomes very low, there is net reabsorption



Summary

Excretion of K^+

- The proximal tubule reabsorbs ~80% of the filtered K^+ .
- K^+ secretion by the principal cells of the distal tubule and collecting duct is mainly responsible for the K^+ in urine.
- An increase in K^+ in plasma stimulates the Na^+/K^+ ATPase on the basolateral membrane of the principal cell, so increasing K^+ uptake into the cell. This increases the driving force for K^+ efflux into the lumen.
- This process is facilitated because an increase in plasma K^+ stimulates aldosterone secretion, which increases the Na^+/K^+ ATPase pump activity and increases the permeability of the luminal membrane to K^+ .
- A decrease in plasma K^+ has exactly opposite effects, so minimizing K^+ loss in urine.

of K^+ all along the nephron, and K^+ loss in urine is minimized.

K^+ secretion is also regulated by the flow rate of tubular fluid and changes in acid–base balance. An increase in flow rate as might be produced by an increase in circulating blood volume, or by diuretics, increases K^+ secretion. This is because the K^+ that is secreted into the lumen is carried downstream more quickly, minimizing the increase in the lumen concentration and preserving the driving force for K^+ efflux across the luminal membrane. A decrease in tubular flow rate has the opposite effect.

Increased plasma hydrogen ion concentration (acidosis) reduces K^+ excretion, at least in the short term, probably because acidosis inhibits Na^+/K^+ ATPase and reduces the permeability of the luminal membrane to K^+ . Alkalosis has the opposite effect.

Hydrogen ion secretion

The mechanism for hydrogen ion secretion was described above (p. 738). Regulation of hydrogen ion and ammonia secretion is dealt with in Chapter 8.7 (p. 773).

Renal regulation

8.5

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Aldosterone 755

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Atrial natriuretic peptide (ANP) 757

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Parathyroid hormone (PTH) and vitamin D 759

Clinical Example: Renal stones and hyperparathyroidism 760

Introduction

Renal function is regulated by **neural** and **hormonal** influences. The most important of these are:

- renal sympathetic nerves
- renin–angiotensin system
- aldosterone
- atrial natriuretic peptide
- antidiuretic hormone
- prostaglandins
- parathyroid hormone and vitamin D.

Renal nerves

The afferent and efferent renal arterioles and the tubules are supplied by **sympathetic** noradrenergic fibres. Although the kidney can autoregulate in response to changes in arterial pressure so that renal blood flow remains constant, this does not mean that renal blood flow is always constant. When arterial pressure falls slightly as during a mild haemorrhage, the kidney shows autoregulation (see p. 727). However, during a more severe haemorrhage, the renal arterioles respond to the increase in renal sympathetic activity caused by the baroreceptor reflex: they show vasoconstriction and renal blood flow falls. During moderate and severe exercise and during emotional stress, renal sympathetic

nerve activity also increases and so reduces renal blood flow. When renal blood flow is reduced, GRF may still be maintained by the action of angiotensin on the efferent arteriole (see below). You should also appreciate that the vasoconstrictor effects of the sympathetic nerves can be limited by the action of prostaglandins (see below).

Activation of the renal nerves not only constricts the blood vessels, but also increases reabsorption of sodium by the proximal tubule with a consequent increase in absorption of chloride and water. In addition, activation of the renal nerves also stimulates renin release.

Qualitatively similar effects to those produced by activation of the renal nerves can be produced when plasma levels of noradrenaline and adrenaline are raised by secretion of these hormones by the *adrenal medulla*. On the other hand, a fall in renal sympathetic nerve activity or in plasma catecholamine levels produces the opposite effects.



Summary

The actions of the renal nerves

- A strong increase in renal sympathetic nerve activity can reduce renal blood flow. Meanwhile, GFR may be maintained by autoregulation, but may fall.
- An increase in renal sympathetic activity also:
 - directly increases reabsorption of Na^+ by the proximal tubule
 - directly stimulates renin release and thereby angiotensin II production.
- The effects of an increase in renal sympathetic activity can be limited by locally released prostaglandins.

Renin–angiotensin system

Renin is an **enzyme** that is synthesized, stored and secreted by granular cells of the afferent and efferent arterioles of the glomerulus (see Fig. 8.1.3, p. 718) in a specialized region known as the **juxtaglomerular apparatus**. This is situated where the distal tubule comes very close to the Bowman's capsule of its own nephron and passes through the angle formed by the afferent and efferent arterioles. The cells of the distal tubule that are closest to the afferent and efferent arterioles and Bowman's capsule are morphologically distinct and are known as **macula densa** cells. They respond to changes in the composition of the tubular fluid.

Renin secretion is stimulated by three factors:

- Increased renal sympathetic nerve activity.
- Reduced renal perfusion pressure. The actual stimulus seems to be a reduction in the pressure within the afferent arteriole and the resulting reduction in the wall tension in this arteriole. This can occur as a direct result of a reduction in systemic arterial blood pressure. It may be reinforced by constriction caused by an increase in sympathetic activity to the kidney, since the site of afferent arteriolar constriction is upstream of the renin-secreting cells.
- Decreased NaCl delivery to the macula densa. It is not clear whether it is Na^+ , or Cl^- concentration, or NaCl concentration or NaCl content that is actually sensed.

However, renin secretion is stimulated by the macula densa mechanism under conditions which would be expected to decrease NaCl delivery to the distal tubule, for example when blood volume is reduced and Na^+ reabsorption by the proximal tubule is increased.

Renin secretion caused by the renal nerves is mediated by β_1 -**adrenoceptors**. Renin secretion that is caused by the macula densa is mediated by prostaglandins, particularly **prostacyclin**. Prostacyclin is released by the macula densa and acts on the renin-secreting cells.

Once formed, renin cleaves the decapeptide **angiotensin I** from **angiotensinogen**, which is an α -globulin. Angiotensin I is then converted into the octapeptide **angiotensin II** by **angiotensin-converting enzyme (ACE)**. Angiotensinogen is produced by the liver and circulates in the blood. ACE is found in high concentrations in vascular endothelium. Therefore, much of the angiotensin II that circulates in the blood is formed in the lungs where there is a large surface area of vascular endothelium. However, angiotensin II can also be produced locally within the kidney itself from intrarenal angiotensinogen, without activation of the systemic renin-angiotensin system. This locally generated angiotensin II may reach a concentration within the kidney that is 1000 times higher than that in the systemic circulation and is very important in the regulation of GFR and sodium excretion.

Angiotensin II has the following effects:

- It causes **vasoconstriction**. Within the systemic circulation as a whole this increases arterial blood pressure. Within the kidney, angiotensin II preferentially constricts the efferent arterioles. This raises pressure in

the glomerular capillaries and helps to maintain GFR constant when renal perfusion pressure is reduced (autoregulation, see p. 727).

- It stimulates **sodium reabsorption** by the proximal tubule, and chloride and water follow passively.
- It stimulates **aldosterone secretion** by the adrenal cortex.
- It stimulates **antidiuretic hormone (ADH)** secretion from the posterior pituitary gland.
- It stimulates **thirst** by an action on the brain.

Angiotensin II also has a negative-feedback effect on renin secretion by the granular cells of the juxtaglomerular apparatus.

Aldosterone

Aldosterone is synthesized and released by the glomerular cells of the **adrenal cortex**. The most important stimuli for its release are an increase in the concentration of angiotensin II and an increase in plasma K^+ concentration. Aldosterone acts within the kidney to stimulate Na^+ absorption and K^+ secretion by the principal cells of the distal tubule and collecting duct (Fig. 8.5.1).

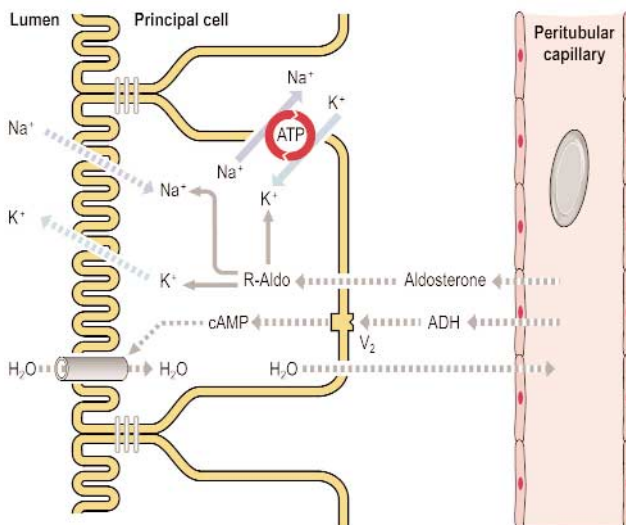


Fig. 8.5.1 Principal cells of the collecting duct. The collecting duct is made up of principal cells and intercalated cells. The intercalated cells secrete H^+ or HCO_3^- . The principal cells secrete K^+ and reabsorb Na^+ and water under the influence of aldosterone, which enters the cell and binds to a cytoplasmic receptor to form the complex R-Aldo that acts on the nucleus to regulate the production of a number of proteins important in Na^+ reabsorption. The effect of ADH on water reabsorption shown in this figure is dealt with later in the text.



Clinical Example

Renal hypertension

The concept of a 'normal' blood pressure is a purely statistical one in that it is a blood pressure that falls within a 'normal' range on either side of the mean of that of the population. However, complications that are characteristic of hypertension are clearly related to the value of diastolic pressure. The World Health Organization recommends that a diastolic pressure of >90–95 mmHg be regarded as hypertensive. About 20% of the adult population of the UK have blood pressures above 160/95. Hypertension is the most important risk factor in strokes and heart failure. In ischaemic heart disease it is as important as hypercholesterolaemia, obesity or smoking.

Arterial blood pressure is the product of cardiac output and peripheral vascular resistance. Because the kidneys receive 20% of the cardiac output, it is little wonder they can have a profound effect on arterial pressure or be profoundly damaged by it. In fact, it is often difficult clinically to decide whether the kidneys are the origin or victims of hypertension.

Both kidneys, or in a small percentage of cases one kidney, may be diseased sufficiently to cause hypertension. The mechanisms involved are:

- *Renal artery stenosis.* This exerts a direct haemodynamic effect of increasing peripheral resistance, but more importantly, it reduces renal perfusion pressure, which in turn affects the renin–angiotensin system.
- *The renin–angiotensin–aldosterone system.* Decreased perfusion pressure leads to activation of the juxtaglomerular apparatus of the nephrons, which, via the production of renin, produce angiotensin II, the most potent hypertensive agent in the body. Angiotensin II

stimulates the release of aldosterone, which in turn stimulates sodium reabsorption. Sodium reabsorption is also favoured by reduced perfusion pressure, which in turn reduces the hydrostatic pressure in the peritubular capillaries, so increasing sodium reabsorption from the proximal tubule.

- *Retention of sodium.* Sodium retention by the mechanisms described above, together with reduced excretory ability, results in increased blood volume and hence blood pressure.

Hypertension has its most profound effect in glomerulonephritis (see Clinical Example, p. 728), and control of hypertension is essential in this condition to prevent further deterioration of renal function secondary to the vascular damage produced by the excess pressure itself.

Hypertension due to renal artery stenosis is the result of a purely physical condition that, in about 50% of cases, is amenable to surgical correction by angioplasty to dilate the lumen. On the other hand, if unilateral renal disease has destroyed most of the useful excretory function of a kidney, which is therefore doing more harm than good, unilateral nephrectomy is indicated.

In the management of hypertension it is important to first establish whether the hypertension is primary, called *essential hypertension*, or secondary as a result of disease in another system, for example the kidneys. These secondary causes should be excluded before essential hypertension (for which no single factor is found responsible) is treated. Medical management of renal hypertension is generally directed to improving the excretory function of the kidneys and their perfusion, which, if successful, brings about a reduction in blood pressure.

It achieves these effects by entering the cells, binding to a receptor and inducing the synthesis of a number of proteins. These, in turn are involved in increasing the number of Na⁺ and K⁺ channels in the luminal membrane and in increasing the activity of Na⁺/K⁺ ATPase in the basolateral membrane.

Atrial natriuretic peptide (ANP)

ANP is synthesized and released by myocardial cells of the **atrium**. It is released by stretch of the atrium. In heart failure, it is released by the ventricles as well. Myocytes contain granules of the precursor (prohormone) of ANP which has 126 amino acids. The ANP that is released has 28 amino acids. ANP has several actions that are not yet fully understood. In general, they tend to oppose the actions of the renin–angiotensin system and include the following:

- vasodilatation within the kidney
- inhibition of renin secretion by the granular cells of the afferent and efferent arterioles
- inhibition of aldosterone secretion by the adrenal cortex
- inhibition of ADH secretion by the posterior pituitary and of the actions of ADH on water transport in the collecting duct
- an increase in sodium and water excretion.

The inhibition of aldosterone secretion caused by ANP is, in part, secondary to inhibition of renin secretion, but also reflects a direct action of ANP on the renin-secreting cells. The increase in sodium and water excretion is partly explained by the other actions of ANP. However, ANP may also act directly on the cells of the collecting tubule to close Na⁺ channels on the luminal membrane.

The physiological importance of ANP is not yet clear.



Clinical Example

Atrial natriuretic peptide and heart failure

Measuring the level of hormones can be a useful way of assessing body function in health and disease. Thus after the menopause when ovarian hormonal function declines, the level of the controlling hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), rise dramatically. These high levels indicate that the body itself has evaluated ovarian hormonal function and declared it severely reduced. Similarly, in hypothyroidism, the pituitary ‘diagnoses’ an inadequate level of thyroid hormones and increases the level of thyroid-stimulating hormone (TSH) to stimulate the flagging thyroid, at the same time providing a useful diagnostic aid for the condition. In atrophic gastritis, when the stomach cannot

produce an acid secretion, the controlling hormone gastrin rises to very high levels. In the same way the level of atrial natriuretic peptide (ANP) provides a diagnostic aid for the presence and severity of congestive heart failure.

Atrial muscle fibres contain granules of this peptide and, when stretched beyond a certain point, they release the peptide hormone into the circulation. This occurs in normal people when the extracellular fluid volume increases. An increase in extracellular volume is reflected in a rise in plasma volume and hence blood volume. Since the bulk of the blood is contained in the venous system, a surplus volume leads to increased stretching of the atria. The released ANP plays a role, albeit probably a minor one, in returning the volume to normal by favouring excretion of salt and water.

Clinical Example (Continued)

In heart failure the increase in extracellular volume exceeds normal variations and the atria become very distended by the heart's inability to keep up with the venous return. Even in early heart failure there is quite severe stretching of the atria and this causes massive release of natriuretic peptide so that the circulating blood level exceeds the normal limits and, in severe cases, can rise five- to tenfold. As well as opposing to some extent the increase in extracellular volume, the hormone provides a useful marker, confirming the presence of heart failure and indicating its severity and progress. This is a very 'physiological' assessment, as the secretion of peptide is related directly to the stretching strain on the heart.

Until recently the use of atrial natriuretic peptide in the diagnosis and monitoring of heart failure was confined mainly to research studies, but development of the assays used in its

measurement should make it increasingly practical for routine use. In this connection it can be noted that, in fact, more than one natriuretic peptide is released from the atria, including confusingly named brain natriuretic peptide (BNP), so called because it was initially identified in the brain. However, the circulating level of this related natriuretic peptide seems to be determined by its release from overdistended atria just as with ANP and its stability may avoid the necessity for the rapid analysis needed for its less stable relative.

These assays are particularly important at a time when treatment of heart failure is improving markedly, thanks to treatment aimed at decreasing the load on the failing heart. An assay which can accurately diagnose heart failure and monitor its progress is very valuable in a condition whose effects are often insidious and hard to quantify.

Antidiuretic hormone (ADH)

ADH is released from the posterior pituitary gland (see Ch. 5.2). The major stimuli for ADH secretion (Fig. 8.5.2) are an increase in **plasma osmolality** (by stimulation of osmoreceptors in the hypothalamus) and a decrease in arterial blood pressure or blood volume (via the afferent pathways from the arterial baroreceptors and volume receptors; see p. 600).

ADH has two main effects:

- It causes **vasoconstriction** of arterioles of the systemic circulation, including the kidney, by acting on vasopressin V_1 receptors.
- It increases **water reabsorption** by the kidney, primarily by increasing water permeability of the collecting duct.

ADH binds to V_2 receptors on the basolateral membrane of the principal cells, which stimulates adenylyl cyclase activity and increases the intracellular concentration of cAMP. This results in the insertion of water channels into the luminal membrane of the cell (Fig. 8.5.1). Any water that enters the cells through these channels can leave through the basolateral membrane which is freely permeable to water. ADH also increases the urea permeability of the medullary portion of the collecting duct by activating specific urea transporters in the membrane. This increase in urea permeability contributes to the ability of the kidney to concentrate the urine.

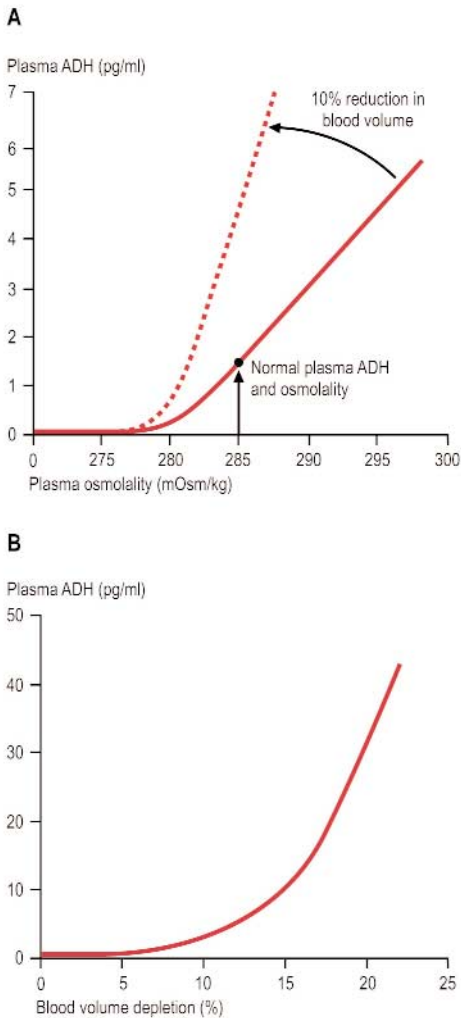


Fig. 8.5.2 Control of ADH secretion. **A.** Control of ADH (antidiuretic hormone) secretion by plasma osmolality is potentiated by blood volume reduction. **B.** Blood volume reduction alone exerts a powerful effect on plasma ADH level.

Prostaglandins

Prostaglandins are lipid molecules synthesized from arachidonic acid and can be produced by most tissues of the body. They do not generally function as circulating hormones, but **act locally**. Within the kidney, their synthesis is increased by renal sympathetic nerve activity, when angiotensin II levels are high and when

renin release is stimulated, i.e. under circumstances of renal vasoconstriction when renal blood flow might be impaired. Renal prostaglandins are **vasodilator** and help to prevent excessive reductions in renal blood flow and renal ischaemia. Renal prostaglandins are important clinically because many patients are taking non-steroidal anti-inflammatory drugs to treat such conditions as arthritis. These drugs inhibit prostaglandin synthesis. They can therefore produce a large fall in renal blood flow and GFR in patients who have raised levels of sympathetic activity and angiotensin II resulting from blood volume depletion or cardiac failure.

Parathyroid hormone (PTH) and vitamin D

PTH is secreted by the parathyroid gland (Ch. 5.6). Its secretion is stimulated by a reduction in the plasma concentration of ionized calcium. PTH stimulates the production of **calcitriol**, which increases Ca^{2+} and phosphate absorption from the gastrointestinal tract (see below) and stimulates bone resorption. In the kidney, PTH stimulates Ca^{2+} reabsorption by the thick ascending limb of the loop of Henle and the distal tubule. Since all of these effects of PTH tend to increase the plasma Ca^{2+} concentration, the filtered load of Ca^{2+} may increase. Thus, Ca^{2+} excretion may actually increase despite the increase in renal reabsorption.

The kidney is important in the production of calcitriol. Vitamin D_3 (cholecalciferol) is a fat-soluble steroid that is normally present in the diet and that can be synthesized in the skin in the presence of ultraviolet light. Vitamin D_3 is converted to 25-hydroxycholecalciferol in the liver and thence to the active metabolite calcitriol in the kidney (mainly in the proximal tubule). The conversion to calcitriol is stimulated by PTH and is therefore indirectly stimulated by a reduction in Ca^{2+} . Calcitriol increases Ca^{2+} and phosphate absorption by the gut and it enhances bone resorption. The effects of calcitriol on the kidney are not fully understood.



Clinical Example

Renal stones and hyperparathyroidism

Stones in the renal tract, often no more than a few millimetres across, can cause excruciating pain known as *renal colic*. This pain is produced when the stone passes down the ureter by peristalsis, just as our urine normally passes quite painlessly. The problem with the unyielding stone is that it severely stretches the smooth muscle wall of the ureter, thereby powerfully stimulating pain endings there – just like the parallel situation when spasm of the gut wall causes intestinal colic.

As at other sites (parotid gland, gall bladder), stones in the urinary tract have varying compositions, but calcium is often an important component (such stones are often referred to as *renal calculi*). The causes of these stones are often obscure and multifactorial. However, in a relatively small number of patients, their renal tract stones can be clearly related to overactivity of the parathyroid gland. The reason is that in *hyperparathyroidism* the urine is unusually rich in both calcium and phosphate ions so that the product of their concentrations – $[\text{calcium}] \times [\text{phosphate}]$ – can exceed the value up to which the ions are soluble (the *solubility product*) and calcium phosphate comes out of solution.

The parathyroid glands mobilize calcium from bone through their hormone, parathormone, which stimulates osteoclasts to digest bone matrix and releases calcium and phosphate into the extracellular fluid. Excessive amounts of the hormone are usually produced by an autonomous tumour. Unlike normal parathyroid tissue, the tumour is not suppressed by the high level of circulating calcium ions produced by its activity. (About half the circulating plasma

calcium is normally bound to plasma proteins, but it is the level of ionized calcium that influences physiological functions such as nerve conduction.)

The excess calcium ions are freely filterable at the glomeruli and so the amount of calcium in the filtrate rises sharply. Although much of this is reabsorbed, the net effect is that the urinary calcium concentration rises.

A second action of parathormone is to impair the renal reabsorption of filtered phosphate ions (the logic of this normal action is that it helps to maintain the level of circulating calcium by lowering the level of circulating phosphate and hence reducing the $[\text{calcium}] [\text{phosphate}]$ solubility product). The consequence is that a high level of parathormone greatly increases the phosphate content of the urine. Thus overactivity of the parathyroids leads to very high levels of both calcium and phosphate ions, exceeding the solubility product, and crystals of calcium phosphate are formed in the urinary tract, often in the renal pelvis just above the start of the ureter. Over time these crystals can grow into calculi, and the very severe pain (said to resemble the unrelieved pain of childbirth) produced as they are passed by peristalsis down the ureter may be the first symptom of the underlying hyperparathyroidism.

It is therefore good practice to confirm or exclude hyperparathyroidism in people with renal calculi. A tumour is suggested by an increased level of calcium ions and a reduced level of phosphate ions in the blood, and there may be X-ray signs of bone erosion. If a parathyroid tumour (adenoma) is indeed present, then its removal is part of the treatment of the renal calculi.

Regulation of body fluids

8.6

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Introduction

Water balance in the normal individual is regulated by mechanisms that are able to prevent large changes in plasma osmolality, which is itself primarily determined by the plasma sodium concentration. On the other hand, sodium balance in the normal individual is regulated by mechanisms that are able to prevent large changes in extracellular fluid volume. In practice, the important component of extracellular fluid volume is plasma volume, since this perfuses the tissues. Further, it is plasma volume, or more precisely blood volume (i.e. plasma volume plus red and white cells), that is regulated, in that there are receptors that are sensitive to the 'fullness' or 'pressure' within the blood vascular system.

Because of the relationship between plasma osmolality and plasma sodium concentration, it might be thought that an abnormal plasma concentration of Na^+ in an individual can be explained by an abnormality in sodium balance. However, this is not the case; it actually reflects an abnormality in water balance. Changes in Na^+ balance lead to changes in the volume of extracellular fluid, not in its osmolality. Put briefly, plasma osmolality is regulated by changes in water intake and excretion, whereas sodium balance is regulated by changes in sodium excretion.

Regulation of body fluid osmolality

Water is lost from the body via the lungs during breathing, from the skin by sweating, from the gastrointestinal tract in faeces and via the kidneys as urine. Of these, the **kidneys** are the most important route because water excretion can be controlled independently of solutes, to keep plasma osmolality constant. Water is provided for the body by drinking, by the water content in food and by metabolism. Of these, the volume of fluid ingested by drinking regulated by the sensation of thirst is most important. **Osmoreceptors** that are sensitive to changes in osmolality play a major role in the regulation of water excretion by the kidneys and in thirst. **ADH** is the major factor involved in regulating water excretion and thereby osmolality.

Osmoreceptors in the supraoptic and paraventricular nuclei of the anterior hypothalamus respond to changes in the osmolality of the plasma that perfuses them from the carotid artery. They sense changes in osmolality by shrinking or swelling and this changes the output of ADH from the neurohypophysis (posterior pituitary gland). Osmoreceptors in the same region, which may or may not be the same cells as those that regulate ADH output, induce the sensation of thirst.

If excessive water is lost from the body by sweating or in faeces, or if water intake is severely restricted, plasma osmolality is increased and the osmoreceptors stimulate the secretion of ADH and cause the sensation of thirst. The actions of ADH upon the kidney then conserve water, so that a small volume of urine is produced which is hyperosmotic to plasma. In addition, the individual will actively seek water or fluid to drink. As plasma osmolality returns towards normal by these mechanisms, so the secretion of ADH and the sensation of thirst are reduced. On the other hand, if a large water load is consumed and plasma osmolality falls below normal, osmoreceptors will decrease the release of ADH and remove the sensation of

thirst. ADH secretion will rise again as the plasma osmolality returns towards normal.

The osmoreceptors are extremely sensitive. They respond to changes in osmolality of as little as 1%, or 3 mOsm/kg H₂O from the normal plasma osmolality of ~285 mOsm/kg H₂O. The relationship between plasma osmolality and ADH production is steep (Fig. 8.5.2A, p. 759) as is the relationship between plasma ADH concentration and urine osmolality. Thus, the sensitivity of the system that regulates osmolality is very high. Further, because ADH is rapidly degraded in plasma, circulating levels of ADH can be reduced to zero within minutes of ADH secretion being inhibited. Thus, the system can respond very rapidly to changes in plasma osmolality.

Normally, ADH is far more important than thirst in regulating plasma osmolality because most of our drinking is habitual or social and not regulated by osmoreceptors. Also, the osmotic regulation of thirst is far from perfect; the sensation of thirst can be satisfied by the act of drinking before sufficient water has been absorbed from the gastrointestinal tract to reduce the plasma osmolality to normal. This is probably due to the input from receptors in the oropharyngeal regions and upper gastrointestinal tract.

Regulation of extracellular fluid volume

We have seen that **extracellular fluid volume** (EFV) is dependent upon Na⁺. Thus, if a hyperosmotic solution of NaCl were added to the extracellular fluid, then both the Na⁺ concentration and the osmolality of the extracellular fluid would increase and, via the osmoreceptors, this would stimulate ADH secretion and thirst. The resulting decrease in water excretion by the kidneys and the increased drinking of water would restore the osmolality of plasma and other extracellular fluid to normal. However, the volume of the extracellular fluid would show a parallel increase.

On the other hand, if NaCl were to be lost from the extracellular fluid, then the volume of the extracellular fluid would decrease.

The EFV is regulated by regulating Na⁺ excretion, and in the normal individual this works well. However, problems arise in certain disease states. For example, in congestive heart failure, cardiac output is decreased, but the EFV, including plasma volume, is increased. This occurs because the reduction in cardiac output leads to retention of Na⁺ by the kidney. (This is considered further, below.)

Of the various mechanisms that regulate EFV in the normal individual, it should first be stated that maintenance of a normal EFV depends upon there being adequate Na⁺ in the diet. If this is the case, then Na⁺ excretion by the kidneys regulates EFV.

If EFV falls, then the following occur:

1. Reduction in blood volume *reduces the pressure in the venous part of the systemic circulation*. This change is transmitted back into the kidney so that hydrostatic pressure in the peritubular capillaries that supply the proximal tubules is reduced. The reabsorption of Na⁺ and fluid by the proximal tubule is therefore automatically increased, since it is dependent upon the balance of hydrostatic forces between the lateral intercellular spaces and the capillaries.
2. The decrease in venous pressure also *reduces the stimulus to* (i.e. unloads) the volume or stretch receptors in the great veins and atria. This results in a reflex increase in the sympathetic activity to the kidney.
3. If the reduction in EFV and blood volume is sufficiently large to produce a *reduction in arterial blood pressure*, this will reduce the stimulus to (i.e. unload) the baroreceptors in the carotid sinuses and aortic arch. Even if mean arterial pressure does not fall, a small decrease in blood volume normally reduces arterial pulse pressure and this will unload the arterial baroreceptors. A reduction in baroreceptor afferent activity results in a reflex increase in sympathetic activity.
4. An increase in sympathetic activity in the kidney, if sufficiently pronounced (see Ch. 8.5), causes *renal vasoconstriction*. This decreases renal blood flow and can, in turn, decrease capillary hydrostatic pressure in the glomerulus and GFR.
5. The increase in renal sympathetic activity also directly stimulates *renin* release, this being augmented by the decrease in pressure in the afferent arteriole caused by vasoconstriction proximal to the afferent arteriole (see Ch. 8.5) and by any fall in mean arterial pressure or in pulse pressure.
6. The increase in renin activity stimulates the production of *angiotensin II*.
7. The constriction of the afferent and efferent arterioles caused by increased sympathetic activity and angiotensin II may further reduce hydrostatic pressure in the peritubular capillaries, so augmenting Na⁺ and fluid reabsorption. The increase in renal sympathetic activity and angiotensin II also directly stimulate Na⁺ reabsorption by the proximal tubule.
8. The increase in the plasma concentration of angiotensin II stimulates the *release of aldosterone*. This increases the reabsorption of Na⁺ by the late part of the distal tubule and collecting duct.
9. A reduction in venous pressure and thereby atrial pressure reduces the stimulus to atrial cells that secrete ANP. Since ANP promotes Na⁺ and water excretion by the kidney by various mechanisms (see Ch. 8.5) a reduction in plasma ANP would tend to support the other effects described above.
10. As Na⁺ excretion begins to fall as a result of the above mechanisms, so *plasma osmolality* may begin to increase. This stimulates the secretion of ADH. ADH secretion is also stimulated by a reduction in the activity of the volume receptors and arterial baroreceptors (see p. 600). ADH reduces water excretion. It should be noted that if

the initial fall in EFV causes a large enough decrease in the activity of the volume receptors and arterial baroreceptors, this will stimulate the secretion of ADH from the outset (see below).

11. *Thirst* is stimulated. This probably occurs by the action of angiotensin II on the brain.

Thus, these integrated effects upon the kidney mean that Na^+ and water are retained by the kidneys such that EFV is restored and plasma osmolality remains constant.

If EFV increases, exactly the opposite changes occur. Na^+ and water excretion by the kidneys are increased so that EFV decreases towards normal, while osmolality remains constant.



Summary

Principles of regulation of plasma osmolality and plasma sodium

- Plasma osmolality is largely determined by plasma sodium concentration.
- A change in plasma sodium normally leads to an osmotic flux of water between extracellular and intracellular space and thence to a change in plasma volume. Therefore, an abnormal plasma Na^+ concentration reflects an abnormality in water balance, rather than an abnormality in sodium balance.
- Plasma osmolality is largely regulated by changes in water intake and excretion via changes in the secretion of ADH that are mediated by hypothalamic osmoreceptors.
- Plasma volume is largely regulated by changes in sodium excretion via direct effects on the kidney and via reflex mechanisms involving:
 - stretch receptors in the atria and great veins
 - arterial baroreceptors.

Interaction between osmoregulatory and volume regulatory influences upon ADH

We have seen that secretion of ADH is regulated by the osmoreceptors, which respond to changes in plasma osmolality, and that this regulatory mechanism is very sensitive. Secretion of ADH is also regulated by **volume receptors** and **arterial baroreceptors**. The sensitivity of the influence of these receptors upon ADH release is less than that of the osmoreceptors; blood volume or arterial pressure has to decrease by 5–10% before ADH secretion is stimulated (Fig. 8.5.2B, p. 759). However, changes in blood volume and arterial pressure do affect the relationship between plasma osmolality and ADH secretion (see Fig. 8.5.2A, p. 759). The importance of this effect is seen particularly when blood volume is decreased. The relationship between osmolality and ADH is shifted to the left and the slope of the relationship is increased. This means that if blood volume falls substantially, ADH secretion can be maximal or near maximal even when plasma osmolality is substantially below normal. In other words, faced with a life-threatening reduction in blood volume and arterial pressure, the influence of the volume receptors and baroreceptors over ADH secretion predominates over the influence of the osmoreceptors. Thus, the kidneys retain water and defend **blood volume** even though the penalty is a reduction in plasma osmolality.

Regulation of EFV in pathological states

Chronic heart failure

In chronic heart failure, impairment of myocardial contractility, usually of the left ventricle, results in a reduction in cardiac output and consequently a reduction in arterial pressure and in renal perfusion pressure. These factors lead to the retention of NaCl and water by the kidney. This fluid retention results in an increase in the

volume of blood held within the venous vessels of the systemic circulation, since these are the distensible vessels of the systemic circulation. As a consequence, central venous pressure will rise when the venous vessels have reached the limit of their distensibility and capillary hydrostatic pressure may also rise. A rise in capillary hydrostatic pressure together with the fall in plasma oncotic pressure that is caused by water retention favours the movement of fluid out of the capillaries into the interstitial fluid and peripheral **oedema** – the accumulation of excess fluid in the interstitial space. The increase in central venous pressure, the filling pressure for the right side of the heart, will help to increase right ventricular output, by Starling's law of the heart (Fig. 8.6.1). This, in turn, will increase filling pressure for the left side of the heart.

If the disease of the ventricle is mild, then the increase in filling pressure and therefore volume may improve left ventricular performance, according to Starling's law of the heart, so that stroke volume and cardiac output move towards normal. A new, **compensated** state can therefore be reached when arterial pressure, renal perfusion pressure and thereby sodium excretion return to normal, but at the expense of a raised plasma volume and oedema.

On the other hand, if the disease is severe, then the increase in left ventricular filling pressure may not improve its performance significantly (Fig. 8.6.1). In fact, stroke volume and thereby cardiac output remain below normal in this situation; the rise in left ventricular filling pressure will be transmitted back to the pulmonary circulation, so producing pulmonary oedema. Moreover, the reduced left ventricular output leads to further retention of NaCl and water by the kidney and a further rise in capillary hydrostatic pressure and oedema formation. In untreated cardiac failure, this positive feedback in the systemic circulation can eventually be limited because the accumulation of fluid in the tissues spaces will cause tissue hydrostatic pressure to rise, so neutralizing the effect of the rise in capillary hydrostatic

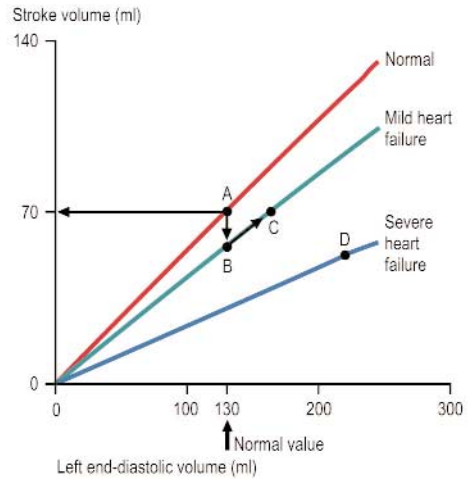


Fig. 8.6.1 Heart failure. Mild heart failure (A to B) can be compensated for by an increase in filling pressure and thereby in left end-diastolic volume (LEDV) and stroke volume (SV) (B to C). In severe heart failure the filling pressure and end-diastolic volume are already greatly increased (D) but the heart is working on a lower function curve; a further increase in filling pressure and LEDV cannot improve the situation.

pressure. However, the pulmonary oedema is potentially life-threatening because it impairs alveolar gas exchange.

Peripheral oedema cannot be detected clinically until 2–3 litres of excess fluid have accumulated in the interstitial fluid compartment. Therefore, patients with chronic heart failure and peripheral oedema have a greatly increased interstitial fluid volume and an increased plasma volume, i.e. a greatly expanded EFV and yet they behave as if they are volume depleted. The problem from the regulatory point of view is that they have a reduced circulating blood volume and the compensatory mechanisms that are brought into play make the condition worse.

Liver disease

Regulation of EFV may also be disturbed in liver disease. In liver disease there is commonly a rise in hydrostatic pressure in the hepatic portal vein, because of:

- obstruction within the liver, and
- vasodilatation of the splanchnic circulation.

There is a consequent rise in pressure in the capillaries of the intestine which forces fluid out into the abdominal cavity. This causes oedema formation in the abdominal cavity, known as **ascites**. The splanchnic vasodilatation, whose cause is unclear, together with the loss of plasma fluid into the abdominal cavity cause systemic arterial pressure to fall. This fall may be exacerbated because of the development of anatomical arteriovenous fistulae (shunts) throughout the body, which causes total peripheral resistance to fall further. As a compensatory response to the fall in systemic arterial pressure, cardiac output may be raised above normal via the baroreceptor reflex, contrasting with the low cardiac output of congestive heart failure. However, this increase in cardiac output is not sufficient to raise the arterial pressure in the face of reduced total peripheral resistance and loss of plasma volume into the interstitial space. Thus, as in congestive heart failure, patients with liver disease behave as if they are volume depleted; the kidneys retain sodium and water, even though the EFV is raised above normal.



Summary

Interactions between the regulation of plasma osmolality and plasma volume

- ADH secretion is regulated by osmoreceptors.
- ADH secretion is also regulated by volume receptors and arterial baroreceptors.
- The sensitivity of the influence of volume receptors and arterial baroreceptors on ADH secretion is less than that of the osmoreceptors.
- However, a decrease in blood volume greatly increases the sensitivity of the relationship between osmolality and ADH and shifts it to the left.
- Thus, if blood volume falls substantially, ADH secretion can be maximal even when plasma osmolality is below normal; plasma volume is defended at the expense of plasma osmolality.



Clinical Example

Diuretics

In broadest terms a diuretic is something that produces a diuresis or increased urine formation. Thus 1 litre of water drunk surplus to normal requirements is a powerful diuretic, as demonstrated by generations of students in their physiology practical classes. However, in medical terms a diuretic usually refers to a drug which causes a diuresis in someone who would otherwise pass much less urine. In practice the definition is even more restricted since, in general, diuretics act by causing a loss of excess

sodium, chloride and water (though other ions are often lost in excess too) thereby *reducing the extracellular fluid volume*, which is the dominant site of sodium and chloride.

Sodium has been described as the skeleton of the extracellular fluid. The intracellular sodium level is relatively low and fixed, so extra sodium taken into the body is added to the extracellular fluid, and sodium lost from the body is lost from the extracellular fluid. Given a certain amount of sodium in the extracellular fluid, electrical neutrality demands an equal amount of anion. Thus chloride is retained to balance the

Clinical Example *(Continued)*

sodium ions. To maintain normal osmolality, an equivalent amount of water is retained. Thus the extracellular fluid clothes the sodium skeleton.

In normal circumstances the body tolerates moderate fluctuations in extracellular fluid volume. When we eat a salty meal and are compelled by the accompanying thirst to drink more fluid, our extracellular volume may go up by a litre or more without disturbing body function. The extra fluid is excreted in a leisurely fashion over a day or two under the influence of reduced aldosterone and increased natriuretic hormone. Both these hormones act primarily by regulating body sodium.

However, in some diseases there are gross changes in body sodium and consequently extracellular fluid. In heart failure the volume may rise from around 10–15 litres (depending on body size) by several litres in mild cases and by 5–10 litres in severe cases. Similar changes can occur in liver and renal failure. The excessive extracellular fluid is distributed between the interstitial compartment, where several extra litres are manifested as oedema, and the intravascular compartment, where increased blood volume leads to venous congestion and cardiac strain. In these circumstances, diuretics can improve the situation dramatically.

Essentially diuretics are selective poisons of the kidney's ability to reabsorb sodium from the glomerular filtrate. They do not affect the obligatory reabsorption in the proximal convoluted tubule, but act on the distal convoluted tubule, and in the case of the highly potent loop diuretics on the cells of the ascending limb of the loop of Henle. By reducing sodium reabsorption, diuretics increase sodium loss in the urine, and this is accompanied by loss of chloride and of water. The benefits can be immediate and dramatic in the case of heart

failure. In advanced heart failure excessive extracellular fluid leads to severe dependent oedema (which is mainly an inconvenience), and an increased intravascular volume which places a severe burden on the failing heart and favours the development of life-threatening pulmonary oedema. Intravenous administration of a powerful diuretic can relieve the pulmonary oedema and improve the cardiac state within the hour, with continuing improvement in the next few days. The loss of fluid is apparent in the huge quantities of urine passed, e.g. 5 litres in the first few hours. It can also be monitored by the simple measure of weighing the patient. Loss of, say, 7 litres of surplus extracellular fluid in a week results in a loss of weight of 7 kg, since each litre of urine or extracellular fluid weighs very close to 1 kg. Nutritional changes over this period of time would normally produce little change in weight.

Diuretics are also used in the treatment of hypertension, particularly as an initial treatment of mild hypertension. Their action is complex, but at least part of the effect is due to loss of extracellular fluid, leading to a reduced plasma volume, a fall in stroke volume and hence a fall in arterial blood pressure. Excessive diuretic therapy can sometimes lead to inappropriately low blood pressure, by excessively reducing circulating blood volume.

Diuretics vary in their effects on electrolytes other than sodium and chloride. In general, a diuresis tends to reduce the opportunity for reabsorption of other ions such as potassium, and so potassium depletion is a risk, requiring in some cases potassium supplements. In contrast, diuretics which antagonize the actions of aldosterone tend to raise body potassium by antagonizing aldosterone's promotion of potassium excretion in exchange for sodium reabsorption.

Regulation of acid–base balance

8.7

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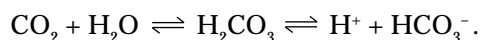
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Introduction

It is very important that the H^+ concentration of the body fluids is kept relatively constant because the activities of many of the body's enzymes are critically dependent on H^+ concentration; they only function normally within a narrow range. The normal plasma concentration of H^+ is 40 nmol/litre or 0.00004 mmol/litre, which is very low relative to the concentration of, for example, Na^+ (140 mmol/litre or 140 000 000 nmol/litre). Because the H^+ concentration is so low, it is often expressed as the negative logarithm to base 10 of the H^+ concentration in mol/litre, i.e. $-\log [H^+]$ or $\log 1/[H^+]$ or pH. Thus, 40 nmol/litre equals 0.00000004 mol/litre which is equivalent to pH 7.4. The pH range 7.8–6.8 (16–160 nmol/litre) can be tolerated, but in healthy individuals pH is generally kept between 7.36 and 7.44 (36–44 nmol/litre).

Hydrogen ions are generated by the normal metabolism of food.

1. The metabolism of carbohydrates and fats produces large quantities of CO_2 . This combines with water to form H_2CO_3 which generates H^+ by the following reaction the first part of which is catalysed by carbonic anhydrase:



This CO_2 does not normally result in a net increase in H^+ concentration in plasma

because the CO_2 can be excreted from the body via the lungs. The H_2CO_3 is therefore known as a **volatile acid**.

2. The metabolism of proteins generates **non-volatile acids** that cannot be excreted via the lungs. Thus, sulphuric acid is formed from the metabolism of the amino acids cysteine and methionine, and hydrochloric acid is formed from the metabolism of lysine, arginine and histidine. In addition, certain organic acids, such as H_2PO_4^- are simply consumed in the diet. This gain of H^+ is partly offset by the metabolism of aspartate, glutamate and citrate which results in the production of HCO_3^- which can then buffer the H^+ (see below). Nevertheless, there is a net gain of H^+ of 65–74 mmol/day in an individual who has a normal western diet. These H^+ must be dealt with if the pH is to remain normal.

The astute student will remember that we have already touched upon the effect of CO_2 on plasma pH in the section on respiration. The chemistry that follows here is a detailed description of what was outlined there; and reinforces the fact that the kidneys and respiratory system are inextricably entwined in the control of body fluid pH.

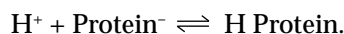
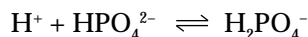
Buffering in body fluids

If the H^+ gained by ingestion and metabolism were to be freely distributed in total body water (about 40 litres), then a net gain of say 70 mmol H^+ in a day would increase the H^+ concentration in body water by 17.5 mM, i.e. to almost 1 million times normal. This does not happen because the rise in H^+ concentration is limited by various buffer systems. Two factors determine the capacity of a buffer system to stabilize pH:

- the pK of the buffer system in relation to the ambient pH (see Basic Science 8.7.1), and
- the quantity of the buffer present.

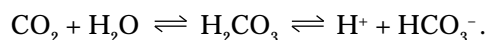
In the intracellular fluid, the major buffers are *phosphates* and *proteins*, including the

haemoglobin in red blood cells. The reactions may be written as:

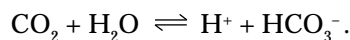


In the extracellular fluid, proteins, phosphate and bicarbonate are important, and in bone, carbonate (CO_3^{2-}).

In plasma, the bicarbonate–carbon dioxide system is of major importance:



Since the H_2CO_3 concentration is very small, H_2CO_3 can be ignored and the reactions can be simplified to:



The Henderson–Hasselbalch equation for this buffer system can then be written as:

$$\text{pH} = pK + \log \frac{[\text{HCO}_3^-]}{[\text{CO}_2]}.$$

Since the concentration of CO_2 depends on its partial pressure (P_{CO_2} in mmHg) and on its solubility in plasma (0.03 mmol/litre·mmHg⁻¹), we can write:

$$\text{pH} = pK + \log \frac{[\text{HCO}_3^-]}{0.03 \times P_{\text{CO}_2}}.$$

The pK of this system is 6.1, the pH at which the buffer is most effective (which is more than 1 pH unit from the normal plasma pH of 7.4). On this basis, the bicarbonate system is not a very effective buffer in plasma. However, physiologically, it is very important because:

- $[\text{HCO}_3^-]$ is relatively high
- $[\text{HCO}_3^-]$ and P_{CO_2} are controlled independently, by the kidneys and lungs respectively.

In the normal individual who is in acid–base balance, $[\text{HCO}_3^-]$ is 24 mM and P_{CO_2} is 40 mmHg. Therefore the equation can be written as:

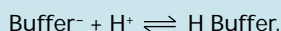
$$\text{pH} = 6.1 + \log \frac{24}{0.03 \times 40} = 6.1 + \log \frac{24}{1.2} = 7.4.$$



Basic Science 8.7.1

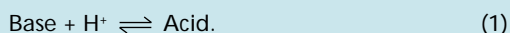
Buffers

A buffer solution is one which minimizes, or resists, changes in H^+ concentration. The general form of a buffering reaction is:



Buffer^- is known as a base – it can accept H^+ ; whereas $H \text{ Buffer}$ is an acid – it can donate H^+ .

Therefore, we can rewrite the equation above as:



The H^+ concentration (pH) of the solution changes little when H^+ is added to the base because the acid generated is a **weak acid** which means it does not dissociate very readily. In other words, the added hydrogen ions are ‘mopped up’; they do not appear as free H^+ .

The equilibrium or dissociation constant K for Equation 1 can be expressed as:

$$K = \frac{[H^+][\text{Base}]}{[\text{Acid}]} \quad (2)$$

or solving for H^+ , this can be rearranged as:

$$[H^+] = \frac{K \times [\text{Acid}]}{[\text{Base}]} \quad (3)$$

The constant, K , has the dimensions of concentration and is a measure of the strength of the acid. The larger the K , the stronger the acid, i.e. the more completely it dissociates. Since K is usually a very small number, it is usually expressed as the negative logarithm to base 10 (pK), in analogy with the relationship between H^+ concentration and pH.

If we take the negative logarithm of both sides of Equation 3, then we get:

$$\text{pH} = \text{pK} + \log \frac{[\text{Base}]}{[\text{Acid}]} \quad (4)$$

This is the **Henderson–Hasselbalch equation** (see also Ch. 7.3). It follows from this equation that if we know the ratio of the base to acid concentrations and the pK of a given buffer system, then the pH can be calculated. It also follows, since pK is the equilibrium constant of the reactions of Equation 1, that buffer solutions most strongly resist changes in pH near the point of half dissociation of the acid, i.e. when the concentrations of the base and acid are equal and therefore $\text{pH} = \text{pK}$ and the equilibrium has the greatest ‘room to move’ in either direction. The range over which a buffer is effective is about 1 pH unit on either side of the pK.

Buffering of blood by the bicarbonate–carbonic acid system is illustrated in Figure BS8.7.1.

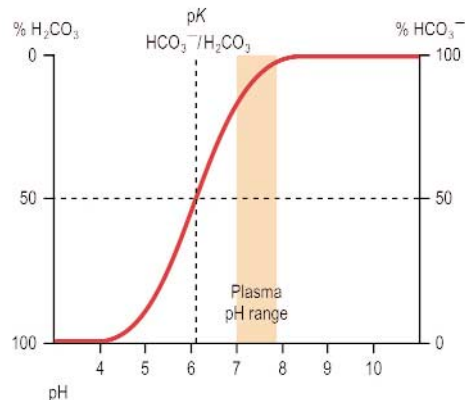
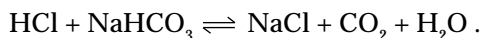
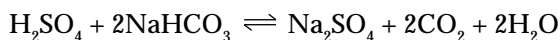


Fig. BS8.7.1 Blood buffering. An important buffer in the blood is the bicarbonate (HCO_3^-)–carbonic acid (H_2CO_3) system. The ratio of this weak acid to its base (bicarbonate) determines the pH of a solution containing them (plasma). This buffer would be chemically most effective at its pK, a pH of 6.1, where the line is steepest and changes in the concentration of the two components would produce the smallest changes in pH. However, plasma has a pH of 7.4. This system is nevertheless a very important buffer of the blood for reasons which are explained in the section on Respiration (see p. 686).

The ratio of $[\text{HCO}_3^-]$ to $[\text{CO}_2]$ is therefore 24:1.2, i.e. 20:1. This means that if either the nominator or denominator is changed, the pH can be brought back to 7.4, when this ratio is brought back to 20:1.

Having considered the principles of buffering, we can now consider how the body deals with the *volatile* and *non-volatile* acids that are the products of metabolism. The hydrogen ions that are generated from the volatile acid H_2CO_3 , are very effectively buffered during their transit in the blood from tissues to lungs, mainly by the **haemoglobin** (protein) in the red blood cells (see p. 680). The non-volatile acids H_2SO_4 and HCl are predominantly buffered by the **bicarbonate** in plasma, which circulates combined with the major cation in plasma, Na^+ .

Thus:



These reactions are backed up by the other buffer systems of plasma, interstitial fluid, intracellular fluid and bone. The reactions that occur in extracellular fluid occur in minutes, whereas those that operate within cells, or involve bone, can take hours.

The important consequences of this buffering is that free hydrogen ions have become hydrogen atoms in water, while HCO_3^- has been removed from the plasma to produce CO_2 , which in normal individuals can be excreted from the body via the lungs. A normal acid load can therefore be buffered very effectively.

The buffering is made more efficient because even a small increase in $[\text{H}^+]$ (fall in pH) stimulates respiration via the peripheral chemoreceptors (see p. 691), so tending to reduce P_{CO_2} below normal. The buffer reactions shown above are therefore driven further to the right, reducing $[\text{H}^+]$ but at the expense of losing more HCO_3^- from plasma. In this way, the ratio $[\text{HCO}_3^-]$ to $[\text{CO}_2]$ in the Henderson-Hasselbalch equation can return to normal and the pH returns to normal.

The consequence of this is that the absolute concentration of HCO_3^- is reduced. Therefore, to ensure enough HCO_3^- to maintain acid-base balance in the future, the $[\text{HCO}_3^-]$ must be restored. This is done by the kidney. The filtered load of HCO_3^- at the kidney is very large, ~24 mmol/litre in 180 litres per day, i.e. 4320 mmol/day. Thus, not only must all of the filtered HCO_3^- be reabsorbed, but an *additional* amount must be reabsorbed equal to that lost by buffering H^+ . The reabsorption of HCO_3^- and the generation of new HCO_3^- depend upon the secretion of H^+ by the nephrons.

Bicarbonate reabsorption, hydrogen secretion and buffering

The majority (85%) of bicarbonate filtered is reabsorbed in the **proximal tubule**. The remaining 15% is reabsorbed by the **distal tubule** and **collecting duct**. (The processes involved have been described in previous chapters, and are summarized in Fig. 8.3.4, p. 739.) In both regions, bicarbonate reabsorption is linked to H^+ secretion, but in the proximal tubule, H^+ secretion mainly occurs via the Na^+/H^+ countertransporter, whereas in the later parts of the nephrons, H^+ secretion is mainly mediated by the H^+ -ATPase pump. Although the hydrogen ions are buffered in the lumen, $[\text{H}^+]$ does rise substantially; pH falls from 7.4 to about 7 in the proximal tubule and to as low as 4.5 in the collecting duct. The H^+ -ATPase in the later parts of the nephron is therefore very important in allowing H^+ to be secreted against a substantial $[\text{H}^+]$ gradient.

The H^+ that is secreted by the proximal tubule is predominantly buffered by HCO_3^- that was filtered at the glomerulus, to form H_2CO_3 . This is converted to CO_2 and H_2O in a reaction catalysed by **carbonic anhydrase** in the brush border of the luminal membrane. The CO_2 and H_2O rapidly diffuse into the cell where HCO_3^- formation is again catalysed by the action of carbonic anhydrase, and this HCO_3^- is reabsorbed into the blood. Thus, this process allows one HCO_3^- to be reabsorbed for each H^+ that is secreted.

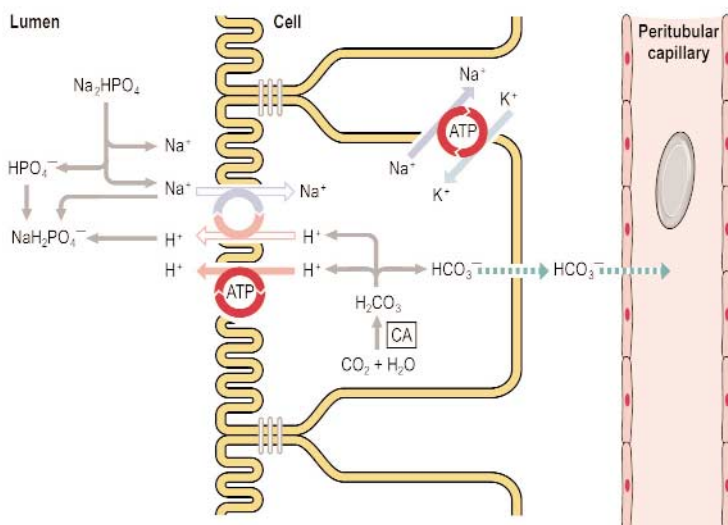


Fig. 8.7.1 Tubular fluid buffering by phosphate.

Because it is operating near its pK of 6.8, the phosphate system is chemically very efficient as a buffer in the tubular lumen and is the primary urinary buffer. However, its effect is limited by the amount of phosphate present.

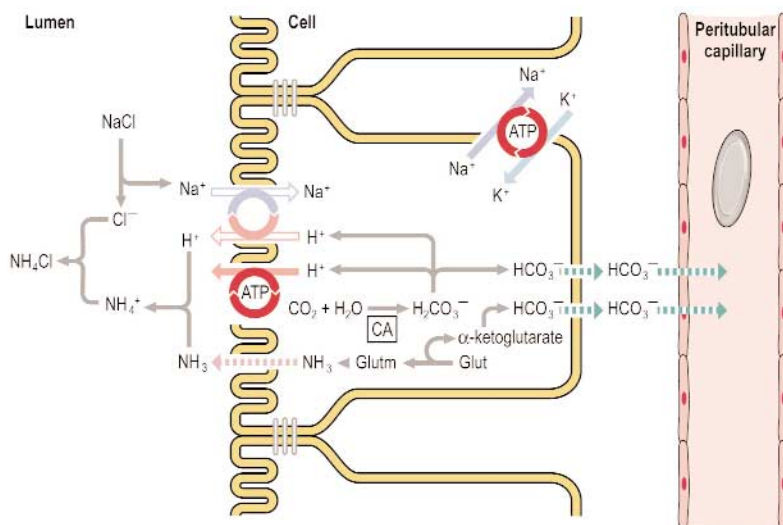


Fig. 8.7.2 Formation of NH_3 in the distal tubule.

Glutamine (Glut) is converted to α -ketoglutarate, which generates bicarbonate, and glutamic acid (Glut) with the formation of NH_3 . The NH_3 diffuses into the lumen and captures an H^+ to form NH_4^+ , which cannot diffuse back into the body. This mechanism generates HCO_3^- which enters the blood. NH_4^+ formation becomes important at low tubular pH (<6.0).

Buffers other than bicarbonate

Phosphate

H^+ that is secreted into the lumen can also be buffered by HPO_4^{2-} that is filtered at the glomerulus, so as to form H_2PO_4^- (Fig. 8.7.1). As the H^+ secreted is formed within the tubule cell from the dissociation of H_2CO_3 , this process allows additional HCO_3^- to be generated, over and above the amount that is reabsorbed from the tubule lumen as an indirect consequence of

urinary buffering by HCO_3^- . The phosphate reaction is very effective at buffering H^+ in the tubular fluid because its pK is 6.8. However, its importance is limited because the concentration of H_2PO_4^- in the filtrate is low and much of it is reabsorbed in the proximal tubule.

Ammonia

It is the production of ammonia by the kidney that is of major importance both in excreting

H^+ and in generating new bicarbonate for the plasma (Fig. 8.7.2). Ammonia is produced in the cells of the proximal and distal parts of the nephron by the conversion of **glutamine** to glutamic acid and α -ketoglutarate. The further metabolism of α -ketoglutarate generates HCO_3^- that is reabsorbed into plasma. The NH_3 diffuses out of the cell into the lumen where it combines with secreted H^+ to form NH_4^+ . The NH_4^+ is trapped in the lumen because the tubule cells are relatively impermeable to it. The excretion of NH_4^+ normally amounts to 30–50 mmol/day, so

allowing an equivalent production of HCO_3^- . During acidosis, NH_4^+ excretion can increase to over 300 mmol/day with a corresponding increase in HCO_3^- reabsorption.

Regulation of bicarbonate reabsorption and hydrogen secretion

The kidney behaves as if there is a transport maximum (T_m) for HCO_3^- excretion. This means that when plasma $[HCO_3^-]$ is normal (24 mmol/litre) or below, there is virtually no HCO_3^- in urine because it is reabsorbed, whereas when $[HCO_3^-]$ in plasma is above normal, then HCO_3^- is readily excreted.

Since HCO_3^- is dependent on H^+ secretion, as explained above, HCO_3^- reabsorption is changed by factors that change H^+ secretion. Thus the T_m for HCO_3^- can be increased, i.e. more HCO_3^- is reabsorbed when H^+ secretion is increased. When H^+ secretion decreases, the opposite occurs.

A major determinant of H^+ secretion is plasma pH. When plasma pH falls, either because of addition of H^+ or a decrease in $[HCO_3^-]$, then H^+ secretion increases (as does HCO_3^- reabsorption). This is believed to be the result of an increase in intracellular $[H^+]$, which has several effects:

- the **gradient** for H^+ excretion between tubule cell and lumen is increased with a consequent increase in Na^+-H^+ exchange via the countertransporter
- there is an increase in activity of the H^+ -ATPase **pump** owing to the insertion of new pumps in the membrane
- there is stimulation of the production of **ammonia**.

When plasma pH rises, exactly the opposite happens and H^+ secretion is decreased (as is HCO_3^- reabsorption).

Since H^+ secretion and Na^+ reabsorption are linked, H^+ secretion is affected by factors that influence Na^+ reabsorption. Thus, a decrease in



Summary

H^+ buffering in the renal tubule

- H^+ secreted into the lumen by the proximal tubule is primarily buffered by HCO_3^- that is filtered at the glomerulus. The H^+ that is secreted originates from the dissociation of H_2CO_3 within the cell. One HCO_3^- is reabsorbed for every H^+ secreted.
- H^+ secreted into the tubular lumen can also be buffered by:
 - HPO_4^{2-} that is filtered at the glomerulus, so forming $H_2PO_4^-$
 - NH_3 that is produced by the tubular cells and secreted into the lumen, so forming NH_4^+ .
- Buffering by HPO_4^{2-} and by NH_3 both allow an additional HCO_3^- ion to be generated over and above that reabsorbed as an indirect consequence of H^+ buffering by filtered HCO_3^- .
- Buffering by HPO_4^{2-} is relatively unimportant because the concentration of HPO_4^{2-} in tubular fluid is low.
- Buffering by NH_3 can become very important: in acidosis, NH_4^+ excretion can be >300 mmol/day and there is a corresponding increase in circulating HCO_3^- , which is then available to buffer plasma H^+ .

effective circulating volume, which results in an increase in Na^+ reabsorption by the proximal tubule (see Ch. 8.6), also increases H^+ secretion (and HCO_3^- reabsorption). In addition, stimulation of Na^+ reabsorption by the action of aldosterone on the distal tubule and collecting duct, increases H^+ secretion (and HCO_3^- reabsorption). This is thought to be because the reabsorption of Na^+ into the tubule cell creates a positive charge which improves the gradient for H^+ secretion into the lumen. Conversely, a decrease in Na^+ reabsorption leads to a reduction in H^+ secretion (and HCO_3^- reabsorption).

Acidosis and alkalosis can affect K^+ excretion by the kidney (see Ch. 8.4). It is also the case that changes in plasma $[\text{K}^+]$ can affect acid–base

balance, H^+ secretion (and HCO_3^- reabsorption). Thus, if plasma $[\text{K}^+]$ falls, for example as a consequence of hyperaldosteronism (see p. 442), then K^+ tends to diffuse out of cells down its concentration gradient and electroneutrality is maintained by movement of H^+ (and Na^+) into the cells. Thus, plasma pH tends to rise. In the kidney, the movement of H^+ into tubule cells increases H^+ secretion (and HCO_3^- reabsorption), so augmenting the alkalosis. An increase in plasma $[\text{K}^+]$ to above normal has the opposite effects, resulting in acidosis.

Disturbances of acid–base balance

Normal plasma pH is 7.4. Acidosis exists if arterial plasma pH is below 7.4. Alkalosis exists when pH is greater than 7.4. If the disturbance is caused by the respiratory system, it is called a **respiratory acidosis** or **respiratory alkalosis**. If it is caused by a factor other than the respiratory system, it is called a **metabolic acidosis** or **metabolic alkalosis**. In the equations:



and:

$$\text{pH} = \text{pK} + \log \frac{[\text{HCO}_3^-]}{\text{CO}_2} = \text{pK} + \log \frac{20}{1}$$

respiratory disorders primarily affect CO_2 , whereas metabolic disorders primarily affect $[\text{HCO}_3^-]$. When a change in pH occurs, the buffer systems of the body, the kidney and the respiratory system act to restore pH to normal, the respiratory system controlling CO_2 and the kidney controlling HCO_3^- .

Respiratory acidosis

This disorder is characterized by raised P_{CO_2} and reduced pH. The raised P_{CO_2} can be caused by a reduction in ventilation due to the actions of drugs such as anaesthetics and barbiturates on the respiratory neurones in the brain or to central neural lesions. More commonly it is caused by chronic bronchitis or emphysema



Summary

Regulation of HCO_3^- reabsorption and H^+ secretion

- There is an apparent T_m for HCO_3^- excretion. If plasma $[\text{HCO}_3^-]$ is normal (24 mM), HCO_3^- is reabsorbed, but when plasma $[\text{HCO}_3^-]$ is >24 mM, the excess is excreted.
- However, the T_m for HCO_3^- can be increased when H^+ secretion is increased, or decreased when H^+ secretion falls.
- H^+ secretion is dependent on plasma $[\text{H}^+]$; an increase in plasma $[\text{H}^+]$ increases H^+ secretion and vice versa.
- Since H^+ secretion and Na^+ reabsorption are linked, an increase in Na^+ reabsorption can increase H^+ secretion into the tubule.
- A decrease in plasma $[\text{K}^+]$ can also increase H^+ secretion into the tubule; K^+ diffuses out of all cells down its concentration gradient and H^+ moves in, down the electrical gradient. The movement of H^+ into the renal tubule cells leads to H^+ secretion, so augmenting the fall in plasma $[\text{H}^+]$ (and increasing plasma pH).

which impairs the removal of CO_2 from the lungs. The reaction:



is therefore shifted to the right and $[\text{H}^+]$ and $[\text{HCO}_3^-]$ rise (Fig. 8.7.3). In fact, because CO_2 diffuses easily into body cells, and because cells contain carbonic anhydrase, this reaction occurs most quickly within the cells and the $[\text{H}^+]$ of all cells including those of the kidney tends to increase. This H^+ is mainly buffered by **proteins** and HCO_3^- diffuses out, so raising plasma $[\text{HCO}_3^-]$. This occurs *within hours*, but the return of pH towards normal is limited by the efficiency of the available buffers to buffer the H^+ . This, in turn, limits the extent to which the reaction can shift to the right and limits the rise in HCO_3^- . Thus, the rise in $[\text{HCO}_3^-]$ is actually rather modest. Therefore, the ratio $[\text{HCO}_3^-]$ to

$[\text{CO}_2]$ in the Henderson–Hasselbalch equation stays less than 20, the Pco_2 remains high and, consequently, the pH is low ($[\text{H}^+]$ is high).

In the kidney, the rise in intracellular $[\text{H}^+]$ stimulates H^+ secretion and HCO_3^- reabsorption, as explained above. This provides additional HCO_3^- for the plasma, which is used to buffer the H^+ generated from CO_2 and, at the same time, additional H^+ is excreted by the kidney. The kidney can therefore compensate *over several days* for respiratory acidosis and return the pH towards normal by increasing $[\text{HCO}_3^-]$ and bringing the ratio $[\text{HCO}_3^-]$ to $[\text{CO}_2]$ closer to 20:1 (Fig. 8.7.3).

However, clearly all is not normal; the plasma $[\text{HCO}_3^-]$ was increased as a primary effect of the rise in CO_2 and has been increased further as a secondary consequence of the actions of the kidney. Thus, the other characteristic of a

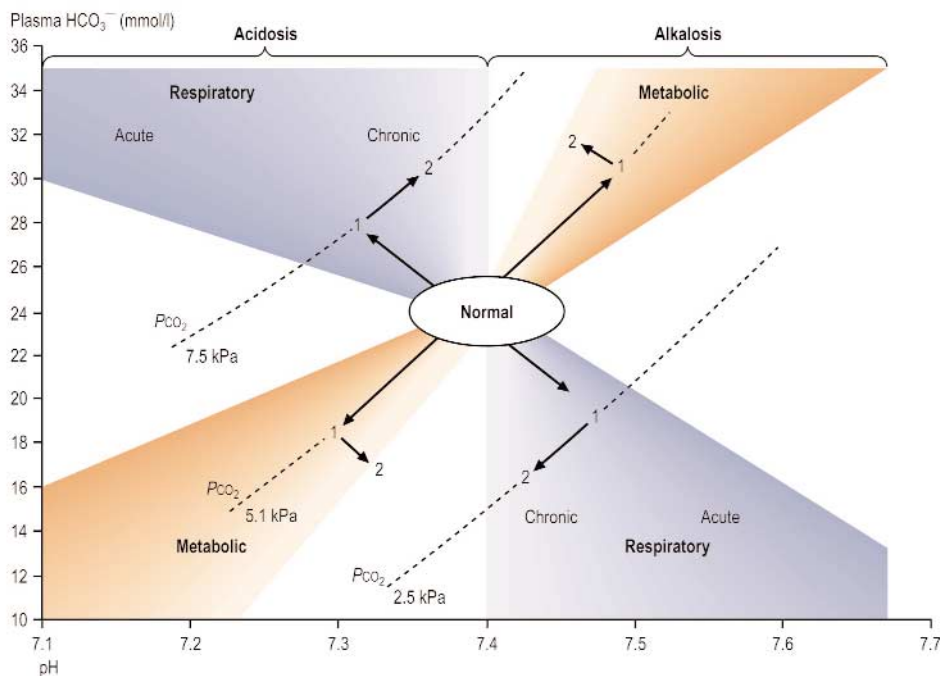


Fig. 8.7.3 Acid–base abnormalities. The relationship between plasma HCO_3^- and pH at different Pco_2 (the dotted lines) is shown in this diagram, which is sometimes known as a Davenport diagram. It allows us to illustrate what happens to the acid–base situation in respiratory disturbances (blue) and metabolic disturbances (pink). The primary disturbance moves the situation to the acute position 1. The body then *compensates* by using the intact, undisturbed, system (lungs or kidney) to restore pH to as near normal as possible – position 2.

chronic respiratory acidosis, apart from raised P_{CO_2} and reduced pH, is a raised $[\text{HCO}_3^-]$. The only way acid–base balance can be restored completely to normal is by correction of the primary respiratory disorder.

Respiratory alkalosis

This is caused by **hyperventilation** when the individual ventilates more than is necessary to remove the CO_2 generated by metabolism. Excess CO_2 is therefore ‘blown off’ and plasma P_{CO_2} falls (Fig. 8.7.3). This can be induced voluntarily (experimentally) and it can occur in anxiety states or emotional stress (hyperventilation syndrome). Hyperventilation also occurs at high altitude when respiration is stimulated by hypoxia (see p. 692).

The reaction:



is therefore shifted to the left, resulting in a decrease in $[\text{H}^+]$ and $[\text{HCO}_3^-]$. What happens is essentially the opposite of what happens in respiratory acidosis. Less CO_2 diffuses into the cells and less HCO_3^- diffuses out into the plasma so that $[\text{HCO}_3^-]$ is reduced. This fall in $[\text{HCO}_3^-]$ tends to decrease the ratio of $[\text{HCO}_3^-]$ to $[\text{CO}_2]$, but it is not sufficient to reduce it to 20:1 and the pH therefore stays high ($[\text{H}^+]$ is low). The decrease in $[\text{H}^+]$ in the tubule cells reduces H^+ secretion and decreases HCO_3^- reabsorption. Thus, over days, this renal compensation alters the ratio of $[\text{HCO}_3^-]$ to $[\text{CO}_2]$ so that it falls closer to 20:1 and the pH returns towards normal. The plasma $[\text{HCO}_3^-]$ fell as a consequence of the primary disturbance and falls again as a secondary consequence of renal compensation (Fig. 8.7.3). For the acid–base disturbance to be completely corrected, ventilation must return to normal.

Metabolic acidosis

This can occur because of the ingestion of abnormally large quantities of acids, or because

of the excess generation of acids. The latter occurs in severe **exercise** when lactic acid is produced and in diabetes when keto acids are formed. Acidosis also occurs when excess bicarbonate is lost from the gastrointestinal tract by diarrhoea and in renal failure when the kidney fails to excrete H^+ . Clearly, the reaction:



is shifted to the left if the primary change is a rise in $[\text{H}^+]$. If the primary change is a fall in $[\text{HCO}_3^-]$, then there will be less buffer available to buffer H^+ , the free $[\text{H}^+]$ rises and again the reaction shifts to the left. Thus, in all cases there is a reduction in $[\text{HCO}_3^-]$, the ratio $[\text{HCO}_3^-]$ to $[\text{CO}_2]$ falls and the pH falls ($[\text{H}^+]$ rises; Fig. 8.7.3).

Assuming there is no respiratory disorder, the rise in $[\text{H}^+]$ stimulates respiration, by acting on the peripheral chemoreceptors. Thus, more CO_2 is blown off, the reaction is driven further to the left, the P_{CO_2} falls and the $[\text{HCO}_3^-]$ falls further (Fig. 8.7.3). This **respiratory compensation** allows the pH to return towards normal because the ratio $[\text{HCO}_3^-]$ to $[\text{CO}_2]$ rises towards 20:1.

However, because the buffering and hyperventilation are not fully effective in preventing a rise in $[\text{H}^+]$, the $[\text{H}^+]$ remains raised throughout the body. In the kidney, this stimulates H^+ secretion and HCO_3^- reabsorption. Over days, the kidney (except in renal failure) may be able to correct the disturbance by excreting the excess H^+ and adding to the plasma the HCO_3^- that was lost both as a direct consequence of the primary disturbance and as a secondary consequence of the respiratory compensation. Once this has happened, plasma $[\text{H}^+]$ returns to normal and ventilation is also normalized.

Metabolic alkalosis

The most common explanation for this disturbance is the loss of H^+ from the gastrointestinal tract by **vomiting** because gastric secretions are highly acidic. It can also be induced by ingestion

of NaHCO_3 -containing, alkaline antacid indigestion mixtures. In addition, metabolic alkalosis is frequently associated with **volume depletion** because avid reabsorption of Na^+ leads to H^+ secretion and HCO_3^- reabsorption by the kidney (see above). It is also associated with **K^+ depletion** such as can be caused by hyperaldosteronism (see above).

Because metabolic acidosis can be regarded as the addition of a base (or any kind of H^+ acceptor) to the plasma, the reaction:



shifts to the right. What happens is essentially the opposite of what happens in metabolic acidosis (Fig. 8.7.3). The fall in $[\text{H}^+]$ reduces the stimulation of the peripheral chemoreceptors, ventilation is reduced and therefore less CO_2 is blown off ($[\text{CO}_2]$ rises). This **respiratory compensation** therefore drives the reaction further to the right so that more H^+ is generated and $[\text{HCO}_3^-]$ rises further (Fig. 8.7.3). Thus, pH returns towards normal because the ratio $[\text{HCO}_3^-]$ to $[\text{CO}_2]$ falls towards 20 : 1.

As in metabolic acidosis, the kidney may correct the disturbance over several days. The rise in pH (fall in $[\text{H}^+]$) in renal tubule cells reduces H^+ secretion (and HCO_3^- reabsorption) so allowing plasma $[\text{H}^+]$ to rise, reducing plasma (HCO_3^-) and finally removing the inhibitory effect on ventilation. However, it should be noted that this cannot occur in metabolic alkalosis resulting from volume depletion. In this case, HCO_3^- reabsorption (and H^+ secretion) continues in association with increased Na^+ reabsorption. The acid-base disturbance can only be corrected if the volume depletion is corrected.

Identification of acid-base disturbances

In the clinical setting, it is important not only to be able to recognize that an acid-base

Table 8.7.1 Changes in arterial blood composition in acid-base disturbances

Disturbance	pH	$[\text{HCO}_3^-]$	CO_2
Respiratory alkalosis	↑	↓	↓
Metabolic alkalosis	↑	↑	—
Respiratory acidosis	↓	↑	↑
Metabolic acidosis	↓	↓	—

Key: ↑ = above normal; ↓ = below normal; — = normal

disturbance is present, but to be able to identify the cause of the disturbance so that it can be treated appropriately. A simple key is provided in Table 8.7.1. (The degree of these changes depends on the amount of compensation that has taken place.)

The first step is to look at the plasma pH. The buffering, compensatory and corrective mechanisms described above cannot fully correct an acid-base disturbance. Therefore, the pH will still indicate the direction of the original disorder. If pH is >7.4 the disturbance is an alkalosis; if it is <7.4 , it is an acidosis.

Next the $[\text{HCO}_3^-]$ and P_{CO_2} must be studied (see Fig. 8.7.3). An uncompensated **respiratory** alkalosis would be associated with $P_{\text{CO}_2} < 40$ mmHg and $[\text{HCO}_3^-] < 24$ mM. A **metabolic** alkalosis would initially be associated with $[\text{HCO}_3^-] > 24$ mM. When renal and respiratory compensation occur for respiratory and metabolic alkalosis respectively, then the pH moves nearer to normal, but $[\text{HCO}_3^-]$ falls even further *below* normal in respiratory alkalosis, whereas $[\text{HCO}_3^-]$ rises even further *above* normal in metabolic alkalosis. Moreover, in compensated respiratory alkalosis, P_{CO_2} remains low, whereas in compensated metabolic alkalosis P_{CO_2} is high.

On the other hand, respiratory acidosis can be recognized by $P_{\text{CO}_2} > 40$ mmHg and $[\text{HCO}_3^-] > 24$ mM, the $[\text{HCO}_3^-]$ rising even

further as a consequence of renal compensation. Metabolic acidosis can be recognized by $[\text{HCO}_3^-] < 24$ mmol/litre and $P_{\text{CO}_2} < 40$ mmHg.

If the pattern of the pH, $[\text{HCO}_3^-]$ and P_{CO_2} disturbance does not correspond with one of these four categories, then a mixed disorder is present, which means that there are two or

more underlying causes for the disturbance. An example would be an individual who has chronic bronchitis with a consequent compensated respiratory acidosis who then develops a gastrointestinal infection that leads to vomiting. Metabolic alkalosis will then be superimposed upon the original disorder.



Summary

The structure and functions of the kidney

- The function of the kidneys is to regulate volume and composition of the extracellular fluid. This they do by the processes of filtration, reabsorption and secretion.
- The gross structure of the kidney is a cortex surrounding a medulla and an innermost cavity, the pelvis.
- The functional unit of the kidney is the microscopic nephron (1 million in each kidney).
- Fluid filters into the nephrons at a rate of about 180 litres/day; the vast majority is reabsorbed.
- Filtration is influenced by renal blood flow, which is subject to a high degree of autoregulation, and to control by renal nerves and the renin–angiotensin system.
- There is active reabsorption of substances from the nephron while water flows passively.
- Regulation of absorption is by endocrine factors including prostaglandins, the renin–angiotensin–aldosterone system, atrial natriuretic peptide and the antidiuretic hormone.
- The shape of the loop of Henle enables a process called countercurrent multiplication to produce a hyperosmotic extracellular fluid in the medulla. This is reinforced by movement of urea.
- The kidneys excrete the fixed acids formed and absorbed by the body.
- They control the acid–base balance of the body by reabsorbing bicarbonate, secreting hydrogen ions and forming ammonia at variable rates.
- In disturbances of acid–base balance, the kidneys and lungs act together to restore normality.

Recent Advances

Recombinant erythropoietin and its use in renal failure

Renal failure is characterized by a substantial reduction in GFR, usually to less than 20% of normal, which results in an increase in plasma concentrations of urea and creatinine, substances that are normally cleared by the kidney. Approximately 8000 people die annually in the UK of chronic renal failure and almost 40% of them are in the prime of life. The most common causes of chronic renal failure are diabetes, atherosclerosis that affects the renal artery and damage to the glomeruli secondary to infections of the urinary tract and to congenital renal abnormalities such as polycystic kidney disease. In all cases the number of functioning glomeruli is reduced. This eventually results in an inability to regulate electrolytes and water balance and to excrete organic solutes that include not only urea and creatinine which are non-toxic, but other protein metabolites that are toxic. Thus, oedema, low plasma sodium, high plasma potassium and phosphate, and metabolic acidosis are generally present in patients with untreated renal failure. Dialysis can be used very effectively to remove fluid, regulate electrolyte balance and remove organic solutes, providing the patient is also willing to control the dietary intake of fluid, protein and certain ions. However, even when these factors are well controlled, patients with renal failure are still likely to develop bone disease as a consequence of reduced production of calcitriol, and anaemia as a consequence of reduced production of erythropoietin (EPO) by the kidney.

In the 1980s the gene for EPO was identified on chromosome 7 and, since 1986, human recombinant EPO has been available and has been used increasingly in the treatment of patients with renal failure. It would not be an

exaggeration to state that the recombinant EPO has revolutionized the management of these patients. Indeed, it has become apparent that anaemia, rather than a build-up of toxins, is largely responsible for their general feeling of malaise, muscle weakness and fatigability, cold intolerance, mental sluggishness and loss of appetite. Treatment with EPO not only greatly improves their quality of life, but reduces their tendency to develop left ventricular hypertrophy, a secondary consequence of anaemia that is an independent risk factor for early death.

In parallel with the use of recombinant EPO, our understanding of the synthesis and actions of EPO has been greatly improved by extensive studies on laboratory animals and human tissues, some of which have involved the techniques of molecular biology. The site of production of EPO had been elusive, but it has become clear that the mRNA for EPO is present in the interstitial cells of the renal cortex, near the basal membrane of the proximal tubule cells. Since the proximal tubule cells have a very high O_2 consumption associated with their active transport mechanisms, they are in an ideal position to sense a reduction in O_2 availability. It seems that the O_2 sensor is a haem-containing protein. A reduction in local P_{O_2} causes a conformational change in the haem protein in much the same way as the haem moiety of haemoglobin in the red blood cell is changed when O_2 is given up by haemoglobin. The conformational change in turn causes the production of a protein named hypoxia-inducible factor (HIF), which increases the rate of transcription of the EPO gene, thereby increasing the synthesis of EPO. EPO has been shown to act, via a specific transmembrane receptor, on the progenitor cells of the bone marrow to potentiate their proliferation, and to be

Recent Advances (Continued)

essential for the transformation of progenitor cells into precursor cells. The proliferation and maturation of these cells into erythrocytes is apparently not dependent on EPO.

Therefore, it is clear that in individuals with normal renal function, the kidney plays a pivotal role in determining the O_2 supply to all body tissues. The synthesis of EPO by the kidney is dependent on the supply of O_2 to the kidney, which is itself dependent on the haematocrit as well as on the arterial P_{O_2} . In a normal individual, plasma EPO levels are high enough to keep the haematocrit stable and within the normal range, and EPO synthesis by kidney is increased in anaemia, following haemorrhage and in systemic hypoxia such as occurs in respiratory disease and at high altitude. EPO is also produced by macrophages and the liver, but this extrarenal production contributes less than 20% of the total and cannot compensate for loss of renal production in renal failure.

In fact, many studies have shown that in patients with renal failure there may be such a gross impairment of O_2 sensing and EPO production that the haematocrit is less than 30%

of normal and EPO production fails to show the normal increase in response to acute exacerbation of the anaemic hypoxia. In such patients, administration of human recombinant EPO produces a dose-dependent increase in the plasma concentration of EPO and in the haematocrit, but the sensitivity of this relationship varies between individuals. The cause of this variability has not yet been established; it may be that varying concentrations of an inhibitor of EPO are present in different individuals. The only serious complication associated with the use of EPO is the development of arterial hypertension, which has been reported in about 30% of individuals in some clinical studies. This is thought to be associated with the increase in blood viscosity that results from the increase in haematocrit. It seems that this can be avoided if the upper target for the haematocrit is limited to 30–35% and providing fluid gain is well controlled between periods of analysis. The patient then receives the benefits of amelioration of the anaemia without incurring the risks of hypertension.

Urine collection and micturition



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Passage of urine from kidney to bladder

Urine passes from the collecting ducts of the renal tubules into the renal **pelvis**. Contraction of the smooth muscle of the pelvis aids the movement of urine into the **ureter**. When distended, the smooth muscle of the ureter, which is arranged circularly, contracts. This contraction closes the junction between the pelvis and the ureter and pushes urine further into the ureter, causing distension and subsequent contraction of the next section of the ureter, and so on. Thus a peristaltic wave is initiated, which propagates along the length of the ureter and propels urine into the **bladder**. Peristaltic waves are initiated about five times per minute from the renal pelvis.

Each ureter joins the bladder at an oblique angle, passing between the epithelium and smooth muscle for a short distance before it opens into the bladder. This arrangement helps to ensure that when pressure within the bladder rises, the ureters are compressed, so preventing reflux of urine up into the ureters. If the ureter is blocked by a kidney stone, then the pressure in the ureter rises sharply because of continuing peristaltic contraction. This causes considerable pain (renal colic) but may help to dislodge the stone and push it into the bladder.



Summary

Passage of urine from kidney to bladder

- Urine passes from the renal pelvis into the ureters, aided by contraction of the smooth muscle of the pelvis.
- Contraction of the smooth muscle of the distended ureter initiates a wave of peristalsis that propels urine into the bladder.
- When pressure within the bladder rises, reflux of urine is prevented by pressure on the ureters as they pass through the bladder wall.

Micturition

Micturition is the act of emptying the urinary bladder – urination. Urine is formed continuously at a rate of about 1 ml per minute in normally hydrated subjects. It is stored and released, by adult humans, when it is socially acceptable and convenient to do so. Storage and controlled release is the function of the urinary bladder and its associated sphincters.

The bladder

The bladder lies in the pelvis, below the peritoneum. The bladder can be almost empty or contain up to 400 ml without much increase in pressure (Fig. 8.8.1). This feature is a result of its structure. Because the bladder is essentially spherical, the relationship between pressure in the bladder, its radius and wall tension follows the law of Laplace (see p. 658) which states that lumen pressure is equal to twice the wall tension divided by the radius. Thus, even though the wall tension may increase as the bladder fills, so does the radius and the increase in

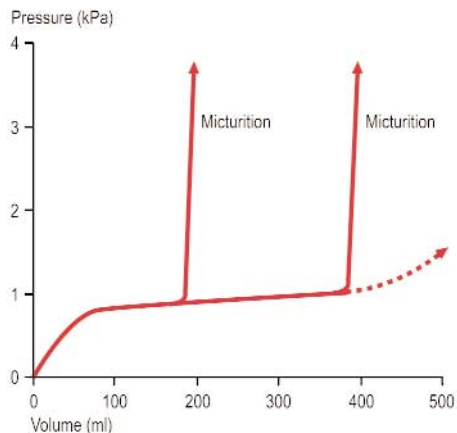


Fig. 8.8.1 Pressure changes in the bladder. Pressure increases a little on initial filling from empty. However, filling from 50–400 ml occurs with very little increase in pressure. When micturition occurs, from a small or larger bladder volume, pressure rises very steeply; the dotted line shows the pressure change that would have occurred, had micturition not happened.

lumen pressure is small, at least until bladder volume becomes large. Importantly, the mucosal lining of the bladder is **transitional epithelium**, well capable of stretch without damage, and thrown into ridges that flatten out as the bladder fills. This epithelium has unique properties: it is very impermeable to salts and water, which means that there is no exchange between the urine and the capillaries of the bladder wall.

The muscle coat around the lining epithelium is made up of bundles of smooth muscle, interlacing, running in all directions and stimulated to contract by **parasympathetic** fibres that run in the pelvic nerves. These layers of muscle are best considered as a single structure, the **detrusor muscle**. The mucosal lining is generally loosely attached to the underlying muscle, except at the base of the bladder where the entrance of the two ureters and the exit of the urethra form a triangle – the **trigone** – where the mucosa is firmly attached. This forms the

thickest and least distensible part of the bladder. The outlet of the bladder into the urethra is guarded by two sphincters: internal and external.

The internal sphincter

The internal sphincter is formed by a loop of muscle that is an extension of the detrusor muscle: it is not under voluntary control. When the detrusor muscle contracts, the fibres forming this loop shorten, so shortening and widening the proximal part of the urethra and opening the sphincter.

The external sphincter

The external sphincter, which is composed of skeletal muscle, is continuous with the **levator ani**: it is under conscious, voluntary control by somatic motor nerves that run in the **pudendal nerve**. These muscles are kept contracted by tonic stimulation from the brain and they are responsible for continence. In women, the structures round this neck are the end of the system and the point of exit of urine from the body. The external sphincter muscle is rather poorly developed and women are more prone to become incontinent, particularly after childbirth. In men, the urethra continues through the penis: urine remaining in the urethra can be expelled by contractions of the bulbocavernosus muscle. These different arrangements mean that men and women tend to develop different pathologies (see below).

Filling and emptying

The muscular wall of the bladder contains **stretch receptors** that measure tension and transmit the sensation of fullness to the spinal cord via the pelvic nerves; from there the information is transmitted to the brain. Filling of the bladder excites the stretch receptors, increasing the afferent activity in the pelvic nerve and causing a reflex increase in the activity of the

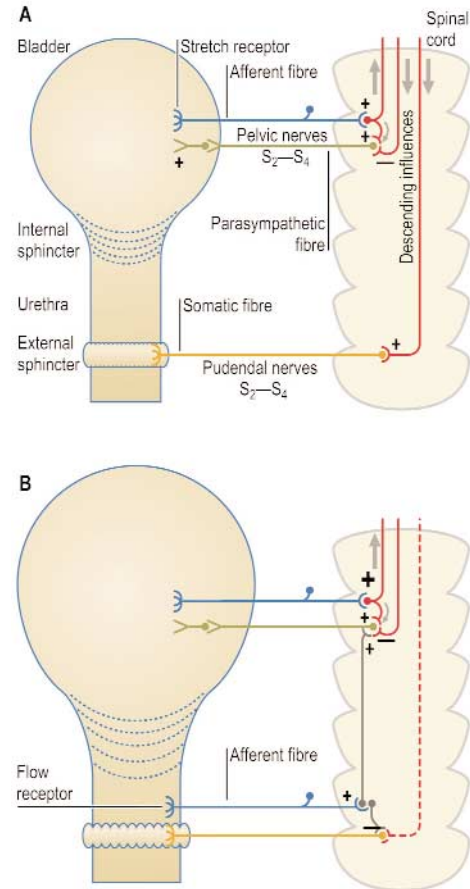


Fig. 8.8.2 Micturition. A. During filling, the descending inhibitory influence on the parasympathetic supply to the detrusor muscle and the descending excitatory influence on the somatic supply to the external sphincter *inhibit* micturition (- and + signs indicate inhibitory and excitatory influences respectively). B. During emptying, *activation* of the parasympathetic supply to the detrusor muscle causes its contraction, and *removal* of the tonic excitatory influence on the somatic supply to the external sphincter causes its opening. Emptying of the bladder is facilitated by the input from the flow receptors in the urethra, which reinforces the contraction of the detrusor muscle and the relaxation of the external sphincter.

parasympathetic fibres in the pelvic nerve. This, in turn, causes contraction of the detrusor muscle and micturition. The sensitivity of this reflex is determined by descending influences from the brain (Fig. 8.8.2A). There is a dominant

tonic inhibitory influence over this reflex such that the bladder is allowed to fill until it contains ~300 ml, even though the person becomes aware of fullness at ~150 ml. When it is socially convenient, the process of micturition can be initiated voluntarily. This can be done at all bladder volumes up to ~600 ml: at this volume, bladder fullness causes the sensation of pain and emptying becomes imperative.

At the onset of micturition the parasympathetic activity increases, the detrusor muscle contracts, the bladder pressure increases, the internal sphincter opens and urine passes through the internal sphincter into the urethra (see Fig. 8.8.2B). This movement of urine stimulates **flow receptors** in the wall of the urethra which have afferent nerve fibres in the pudendal nerves. This afferent activity reinforces the excitation of the parasympathetic neurones that supply the detrusor muscle. It should also be noted that the increase in bladder pressure that results from detrusor muscle contraction increases the tension in the wall, so stimulating the stretch receptors and reinforcing the reflex. Thus, a positive-feedback cycle develops that maintains the contraction of the detrusor muscle.

The afferent activity from the flow receptors also exerts an inhibitory influence over the **somatic neurones** that supply the external sphincter and the strong descending voluntary control over these neurones is also removed (Fig. 8.8.2B). Thus, the external sphincter opens and urine is forced out of the body. Once initiated, micturition normally proceeds until the bladder is emptied. The process is aided by contraction of the abdominal muscles and lowering of the diaphragm. However, micturition can be halted, particularly in men, by voluntary contraction of the external sphincter. This is followed by inhibition of the reflex contraction of the detrusor muscle.

The detrusor muscle also receives a sympathetic nerve supply that originates in the upper lumbar segments of the spinal cord and is carried to the bladder in the **hypogastric nerve**. Stimulation of these fibres causes relaxation of the detrusor muscle and because the internal sphincter is formed by an extension of the detrusor muscle (see above) they also tend to close this sphincter. These fibres may exert a tonic inhibitory influence upon the detrusor muscle that facilitates bladder filling. However, they play no part in micturition. It is thought that they are activated during **ejaculation**: the sympathetic fibres that supply the seminal vesicles and vas deferens via the hypogastric nerves are activated, so propelling semen into the urethra, and the activation of the sympathetic fibres that supply the detrusor muscle closes the internal sphincter, preventing semen from entering the bladder.

Voluntary control of urination normally develops over the first few years of life when the child learns to control the external sphincter and levator muscles. It is thought that voluntary initiation of micturition involves relaxation of the levator ani and external sphincter muscles. Because contraction of these muscles not only closes the external sphincter but compresses the ureters towards the bladder, their relaxation allows the pelvic floor to drop and causes a downward tug on the urethra and bladder. This additional stretch on the detrusor muscle is sufficient to cause reflex contraction of the detrusor muscle via the parasympathetic nerves. This process may be aided by voluntary contraction of the diaphragm and abdominal muscles, which helps to increase the pressure in the bladder.

Disruption of the descending influences or of the pathways involved in the spinal reflexes disturbs normal micturition, for example following spinal transection (see Clinical Example).



Summary

Micturition

- Emptying the bladder (micturition) is a reflex process, which is usually under conscious control.
- The bladder distends as urine flows into it but because of its structure the increase in lumen pressure is small until bladder volume becomes large.
- Micturition can be initiated voluntarily up to bladder volumes of ~600 ml, above which emptying becomes imperative.
- Stretch receptors in the bladder wall are stimulated by distension of the bladder and cause it to contract via a spinal reflex and activation of the parasympathetic supply to the detrusor muscle. This increases pressure in the bladder and the internal sphincter opens.
- Concomitantly the inhibitory influence from the brain over the somatic nerves that contract the external sphincter is removed, allowing urine to pass through into the urethra.
- Stimulation by the urine of flow receptors in the urethral wall provides input that reinforces contraction of the bladder and relaxation of the external sphincter.
- The process of micturition is aided by contraction of the abdominal muscles and lowering of the diaphragm.



Clinical Example

Bladder function in the paraplegic patient

Acute paraplegia results from severing of the spinal cord, often in the lower cervical region, owing to a diving, sporting or road traffic injury. For reasons which are not clear, the sudden withdrawal of an input from the brain causes the spinal reflexes to fail, typically for several weeks, so there is an early *spinal shock* and a later *brisk reflex* stage. Bladder emptying is a spinal stretch reflex and behaves like other such reflexes (e.g. knee and ankle jerks) in the paraplegic patient.

Failure, in the spinal shock phase, of the bladder emptying reflex, whose coordinating centre lies in the sacral spinal cord, means that stretching of the bladder as it fills with urine fails to elicit reflex emptying. Without intervention,

the bladder would continue to distend until overfilling resulted in a slow trickle of urine (overflow incontinence). Constant overdistension for several weeks would lead to damage to the bladder and, to avoid this, a tube (bladder catheter) is passed into it so that drainage can take place and overdistension is avoided.

In the recovery phase after the spinal shock phase, the spinal reflexes, including bladder emptying, return. For the bladder this means that input to the sacral segments of the spinal cord from stretch receptors in the bladder wall leads to reflex activation of coordinated bladder emptying. This is brought about mainly by parasympathetic nerves activating the detrusor muscle of the bladder, with accompanying relaxation of the sphincter muscles.

Clinical Example *(Continued)*

Because of the severing of connections between the brain and the sacral cord, the patient is unaware of the state of the bladder and cannot by volition alone initiate or inhibit micturition. The micturition reflex is now autonomous, with the sacral cord behaving as a small accessory brain, sensing filling of the bladder and deciding when it is to be emptied.

This state of affairs provides satisfactory emptying of the bladder but the time of emptying cannot be predicted with any accuracy. To avoid incontinence, the patient needs a method of initiating the reflex at an appropriate time. This can be provided in several ways. At an appropriate interval from the last emptying, when the bladder can be expected to be approaching the threshold volume for automatic emptying, the patient may be

able to apply pressure to the abdomen to raise bladder pressure and trigger the micturition reflex by stretching the bladder wall. Alternatively, this may be done by an attendant, and the reflex can sometimes also be elicited by stimulation of the perineal area or adjoining thigh.

Another reflex which is centred in the sacral spinal cord and behaves similarly in the paraplegic patient is the defecation reflex. In the spinal shock phase the reflex is lost so that the rectum would distend and eventually semisolid faeces would leak out (faecal incontinence). The solution at this stage is to wash out the rectum regularly by using an enema. Later on, automatic emptying develops and the aim is to develop strategies to ensure that this occurs at a convenient time.

The prostate

The differences in structure between the urinary tracts of men and women result in different incidence of pathologies. Women have much shorter urethras than men and are therefore much more susceptible to bacterial invasion of the bladder. In men, the urethra penetrates the **prostate gland**, which in about half the men over 60 undergoes **benign hyperplasia**. This enlargement only presents a problem when the prostate compresses the urethra

to such a degree that the bladder cannot empty properly. In the early stages, the detrusor muscle hypertrophies, so helping to force urine out against the increased resistance. As the condition progresses, the discomfort of a constantly overfilled bladder and the damage to bladder and kidneys that retention can cause require treatment of the condition. This can be by drugs that shrink the prostate by interrupting the action of hormones that stimulate it or by surgical removal of the gland.



Renal failure

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Introduction – patterns and causes

Renal failure is present when the normal functions of the kidneys, e.g. regulation of the extracellular levels of electrolytes and waste products, are shown to be quantitatively deficient. Often the first indication is a raised blood level of urea and creatinine. For precise diagnosis, the blood creatinine level and the 24-hour creatinine excretion can be combined to measure creatinine clearance and hence demonstrate a *reduced glomerular filtration rate*. (Clearance = [urinary concentration] × [urinary flow ml/min] / [plasma concentration].)

Renal failure is described in terms of its time-course and cause. *Acute renal failure* manifests itself in the course of days, and sometimes is recognized within hours, as when a patient fails to pass any urine (anuria) postoperatively owing to complete loss of renal function as a result of processes operating during the anaesthetic and surgery. It may show rapid recovery when a treatable cause is addressed. *Chronic renal failure* in contrast often unfolds over a period of months or years. Causes of renal failure can be grouped as prerenal, renal and postrenal, referring to the flow of fluid from the circulation, through the kidneys and from the kidneys into the lower renal tract.

Prerenal renal failure

This is due to a failure of renal perfusion. The normal resting renal blood flow of about a fifth of the cardiac output

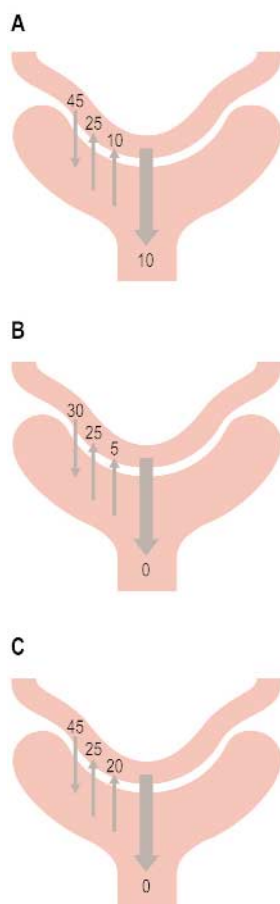


Fig. 8.9.1 Forces determining glomerular filtration, and mechanisms of pre- and postrenal renal failure. **A.** The pressures involved in glomerular filtration are from left to right, glomerular capillary hydrostatic pressure (P_{GC}) and the opposing plasma oncotic pressure (π_{GC}) and Bowman's capsular hydrostatic pressure (P_{BC}). The net filtration pressure (broad arrow) equals $45 - (25 + 10) = 10$ mmHg. **B.** A fall in glomerular capillary hydrostatic pressure results in a zero filtration pressure and cessation of filtration. **C.** A rise in Bowman's capsular hydrostatic pressure results in a zero filtration pressure and abolishes filtration.

provides an important buffer to protect the vital cerebral and coronary circulations in times of circulatory stress. Thus, when a patient suffers a serious haemorrhage, e.g. 20% of the blood volume, non-vital circulations are reduced by the vasoconstrictor action of sympathetic nerves. Such vasoconstriction takes place in the skin initially and as the situation deteriorates, i.e. the blood volume continues to decrease, the vasoconstriction spreads to the viscera, including the kidneys.

The combination of a fall in general arterial pressure and compensatory vasoconstriction of the renal resistance vessels (glomerular afferent arterioles) leads to a fall in glomerular capillary hydrostatic pressure (P_{GC}), so that eventually it no longer exceeds the combined opposing pressures of the plasma oncotic pressure (π_{GC}) and the hydrostatic pressure in the Bowman's capsule (P_{BC}). Filtration and formation of urine then cease (Fig. 8.9.1B).

'Renal' renal failure

Here the cause of the renal failure lies within the kidneys themselves. Firstly, following on from the prerenal circulatory cause just mentioned, an even more severe failure of the renal circulation may, in addition to abolishing the filtration pressure gradient, lead to a blood flow so low that it is

inadequate for the metabolic needs of the renal cells. This typically leads to serious damage or death (necrosis) of the highly active renal tubular cells (acute tubular necrosis) and hence acute (potentially reversible) renal failure.

A great variety of diseases can lead to gradual destruction of the kidneys. These include infectious and other inflammatory causes, the deposition of toxic material and in some cases overstretching when there is raised pressure due to obstruction of the urinary tract (this overlaps with the postrenal renal failure considered below). The end result of all these varied diseases is that the normal finely structured architecture of the kidney, on which normal function relies, is replaced by tiny scarred organs, or by abnormal material, or by thin-walled expanded sacs. Since structure and function are complexly and intimately related in the kidneys, it is not surprising that these abnormal organs steadily decline in their capacity to maintain homeostasis of the body fluids and eventually become worse than useless. Removal is often carried out when the kidneys are actually harming the body, e.g. by causing hypertension.

Postrenal renal failure

In this case the cause of the problem lies distal to the kidneys. Obstruction to the

renal tract can occur in one ureter and lead to loss of function of the corresponding kidney, but to cause renal failure, both kidneys must be affected, so the obstruction is usually in the urethra. Most commonly this is in the male and due to obstruction by an enlarged prostate gland. In this case (Fig. 8.9.1C), glomerular filtration is reduced and eventually abolished by back pressure which elevates the glomerular capsular pressure to cancel out the normal reserve of the glomerular capillary pressure over the opposing plasma protein oncotic pressure. At this stage renal failure develops, but if the obstruction is promptly relieved the kidneys may recover.

Effects

The effects of renal failure are due to impairment of the range of normal functions, which can be grouped under the headings: (a) fluid and electrolyte balance; (b) excretion; and (c) endocrine functions. The distinction between (a) and (b) is that balance is maintained by great variation in the amounts of various substances lost in the urine, whereas excretion refers particularly to unwanted substances which, as far as possible, are totally eliminated from the body.

Failure of fluid and electrolyte balance

Balance is maintained in terms of sodium chloride, which determines extracellular fluid volume, osmolality, which determines total body water, potassium, and hydrogen ions (acid–base balance).

Sodium chloride

Sodium chloride has been called the skeleton of the extracellular fluid. The reason is that its ions constitute the great bulk of the dissolved particles in extracellular fluid. Osmoregulation will determine that these ions are dissolved in an appropriate volume of water, thereby determining extracellular fluid volume. Extracellular fluid volume tends to rise in renal failure because most people take more salt than they need in their diet and the kidney can no longer excrete the surplus. The extracellular volume may increase until the body is seriously waterlogged, with massive dependent oedema and the risk of circulatory overload (blood plasma volume rises and falls with extracellular volume) and fatal pulmonary oedema. Less commonly, the body may lose extracellular fluid, e.g. with diarrhoea or vomiting, and in this case the kidney may make matters worse by failing to conserve salt.

Osmolality

Osmolality of the urine varies widely in the healthy young adult – from around four times the normal body value of 285 mOsm/kg H₂O to around one-third of this (Fig. 8.9.2). The negative feedback system involved has detectors in the region of the hypothalamus. When extracellular osmolality rises, e.g. by the ingestion of salt in the diet, water is drawn out of the detector cells, which shrink. Signals are sent from the hypothalamus down the axons of the pituitary stalk and vasopressin (antidiuretic hormone) is released from the posterior pituitary into the circulation. This acts on the cells of the renal collecting ducts to induce water channels so that most of the water remaining in the glomerular filtrate is reabsorbed owing to the increasing osmolality of the interstitium of the renal medulla as the collecting ducts pass towards the renal pelvis.

In renal failure the whole architecture of the kidney is damaged so that the delicate structure with its countercurrent mechanism, which allows water reabsorption, steadily falls in efficiency. The cells that create the osmotic gradient from renal cortex (osmolality around 300 mOsm/kg H₂O) to inner medulla (around 1200 mOsm/kg H₂O) and that lead to a filtrate osmolality of around 100 mOsm/kg H₂O as

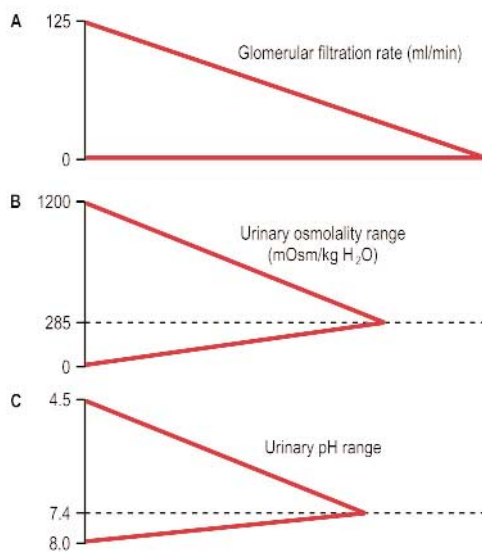


Fig. 8.9.2 Progression of renal failure. The condition worsens from left to right as shown by the decline in the glomerular filtration rate. Meanwhile, the ability to vary urinary composition declines (over a 12-range for osmolality). Eventually, urine of constant tonicity cannot correct errors in body fluid osmolality. The same applies to the ability to produce strongly acid or alkaline urine. The initial values would apply to a healthy young adult.

the fluid leaves the distal convoluted tubules and enters the collecting ducts, decrease in number and the essential structure is disrupted. The remaining nephrons have no power to modify the osmolality of their contents from that of the filtrate so the urine has a fixed osmolality similar to that of the body fluids. Figure 8.9.2B indicates this situation where, as renal failure progresses, the range of urinary osmolality contracts, so that eventually the urine is of fixed composition ('isosthenuria' or 'same strength urine') and cannot correct disturbances in body osmolality.

Potassium

Potassium is normally secreted in the urine in accordance with body needs, by a pump which exchanges absorbed sodium for secreted potassium or hydrogen ions. As the system fails, the body is at the mercy of the amount of ingested ion for its content of that ion. Potentially, either deficiency or excess of potassium could result, but in practice an excess of potassium is much more common, especially in diets which restrict salt and protein in order to minimize accumulation of salt and the toxic products of protein. Potassium can rise quickly,

particularly if there is breakdown of body cells as in acute renal tubular necrosis due to ischaemia. Major cardiac problems are a serious risk and are often preceded by increasingly high T waves in the electrocardiogram.

Hydrogen ions

Hydrogen ion accumulation is one of the most serious problems of renal failure. The degree of accumulation approaches that in diabetic ketoacidosis. In both these examples of non-respiratory acidosis, or *metabolic acidosis*, involuntary hyperventilation (Kussmaul respiration) provides *respiratory compensation*, which limits the fall in pH (see Fig. 8.7.3, p. 776). The Henderson–Hasselbalch relationship indicates that hydrogen ion content is proportional to the ratio: [carbon dioxide concentration]/[bicarbonate ion concentration]. Hydrogen ion accumulation reduces the bicarbonate concentration because of buffering. Reducing the carbon dioxide concentration then helps to restore the ratio, and hence the hydrogen ion concentration, to normal. However, despite this compensation, in severe renal failure, a seriously low pH contributes to coma and death. Figure 8.9.2C indicates how the ability to vary urinary pH is lost as renal failure progresses. Remember that the normal

range of pH (4.5–8) indicates a variation in hydrogen ion excretion of about 3000-fold. In addition, the normal kidney has the ability (again lost in renal failure) to synthesize and secrete ammonia to buffer secreted hydrogen ions.

Failure of excretion

Many toxins are steadily cleared from the body by mechanisms that transport them into the tubular fluid, similarly but in the reverse direction to the transport of glucose out of the tubular fluid. Like the glucose transport mechanism, they have a tubular maximum above which no more can be excreted, but in normal life there is considerable reserve. However, as renal tissue is lost, the capacity to excrete falls below the required level and the toxins accumulate. Many of these toxins are protein-related. The major protein excretory product urea, is not, however, a major toxin. Infusions of urea which raise the level well above normal do not harm normal people, though an osmotic diuresis is likely to be produced as the urea molecules retain water in the tubular fluid. Thus it is assumed that other protein-derived toxins (not fully defined) are responsible for the depression of body function, including drowsiness and impairment of consciousness, associated with renal failure.

Such effects are reduced by restricting protein intake, which also reduces the acid residue of metabolized proteins.

An important consequence of failure of secretion is that *drugs* may accumulate excessively in the body. When a patient with severe renal failure is given the normal daily dose of, for example, antibiotics, the levels may build up over a few days to seriously toxic levels. This can be allowed for if the glomerular filtration rate is known. If it is half normal, then the clearance of the drug will be around half normal; if filtration rate is a quarter normal, then clearance will be correspondingly slowed. A normal loading dose can be given for prompt action and the maintenance dose is reduced in relation to the glomerular filtration rate. This applies to drugs whose elimination is mainly or entirely due to renal excretion. The situation is different for drugs whose elimination is due mainly to metabolic breakdown, e.g. morphine in the liver.

Failure of endocrine functions

Major endocrine functions of the kidney include control of red cell formation via erythropoietin and control of arterial blood pressure via the renin–angiotensin system. Renal failure can lead to anaemia and hypertension.

Anaemia

Anaemia in renal failure, particularly severe renal failure, is related mainly to deficiency of *erythropoietin*. This is evidenced by the dramatic improvement in anaemia in these patients when they are given the hormone therapeutically (a currently very expensive form of treatment produced by genetically modified bacteria, see Recent Advances, p. 780). Erythropoietin is believed to be formed in the renal cortex, in metabolically very active cells able to sense the hypoxia due to anaemia (or arterial desaturation, see p. 693). The patient with renal failure produces less and less of the hormone and in some cases the haemoglobin level falls well below half normal. Treatment with erythropoietin can then double the red blood cell and haemoglobin level, greatly increasing the potential for physical activity by doubling the total available oxygen in the circulation. In fact care has to be taken to avoid the red blood cell concentration becoming too high, as this can increase the risk of vascular occlusion.

Hypertension

Hypertension has long been recognized as a complication of renal disease, including renal failure. The mechanisms involved are complex and have been studied for many decades

without complete elucidation. However, major causes are likely to be secretion of inappropriately large amounts of renin and inability to excrete adequate amounts of salt and water. Particularly in early renal failure, parts of the kidney may suffer from inadequate circulation (ischaemia) and secrete *renin* from the juxtaglomerular cells. The renin activates a circulating peptide to angiotensin I and this is converted in the circulation, particularly the pulmonary capillaries, to angiotensin II with its dual actions of vasoconstriction and stimulation of the salt- and water-retaining hormone aldosterone from the zona glomerulosa of the adrenal cortex. This would account for the hypertension in early renal failure. Later in renal failure, retention of salt and water probably plays a role – the patient's blood pressure can be reduced during dialysis by the removal of salt and water from the circulation.

Investigations

The diagnosis of renal failure may be suggested in a number of clinical situations, e.g. failure to pass urine postoperatively, or gradual development of weakness and drowsiness in someone with recurrent urinary infections. Biochemical studies, however are needed for confirmation.

Quantitative confirmation of failure and assessment of its severity are obtained by measuring the glomerular filtration rate. While inulin clearance is regarded as the gold standard, *creatinine clearance* is also useful and is much easier to measure. Instead of requiring infusion of inulin, use is made of a naturally occurring blood component and clearance can be measured by combining the plasma creatinine level (measured routinely) with measurement of the volume and creatinine level in a 24-hour collection of urine. Glomerular filtration rate equals creatinine clearance, which equals $[\text{urinary creatinine concentration}] \times [\text{urinary volume/minute}] / [\text{plasma creatinine concentration}]$. The average adult value is around 120–150 ml/minute, so a value below 100 suggests possible early impairment, a value below 50 definite failure and a value around 5–10 ml/minute indicates severe failure, requiring dialysis. Normal values, like lung volumes, vary with body size, sex and age, with much smaller values in infants and young children. As usual, *serial measurements* are particularly helpful in deciding whether the condition is getting worse or improving.

Once the diagnosis is established, and particularly in severe failure, details of the

condition and guidance to treatment can be obtained from plasma measurements of various electrolytes, including sodium and potassium, together with acid–base assessment by measuring arterial blood pH and blood gases, and bicarbonate levels. Haemoglobin levels will indicate whether anaemia is present, and, if so, its severity. In appropriate cases, X-ray studies may be used to detect abnormalities of the kidneys. If required, the function of each kidney can be assessed separately by collecting its urine from a ureteric catheter and measuring creatinine clearance.

Finally, a simple but fundamental test, not often used in view of more precise measurements, is to assess the *range of urinary concentration*. This can be done by depriving a person of fluids for up to 24 hours to assess maximal concentration (normally sparse dark-yellow urine with a high specific gravity, around 1.030 or more, and an osmolality around 1000 mOsm/kg H₂O) and then obtaining a urinary sample when the person has taken a surplus litre of fluid when already fully hydrated, to assess minimal concentration (copious clear urine with a specific gravity around 1.001 and an osmolality around 100 mOsm/kg H₂O). In everyday life we can observe these variations. Someone

whose urine varies from deep yellow to clear is unlikely to have renal failure, lying well to the left in Figure 8.9.2.

Treatment

Treatment can be in four forms:

- conservative
- haemodialysis
- peritoneal dialysis
- renal transplantation.

These treatments deal with the problem in very different ways.

Conservative treatment

This refers to the adjustment of food and fluid intake to minimize the load on the kidneys. Because protein provides the bulk of dietary toxins, it is restricted to around a quarter of normal. Because the patient's energy requirements must be met to prevent breakdown of the tissues (releasing amino acids) the carbohydrate and fat content must be fairly high. Fluids should be adjusted to balance the patient's urinary output, and electrolytes adjusted according to the plasma levels. Usually this means a low sodium content. Overall this diet is difficult to maintain, unpalatable and of limited effectiveness, but the general principles are applied, in a rather more relaxed manner, during long-term dialysis as a back-up to this therapy.

Haemodialysis

Introduction of this treatment has dramatically extended life in patients with severe renal failure. The principle is simple. The patient's blood is withdrawn from the circulation and passed through tubing surrounded by a dialysate fluid. The tubing is permeable to water and to the smaller particles in the blood, including ions, glucose, urea and creatinine, but the tubing does not allow plasma proteins and cellular elements to be lost from the blood. The dialysate fluid is free of unwanted items such as urea and contains appropriate amounts of various ions. Thus, if there is need to lose sodium, the dialysate will have a low sodium content. The dialysate should also be free of unwanted materials and care is needed to avoid infection. The patient's 'purified' blood is then returned to the circulation.

Advancing technology has led to increasingly efficient systems which, rather like the kidney, contain multiple fine tubes in a very small space. However, the simple principle of equilibration with a dialysate is much different from the sophistication of normal renal function with its filtration, reabsorption, excretion, medullary osmotic gradient, complex vasculature and hormonal control.

For early 'artificial kidney' treatment, the patient's blood

was drawn from an artery and returned to a vein. However, with dialysis required two or three times per week for an indefinite period, this led to serious problems with arteries damaged by repeated punctures. Then the concept of an *arteriovenous shunt* was developed. Initially a tube connected a forearm artery and vein. The tube rather than the artery and vein could then be punctured for dialysis. However, this tubing was uncomfortable and there was a considerable risk of bleeding. Finally, a *surgical arteriovenous fistula* was devised. An opening, usually in the radial artery, was connected to a nearby vein so that the forearm veins draining the fistula became dilated and carried an adequate flow for dialysis. Haemodialysis using such 'arterialized' veins can maintain health for long periods, provided there are no complications with thrombosis or infection.

Peritoneal dialysis

This is an alternative to haemodialysis – it uses the capillaries of the peritoneal cavity as the tubing, and fluid passed into the peritoneal cavity and withdrawn after an equilibration period as the dialysate. The dialysate is supplied in plastic bags and is passed into the peritoneal cavity under the influence of gravity by raising the bag

above the level of the patient's abdomen. The peritoneal cavity is capable of holding several litres of fluid without any difficulty. In practice, fluid is kept in the peritoneal cavity almost continuously. About four times a day, the patient drains as much fluid as possible by connecting an empty bag to the peritoneal cavity and placing the bag on the floor. When drainage has ceased, a fresh 2-litre bag is hung up well above the patient's abdomen and the fluid run in. Thus solute exchange can proceed throughout the day and night by a procedure analogous in slow motion to gas exchange in the alveolar air, replenished by the tidal ventilation. This process has the advantage of relative simplicity compared with haemodialysis but it is laborious for the patient and still carries the risk of infection.

Treatment with erythropoietin has already been mentioned in relation to endocrine disturbances of renal failure. It is, of course, not required with successful renal transplantation and this is now the definitive treatment which can liberate patients from the onerous demands of either form of dialysis treatment.

Renal transplantation

Renal transplantation is now well established. The requirements are:

1. connection of the renal artery of the transplanted organ to any convenient artery in the recipient
2. a corresponding venous connection
3. connection of the donor ureter to the patient's bladder, and
4. prevention of rejection of the kidney.

In practice, the donor kidney is usually placed in one of the iliac fossae, with attachments to the neighbouring major blood vessels. Prevention of rejection is achieved by as close a match as possible for cellular antigens (identical twins have provided a perfect match on rare occasions) and by drugs, including glucocorticoids, which suppress immune responses. The donor organ may come from a relative, friend, or from the body of someone who has died in circumstances where the kidney can be removed prior to post-mortem deterioration. The organ must then be preserved prior to transplantation, sometimes during a considerable journey,

to a well-matched recipient. It is kept in isotonic solution at around 4–5°C. This temperature is high enough to avoid freezing, with the disastrous formation of destructive ice crystals, and low enough to reduce the metabolic rate of the renal cells to ensure survival for several hours.

Once the organ has been 'plumbed in', it will begin to function and produce urine. While various blood tests may give clues about transplant rejection, measurements of glomerular filtration rate by creatinine clearance provide the definitive indication of function. A substantial and gradually rising clearance indicates good function, whereas a falling clearance suggests that rejection has begun. Prior to transplantation, the kidney had provided half the renal function and the initial glomerular filtration rate of the transplanted kidney will be about half normal. However, as the sole kidney in the recipient, the organ will undergo gradual hypertrophy with an increase in glomerular filtration rate over the next 2–3 months. All functions of the kidney, including appropriate formation of erythropoietin, can be expected to be normal.



Further reading

Holmes O 1993 *Human acid-base physiology*. Arnold, London

Of all aspects of renal physiology, this subject gives students most trouble. This book will help them overcome their problems. It very usefully provides the physical chemistry to understand the principles of the physiology and a substantial glossary of terms. Revision is aided by collecting key material into tables and providing self-tests.

Koeppen B M, Stanton B A 2000 *Renal physiology*, 3rd edn. Mosby, St Louis.

This book focuses on essential points in a concise way. The end of chapter summaries and self-test exams are a great help to learning.

Lote C J 1994 *Principles of renal physiology*, 4th edn. Kluwer Academic Publishers, Dordrecht, Netherlands.

A first-class concise book for undergraduates, written in a very clear style and suitable for systems-based courses. The author has the ability to make complex concepts clear.

Seldin D W, Giebisch G 2000 *The kidney*. Lippincott Williams and Wilkins, Philadelphia.

This comprehensive work in two volumes provides a first line of reference on the subject of renal physiology and pathophysiology.

Questions

Answer true or false to the following statements:

8.1

Glomerular filtration rate:

- A. Can be measured using a substance that is completely cleared from the plasma.
- B. Tends to increase in hypoalbuminaemia.
- C. Tends to increase when the efferent arteriole is constricted.
- D. Increases during strenuous exercise.
- E. Is normally closer to 40% than 20% of the renal plasma flow.

8.2

When renal clearance of a substance X is measured in a normal individual:

- A. If the clearance is 250 ml/min, then X must be secreted by the nephron.
- B. If the clearance is 60 ml/min, then X must be reabsorbed from the nephron.
- C. If the clearance is zero, then X may be glucose.
- D. The clearance of X may be calculated from the arterial-venous concentration difference in the renal vessels.
- E. If the clearance rises linearly with plasma concentration, then it is likely that X is freely filtered but is neither secreted nor reabsorbed in the nephron.

8.3

In the proximal convoluted tubule:

- A. The epithelium is flat and contains few mitochondria.
- B. Reabsorption of water increases the osmolality of the tubular fluid which enters the loop of Henle.
- C. The rate of water absorption increases as the glomerular filtration fraction increases.
- D. Bicarbonate reabsorption is coupled to H⁺ secretion.
- E. The T_m for phosphate reabsorption is increased by parathormone (PTH).

8.4

The loop of Henle:

- A. Actively pumps ions across the epithelium of the descending limb.
- B. Has a low permeability to water in the thick portion of the ascending limb.
- C. Makes use of countercurrent exchange to amplify the ionic concentration gradients generated by active pumps.
- D. Is responsible for the high osmolality in the renal medulla.
- E. Returns a fluid of high osmolality to the distal convoluted tubule.

8.5

Renal sympathetic nerves:

- A. Are adrenergic.
- B. Preferentially constrict the efferent arteriole, helping to maintain GFR.
- C. Reduce renal blood flow during maximal exercise.
- D. Stimulate renin production.
- E. Inhibit Na⁺ reabsorption from the convoluted tubules.



8.6

In heart failure:

- A. The levels of circulating renin are likely to be high.
- B. The levels of angiotensin II are likely to be high.
- C. The levels of aldosterone are likely to be high.
- D. Treatment with an inhibitor of angiotensin-converting enzyme (ACE) may help reduce oedema.
- E. Plasma osmolality is usually reduced because of water retention.

8.7

Antidiuretic hormone:

- A. Is released from the anterior pituitary in response to a rise in plasma osmolality.
- B. Is a vasoconstrictor.
- C. Increases water permeability in the loop of Henle.
- D. Increases urea reabsorption from the medullary portion of the collecting duct.
- E. Is a steroid hormone.

8.8

If a young man, found in a semiconscious state, is dehydrated, has glucose in his urine and the following results on analysis of an arterial blood sample: pH 7.0; P_{O_2} 13.0 kPa (100 mmHg); P_{CO_2} 3.0 kPa (22 mmHg); $[HCO_3^-]$ 4.5 mmol/litre:

- A. He is likely to have been hyperventilating.
- B. He has a metabolic acidosis.
- C. There has been no respiratory compensation in this patient.
- D. He has lost HCO_3^- in his urine.
- E. He is dehydrated because of an osmotic diuresis.

8.9

Following ingestion of 700 ml of water by a normal adult:

- A. Urinary volume increases.
- B. The rate of urinary salt excretion increases.
- C. Antidiuretic hormone levels fall.
- D. The permeability of the collecting ducts to water increase.
- E. There is little or no change in the intracellular fluid volume.

8.10

Aldosterone:

- A. Secretion is stimulated by circulating renin.
- B. Secretion is stimulated by low levels of plasma $[K^+]$.
- C. Increases the permeability of the collecting ducts to water.
- D. Stimulates Na^+/K^+ -ATPase activity in the proximal convoluted tubule.
- E. Promotes loss of Na^+ and H_2O from the body.

Answers

8.1

- A. **False.** Such a substance would provide a measure of renal plasma flow, not GFR.
- B. **True.** This reduces the plasma oncotic pressure in the glomerulus, increasing the net filtration pressure.
- C. **True.** This increases the hydrostatic pressure in the glomerular capillaries.
- D. **False.** Although GFR is autoregulated, there will be a tendency for it to fall in very strenuous exercise because of sympathetic constriction of the renal vasculature.
- E. **False.** If GFR is about 125 ml/min and renal plasma flow, or RPF, is approximately 700 ml/min, then GFR/RPF is about 18%. This is referred to as the filtration fraction.

8.2

- A. **True.** If the renal clearance exceeds GFR, then X must be being secreted within the nephron. The high clearance tells us that more of the substance is appearing in the urine than can be accounted for by filtration.
- B. **False.** This would only be true if one knew for certain that X was freely filtered in the nephron. Any substance which is only poorly filtered, as well as one which is reabsorbed, will have a clearance below the GFR.
- C. **True.** All of the filtered glucose is normally reabsorbed, up to plasma concentrations which exceed the renal threshold, i.e. about 11 mmol/litre.
- D. **False.** One would also need to know the renal plasma flow rate. Clearance would then equal $(A-V \text{ concentration difference}) \times \text{Plasma flow rate} / \text{Arterial plasma concentration}$.
- E. **False.** Clearance is independent of plasma concentration for such a substance; it is always equal to the GFR.

8.3

- A. **False.** It is tall, mitochondria rich and has a brush border of microvilli. These features reflect its high transport capacity.
- B. **False.** NaCl, urea and H₂O are all absorbed in similar proportion to their concentrations in the filtrate, and plasma, and so there is a large decrease in fluid volume along the length of the proximal tubule, with little change in osmolality.
- C. **True.** This helps maintain glomerular–tubular balance, in which a large and fixed fraction of the filtered Na⁺ and H₂O is reabsorbed in the proximal tubule. Part of the mechanism is increased plasma oncotic pressure in the peritubular capillaries due to upstream filtration of a greater fraction of the available plasma volume.
- D. **True.** There is a one-to-one relationship.
- E. **False.** PTH promotes phosphate excretion by the kidney by inhibiting reabsorption.

8.4

- A. **False.** Movement of ions and H₂O is passive in this region, with water being drawn out into the medulla and ions diffusing in.
- B. **True.** This means that as ions are pumped out in this region, H₂O is trapped within the lumen.
- C. **True.** This increases the osmolality achieved within both tubular fluid and interstitium as the loop of Henle descends into the medulla.
- D. **True.**
- E. **False.** The fluid which enters the distal convoluted tubule has a low osmolality due to the diluting effect achieved by ion absorption with H₂O retention in the thick ascending limb.

8.5

- A. **True.**
- B. **False.** They constrict both afferent and efferent arterioles, decreasing renal blood flow and GFR. This effect may, however, be counterbalanced by the actions of angiotensin and prostaglandins.
- C. **True.** This can fall by as much as 70%.
- D. **True.** They have a direct action on the renin-secreting cells.
- E. **False.** They tend to increase reabsorption of Na^+ , Cl^- and H_2O .

8.6

- A. **True.** Reduced cardiac output leads to reduced renal perfusion, a stimulus to renin release from the juxtaglomerular apparatus.
- B. **True.** This is due to the action of renin on angiotensinogen, which produces angiotensin I, which is converted to angiotensin II by angiotensin-converting enzyme in vascular capillaries, especially in the lungs.
- C. **True.** Aldosterone release is stimulated by angiotensin II.
- D. **True.** Treatment with an ACE inhibitor reduces angiotensin II, and thus aldosterone production, so limiting renal reabsorption of Na^+ and H_2O in the distal convoluted tubule.
- E. **False.** The water retention in heart failure is driven by secondary hyperaldosteronism, as described above. This primarily promotes Na^+ reabsorption, so plasma osmolality is unlikely to be changed.

8.7

- A. **False.** ADH is released from the posterior pituitary.
- B. **True.** It is also known as vasopressin.
- C. **False.** It acts on the collecting ducts and the distal convoluted tubule.
- D. **True.** ADH increases the permeability to urea and H_2O in this region of the nephron.
- E. **False.** It is a peptide hormone. Aldosterone is a steroid.

8.8

- A. **True.** The low P_{CO_2} indicates this.
- B. **True.** The low pH indicates an acidosis. The very low bicarbonate tells us that it is metabolic.
- C. **False.** The low P_{CO_2} will partly offset the acidosis by helping to raise the $[\text{HCO}_3^-]:P_{\text{CO}_2}$ ratio. This is classical respiratory compensation for a metabolic acidosis.
- D. **False.** The patient would in fact be reabsorbing all of the filtered HCO_3^- in exchange for secreted H^+ and excreting a highly acid urine. $[\text{HCO}_3^-]$ is low because it is being used up to buffer the additional metabolic acid load.
- E. **True.** This is driven by retained glucose within the tubules which hold H_2O osmotically, preventing its reabsorption. This does not normally occur because all the filtered glucose is reabsorbed. At very high plasma [glucose], however, the T_m for reabsorption is exceeded. This, and the other features of the case, are typical of a diabetic ketoacidosis.

8.9

- A. **True.** There is a diuresis.
- B. **False.** There is usually no change in the rate at which salt is excreted. Since urinary volume is increased, this means that urinary osmolality falls.
- C. **True.** This is a response to the reduction in plasma osmolality and increase in plasma volume. The fall in ADH causes the rapid diuresis.
- D. **False.** Reduced ADH causes reduced H_2O permeability, with less reabsorption into the medulla.
- E. **False.** The reduced osmolality in extracellular fluid leads to an initial osmotic uptake of H_2O by cells. As water is cleared by the kidneys, raising the $[\text{Na}^+]$ towards normal, this fluid is distributed back into the extracellular space, until volume and osmolality have returned to normal throughout the body.

8.10

- A. **False.** Angiotensin II is the direct stimulant.
- B. **False.** High $[\text{K}^+]$ levels stimulate aldosterone, which promotes the secretion of K^+ in the distal convoluted tubule.
- C. **False.** This is an action of ADH.
- D. **False.** Na^+/K^+ -ATPase activity in the proximal convoluted tubule is not modulated by aldosterone. Aldosterone-sensitive Na^+ and H_2O reabsorption occurs only in the distal part of the distal convoluted tubule.
- E. **False.** It promotes reabsorption of Na^+ and H_2O .