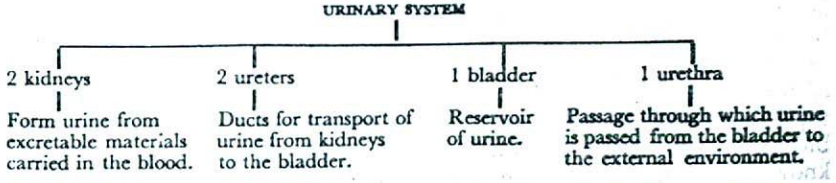
1/Excretion

Introduction. Kidneys skin, lungs, gastro-intestinal tract, salivary glands and liver are the main channels through which excretion takes place. There seems to be a general rule regarding the channels of excretion of different substances. For instance, (1) *the soluble, non-irritant, solid substances and water are mainly excreted through the kidneys and to a lesser extent through the skin,* (2) *volatile substances, such as* CO_2, *ammonia, alcohol, ketone bodies, aromatic oils, water vapour, etc., are excreted through the lungs,* (3) *heavy metals are excreted through the gastro-intestinal tract, especially through the large intestine and slightly through the liver and saliva,* (4) *fats and fat derivatives are passed out of the body through the skin, as sebum, and through the liver along with bile.* These are the broad principles on which excretion from the body takes place. To understand the way in which the kidney carries out these functions, it is essential to understand first the way in which it is supplied with blood. **About 25% of left ventricle's total output of blood in each cardiac cycle is distributed through the renal arteries to the kidneys for filtration at rest.**

Among the main channels of excretion, kidneys are the chief. The kidney performs excretory, homeostatic and endocrince functions. The urinary system consists of those organs which produce urine and eliminate it from the body. These organs comprise two kidneys, two ureters, one bladder and one urethra.



The secretion of urine and its elimination from the body are vital functions because they together constitute one of the most important mechanisms for maintaining the bodily homeostasis. Smith has phrased thus "*The composition of the blood (and internal environment) is determined not by what the mouth ingests but by what the kidney keeps.*"

KIDNEYS

The human kidneys are bean-shaped paired organs situated just behind the vertebral column in the abdomen at the twelfth thoracic to third lumbar segment (Fig. 1.1). An average-sized kidney measures 10 to 12 cm in length, 5 to 6 cm in width and 3 to 4 cm in thickness, each weighing about 150 g in adult male and about 135 g in adult female. Usually the right kidney is slightly smaller than the left one. A deep notch or concavity is present at the medial border—the **hilus** (*hilum*), and it is through this region the blood vessels—renal artery and vein, ureter and nerves pass.

If the kidney is sectioned along its long axis and examined with the naked eye, a dark reddish-brown peripheral region (opposite the hilus), the **cortex,** and the rest lighter area—the **medulla** are distinguishable.

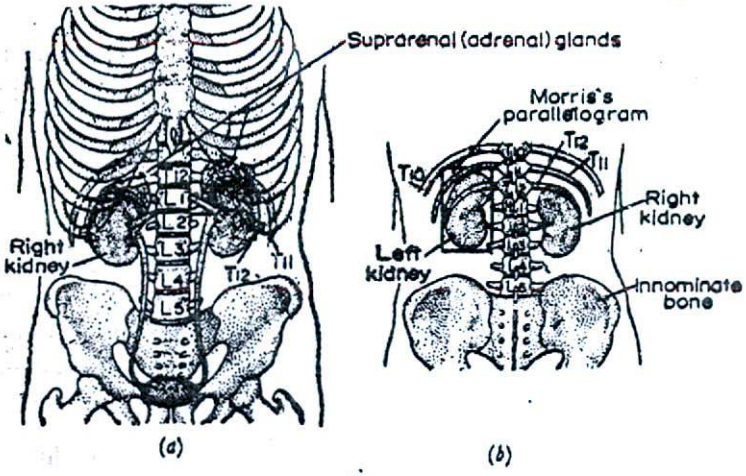


Fig. 1.1. Diagrammatic representation of the normal position of urinary organs—(*a*) ventral view and (*b*) dorsal view.

The medulla is again dividend into 10 to 15 conical areas, the renal pyramids having their broad base towards the cortex and the vertex, apex or papilla projected into the lumen of the minor calyx. The lateral boundaries of the pyramid are formed by the projections of the darker cortex which are named as renal **columns of Bertin**. The substance of the pyramid is radially striated by brownish lines which converge towards the apex which is due to the straight uriniferous tubules and the blood vessels parallel to them. The apex or papilla (the minor calys) is known as the area cribrosa, which is perforated by a number of openings of the collecting tubules to the minor calyx.

The renal medulla is known to be a site of origin for PGA_2, PGE_2 and $PGF_{2}\alpha$ prostaglandins concerned with blood pressure regulation.

The two kidneys are the chief excretory organs of the body. They are made up of numerous functional microscopic units called nephrons. They performs excretory and hemeostatic functions. There are about one million nephrons in each human kidney. The nephrons ultimately drain into the pelvis of the ureter (Fig. 1.2). From here urine passes down the ureters and collect in the urinary bladder.

Uriniferous tubules. They consist of (1) secretory portion or nephron and (2) non-secretory portion or collecting portion or duct system.

Types of nephrons. Histologically there are two types of nephrons, according to their relative position in the cortex: (1) *The superficial nephrons* (superficial glomeruli) occupy the outer two-thirds of the cortex and make up about 85% of the total number, (2) *The juxtamedullary*

nephrons (Juxtamedullary glomeruli) occupy the inner third of the cortex and constitute about 15% of the total number. The superficial nephrons are smaller in size and are fully functioning under normal conditions. The juxtamedullary nephrons are large and work only in conditions of stress.

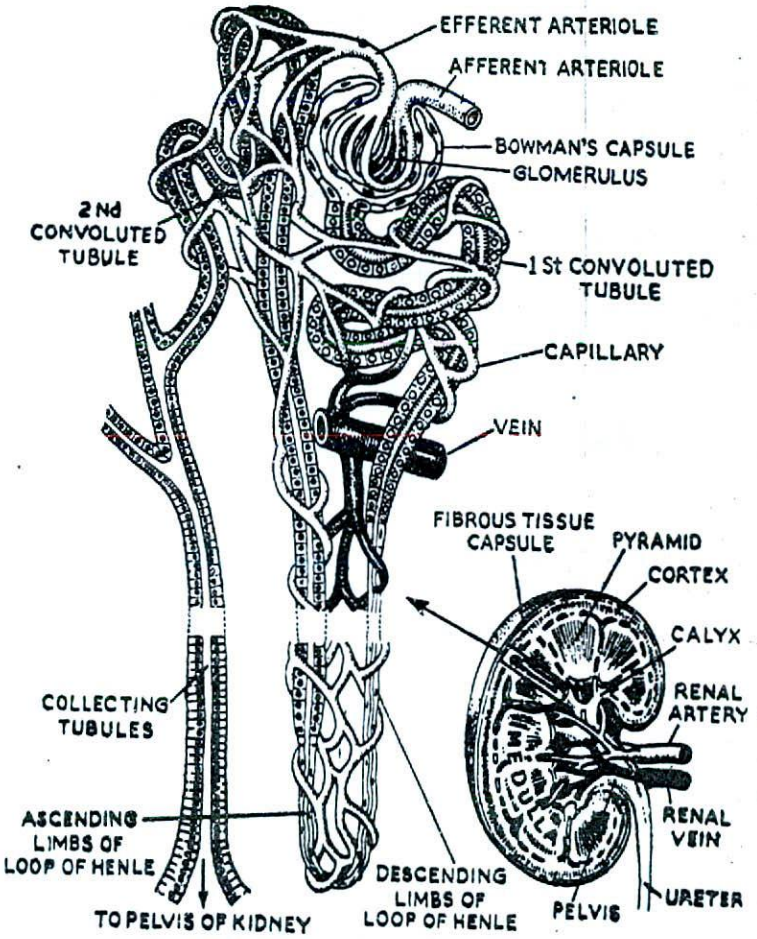


Fig. 1.2. Diagram shows renal tubule on the left side and the inset shows the longitudinal section of the right kidney on the right side.

The nephrons consists of six successive parts: (i) **renal or Malpighian corpuscle,** (ii) **proximal convoluted tubule,** (iii) **thin segment**—loop of Henle, (iv) **proximal straight tubule,** (v) **distal straight tubule** and lastly (vi) **distal convoluted tubule.** The proximal convoluted and distal convoluted tubules are in the cortex and in close proximity to the renal corpuscle. The loop of Henle extends from the cortex to a variable distance in the medulla according to the position of the corpuscle in the cortex.

Malpighian corpuscle (Malpighian body or Renal corpuscle). Found only in the cortex of the kidney. Measures about 200 microns in diameter. The corpuscle consists of two parts: (1) glomerulus, and (2) Bowman's capsule (Fig. (1.3).

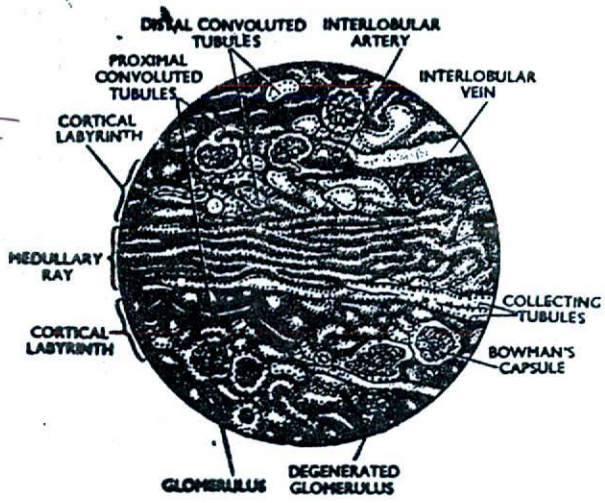


Fig. 1.3. Diagrammatic representation of the cortex of human kidney showing in differeni structnres.

1. **Glomerulus.** It is the capillary tuft which invaginates Bowman's capsule. The afferent arteriole breaks up into about fifty capillary loops and forms the glomicular tuft which lies within Bowman's capsule, a double-walled epithelial sac. Each nephron starts with a tuft of 6 to 8 renal blood capillaries invaginated into the end of a tubule. This structure is named as **glomerulus.** Although these glomerular capillaries are not homogeneous loops, but they make up freely branching anastomotic network. There are about 20 to 50 capillary loops in all. Just before entering the glomerulus, the media of the afferedt arteriole is found to contain a thick cuff of large modified muscle cells—the **juxtaglomerullar cells.** The capillary tuft reunites and forms the *efferent arteriole* which passes out of the glomerulus. *The afferent vessel is short and wide whereas the efferent vessel is narrow and long* (Figs 1.4, 1.5 & 1.20). This arrangement makes the glomerular blood pr:ssure much higher (70 mm Hg) than the capillary bed elsewhere and facilitates filtration. The total surface area of all the glomerular capillaries in two kidneys (i.e., the total filter bed) is about 1·73 square metres.

2. **Bowman's capsule.** It is the dilated blind end of the nephron, invaginated by the glomerular tuft— the vascular end or pole. It consists of two layers —*parietal* and *visceral.* The **parietal layer** is made up of typical squamous epithelium of flat polygonal cells. It gradually becomes continuous with the tubular epithelium at the tubular end of Bowman's capsule.

The filtering membrane of the Malpighian corpuscle (Fig. 1.6) consists of the following layers: (*a*) the endothelial cell layer of the capillaries, (*b*) the basement membrane, (*c*) the epithelial cells of the visceral layer of Bowman's capsule. The cells of the **visceral layer** during development undergoes extensive modification and are known as **podocytes** (glomerulur epithelial cells). These give rise to a

number of radiating *tentacle-like* cytoplasmic processes which in turn give up a large number of small branches—the **pedicels** or **end feet.** The pedicels are actually attached to the basal lamina (Fig. 1.7). It is seen with electron micrograph that the cell body along with the nucleus of the podocyte remains about 1·0 or 2·0 μm away from a single, continuous basal lamina. The space between the basement membrane and the podocyte is

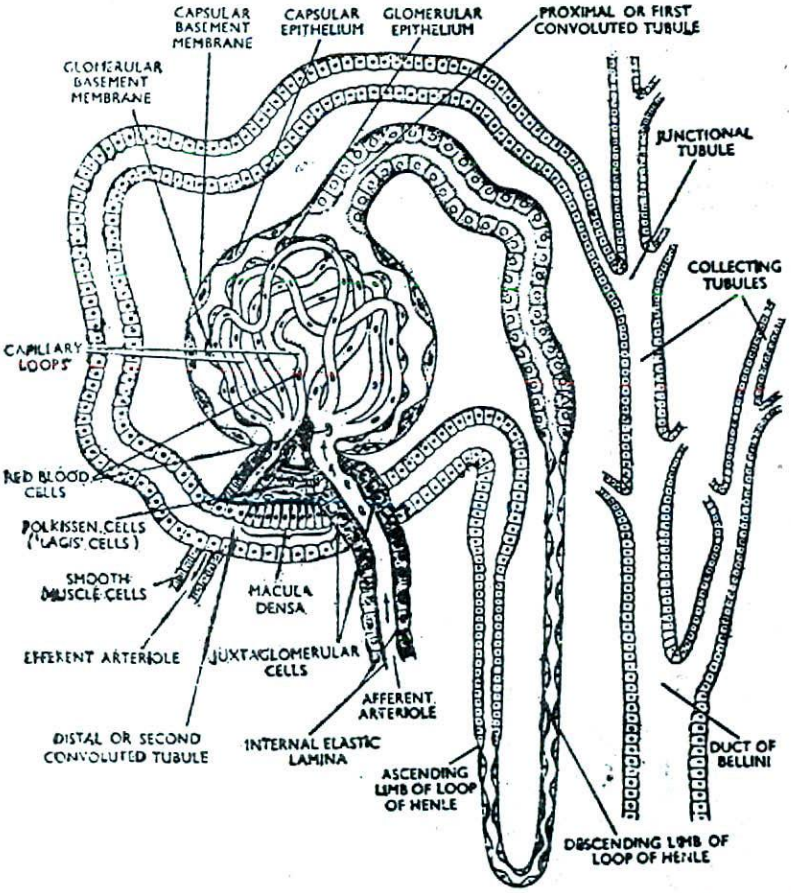


Fig. 1.4. Diagrammatic representation of the juxtaglomerular apparatus showing the respective positions of the juxtaglomerular cells, Polkissen or 'Lacis' cells and macula densa of the same glomerulus and nephron.

known as the **subpodocytic space.** The adjacent foot processes are not in intimate contact with one another but a narrow gap or slit of 25 nm wide is present in between them and is known as the **filtration slit** or **slit pore.** In high resolution of electron micrograph, a thin dark line of about 6 nm in thickness (the **slit membrane**) is observed to bridge the *slit pore.* The nucleus of podocyte has got infoldings and is of a complex form.

The cells of the endothelial lining of glomerular capillaries are flat and fenestrated having circular pores of 50 nm to 100 nm in diameter

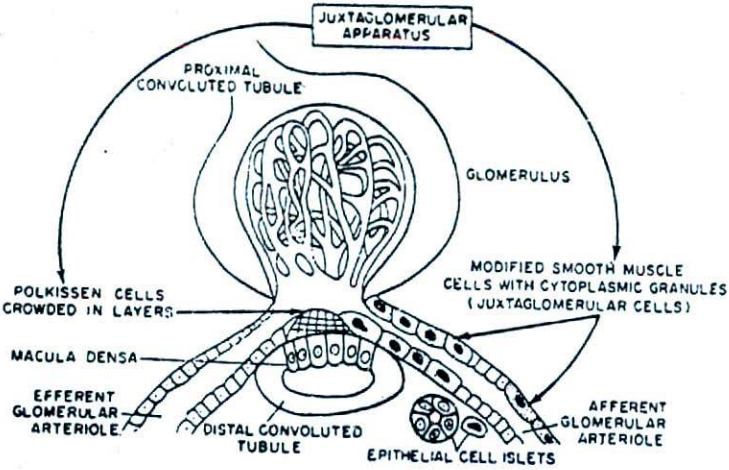


Fig. 1.5. Diagram of renal corpuscle with glomerulus and juxtaglomerulus apparatus. No basement membrane separates the juxtaglomerular from the macula densa cells.

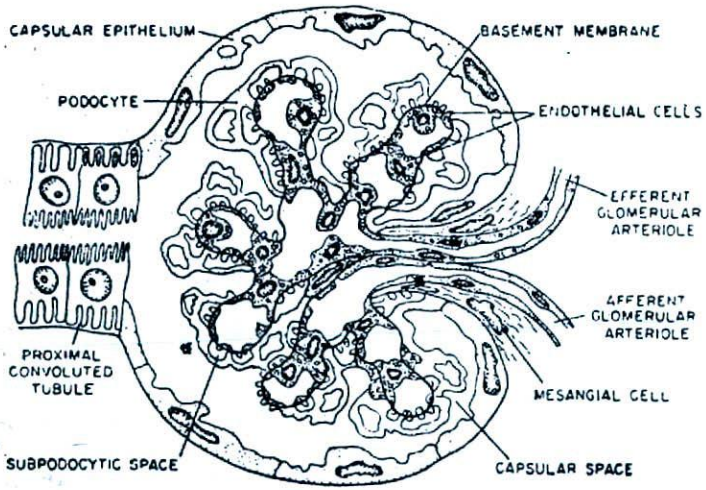


Fig. 1.6. Diagram of renal corpuscle. Note the presence of mesangial cells in the connective tissue skeleton of the tuft.

(Fig. 1.8). These are different from that of the capillaries of any other place, because the fenestrae (pores) do not have the thin diaph-

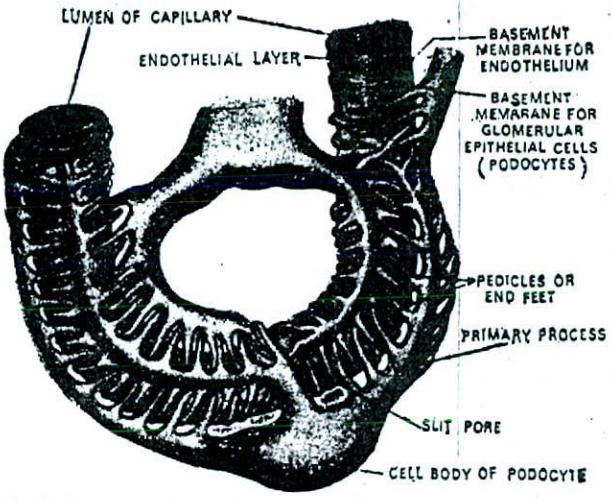


Fig. 1.7. Podocytes or glomerular epithelial cells lining the visceral layer of Bowman's capsule.

ragm and are larger in size and more in number. The nucleus remains towards the lumen of the capillaries. The *endothelium of the glomerulus* also contains between endothelium and basal lamina another type of cells known as **deep cells** or **mesangial (intercapillary or stalk) cells** (Fig. 1.6)—branched stellate cells having similar character to pericytes of capillaries of any other place. The *functions* of these cells may become proliferative and phagocytic in certain pathological conditions.

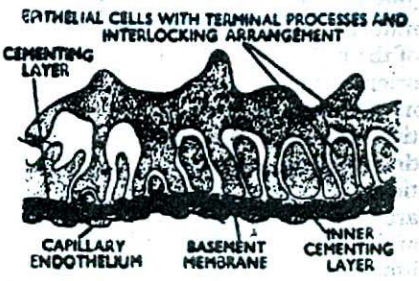


Fig. 1.8. Diagrammatic representation of the electron microscopic structure of the filtering membrane of the Malpighian corpuscle.

In adult kidneys, the endothelium of the glomerulus and the epithelium of the visceral layer are separated by the common single basement membrane of 0·1 to 0·5 μm in thickness. The basement membrane is made up of a felt work of very fine filaments embedded in a homogeneous matrix. This membrane is the only continuous barrier between the capillary lumen and capsular space. Experimental studies by adding silver nitrate to the drinking water of rats supported that the structural elements of the basement membrane are constantly being turned over.

The modern studies with horse reddish peroxidase (mol. wt. 40,000) and myeloperoxidase (mol. wt. 160,000) as protein tracer, it is evidenced that the smaller peroxidase (horse reddish) can pass easily through filtering

membrane but the larger one (myeloperoxidase) can pass up to the basement membrane but held up at the epithelial slits. From this finding it is interpreted that the epithelial slit pores all actually responsible for the differential permeability of the renal corpuscle.

Renal tubules (Fig. 1.2). The glomerulus is described to have two poles: At one pole—the *vascular pole*, the blood vessels are attached. At the opposite pole—the *tubular pole*, the renal tubule begins. The human tubule is about 3·0 cm long, 20-60 microns wide, and since there are about 2 millions of nephrons, the total length of the tubules is about 65 km or 40 miles. Just below the glomerulus, the tubule has a very short constricted portion—the **neck.** After the neck, the tubules consist of the following serial parts:

1. **First or Proximal convoluted tubule** (PCT or Pars convoluta). It is about 14 mm long, external diameter 60 μm and inside diameter 15-25 μm and extremely tortuous. It is lined by a single layer of cubical cells, the free borders (at the lumen) of which are striated or brush-bordered. Electrone microscopy has revealed that the brush border is composed of processes or microvilli (prolongations of the cell cytoplasm) which enormously increase the surface area of the cells for absorption in the lumen of the proximal tubule. There are numerous tubular invaginations arising at the clefts between the microvilli, extending downwards into the apical cytoplasm and are known as **apical canaliculi.** In the apical region, clear vacuoles of various size are also noted, which along with the apical canaliculi are involved in the cellular mechanism of absorption of protein from the filtrate. Protein enzymes are also demonstrated at the brush border (microvilli) and the canaliculi. Inside the cytoplasm there are rod-like structures of mitochondria at the basal half of the cell. The mitochondria are oriented perpendicular to the cell membrane. In well-preserved tissues, this oriented mitochondria give rise to a faint vertical striation. So these cells are also known as rodded and brush-bordered. The lateral limits of these cells are not prominent because the neighbouring cells interdigitate between themselves. At the base there are numerous infoldings of the cell membrane. There are also a number of lateral processes at the base of the cells and are extended under the neighbouring cells to occupy deep recesses in their base (Fig. 1.9). The cells of proximal convoluted tubule are very active metabolically and contain a large number of enzymes. These cells reabsorb about two-thirds of the water of the glomerular filtrate and all the gluose and part of sodiumc, chloride and phosphate.

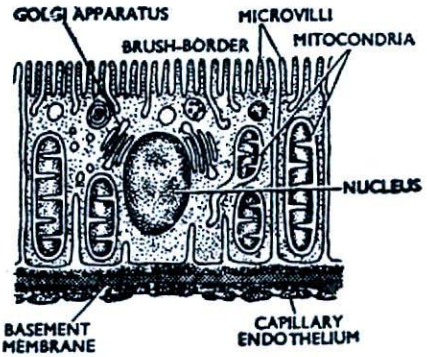


Fig. 1.9. Diagrammatic representation of the electron microscopic structure of a cell lining the proximal or first convoluted tubule. Rod-shaped mitochondria lying across the cell.

2. **Henle's loop** (Pars recta). It is a U-shaped loop, dipping for a variable length into the medulla. Anatomically the loop of Henle can be divided into (i) descending limb, (ii) thin-walled ascending limb and (iii) thick-walled ascending limb. The proximal four-fifths of the descending limb have the same diameter (proximal straight tubule) and epithelium as above but the cells have very few and small mircovilli and have got no striated appearance (Fig. 1.10). The distal one-fifth of this limb (in superficial nephrons) and also a variable part of the ascending limb (only in juxtamedullary nephrons), are lined by *flat epithelial cells*. The cells of the distal portion of the ascending limb are of cuboidal shape with distinct vertical striation due to presence of mitochondria (Fig. 1.11), but they are not brush bordered, i.e., no microvilli. In the superficial nephrons the loop is very short and dips only slightly into the medulla, whereas in juxtamedullary nephrons the loop is of considerable length and passes deep into the medulla. The average length of the loop is about 20 mm.

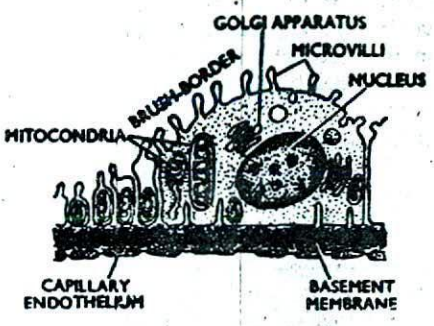


Fig. 1.10. Diagrammatic representation of the electron microscopic structure of a cell lining the descending limb of loop of Henle.

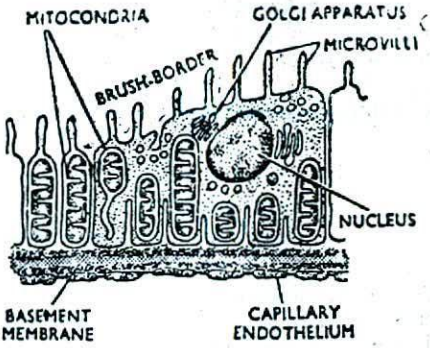


Fig. 1.11. Diagram shows the E/M structure of a cell lining the ascending limb of Henle's loop.

In the thin-walled descending limb being devoid of obvious intracellular structures isosmotic fluid delivered from the PCT becomes increasingly hypertonic as it progresses from the renal cortex towards the renal papilla until it reaches the maximum concentration and the membrane of this portion is more permeable to H_2O than solute urea, NaCl and in order to effect equilibrium, H_2O is removed. In the thin segment of the ascending limb the tubular fluid becomes progressively less concentrated due to its backflow towards the renal cortex as a consequence of loss of NaCl from the renal tubule. The thick portion of the ascending loop is known as *functional* proximal tubule. Reabsorption of NaCl from the both cortical and medullary thick ascending limbs results in by active chloride reabsorption but that reabsorption of sodium occurs by means of a passive reabsorptive process in the maintenance of electrical nutrality.

3. **Distal or Second convoluted tubule.** This portion of the nephron is situated in the cortex having an average length of 4·6 to 5·2 mm and

diameter 20 to 50 μm and lined by *cubical epithelium which is rodded but without any true brush border.* There is extensive infolding of the cell membrance. It has a much smaller number of microvilli (Fig. 1.12). Electron micrograph reveals that the basal invagina- reveals that the basal invagination is more extensive than that of the proximal tubules. The diameter of the lumen of distal convoluted tubule is greater than that of proximal one and the tubules contain a larger number of cells.

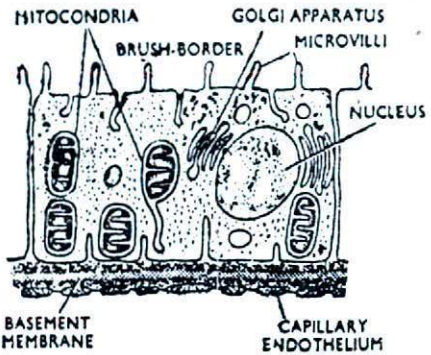


Fig. 1.12. Diagram shows the E/M structure of a cell lining the distal convoluted tubule.

The **proximal part of the distal tubule** *actually comes in contact with the juxtaglomerular cells of the corresponding afferent vessel.* The cells of this region have got closely packed nuclei and form the **macula densa** (Fig. 1.4). Macula densa and nearby juxtaglomerular cells and 'Lacis' cells form **juxtaglomerular apparatus** (*vide* below).

The reabsoptive activity of the distal convoluted tuble is under the influence of ADH, vasopressin, which is one diterminant of the volume of urinary output. Distal tubular cells are able to reabsorb small quantities of water and electrolytes due to a small number of microvilli in addition to determining urinary acid-base balnce (Fig. 1.13).

4. **Collecting or Straight tubule.** It is lined by pale cuboidal cells. It is about 20 mm long. Several collecting tubules, from different nephrons, join successively and form the **duct of Bellini,** which opens at the apex of the renal pyramid.

In the case of the superficial nephrons only the lower parts of Henle's loop and duct of Bellini—lie in the medulla, while the rest lies in the cortex. Whereas in the case of juxtamedullary nephrons—only the upper portions of the convoluted tubules lie in the cortex and the rest in the medulla. There is a **hyaline basement membrane** throughout the nephron upon which the cells are set.

Developmentally, there are three separate units. The glomerular tuft develops independently and grows into Bowman's capsule. Bowman's capsule and the tubule develop from the adjacent mesoderm. The collecting tubules and the ducts of Bellini develop as outgrowths of the ureter and secondarily establish connections with the tubule.

JUXTAGLOMERULAR APPARATUS

Goormaghtigh suggested the term juxtaglomerular apparatus (Figs. 1.4, 1.5 & 1.14) which included the (*i*) granular juxtaglomerular cells in the afferent arteriole, (*ii*) macula densa of the distal convoluted tubule, and (*iii*) agranular **Polkissen** or **'Lacis' cells** situated in the angle created by the entrance and exit of the afferent and efferent arterioles of each glomerulus. But some *have preferred to use the term* **juxtaglomerular complex,** *instead of juxtaglomerular apparatus,* only because of unequivocal functional relationship existing between the

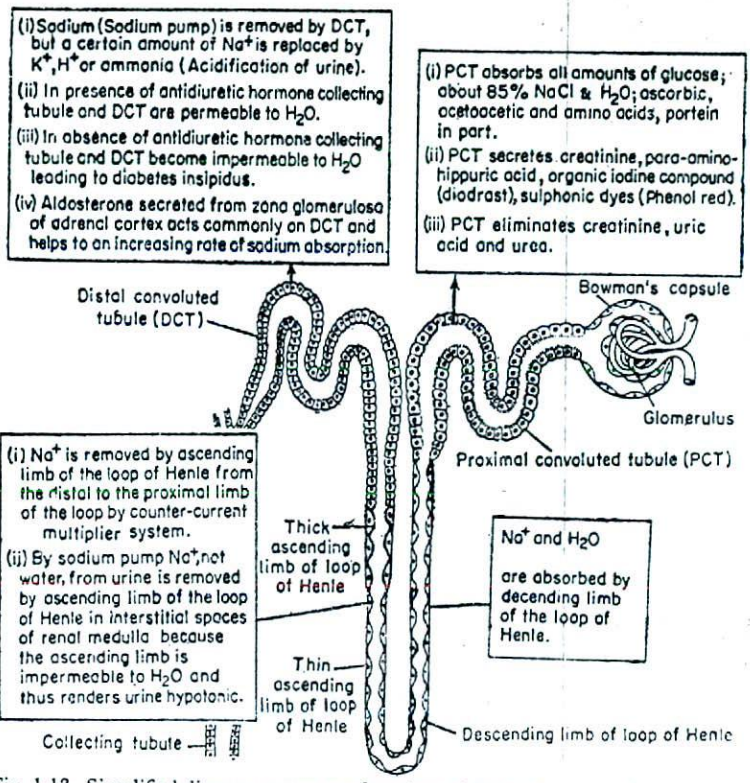


Fig. 1.13. Simplified diagram represents functions of different parts of the nephron.

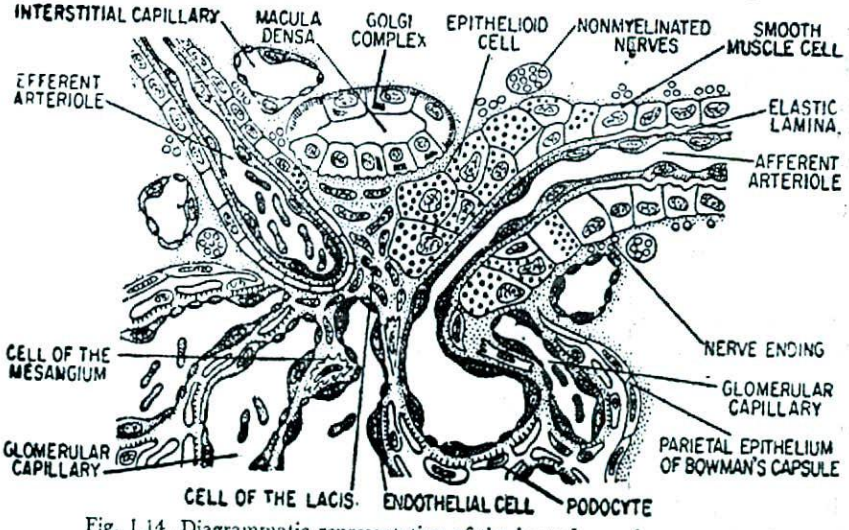


Fig. 1.14. Diagrammatic representation of the juxtaglomerular apparatus.

juxtaglomerular cells and macula densa, and the fundamental structural differences between them. Besides this by virtue of its complexity, and depending upon the prevalent physiological, pathological or experimental conditions, they have included within the juxtaglomerular complex in addition to the three constituents (i.e., the epithelioid cells of the preglomerular afferent arterioles, Lacis cells and the macula densa) all the smooth muscle cells of the afferent and efferent arterioles and the mesangial cells (Figs. 1.6 & 1.14). Because the smooth muscle cells of the afferent and efferent arterioles and also the cells of the Lacis are continuous with the mesangium and undergo the same changes during hyperactivity of the juxtaglomerular apparatus.

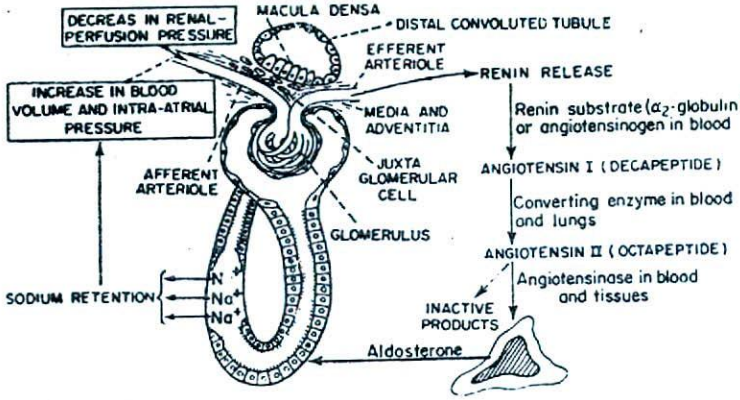


Fig. 1.15. Regulation of aldosterone secretion (renin-argiotensin system).

The components of the juxtaglomerular apparatus have been thought to be related in some way to the *control of blood pressure, renal blood flow, salt balance* and *erythropoiesis*. Renal hypertension is claimed to be the cause of secretion of renin from the juxtaglomerular apparatus thus helping in the formation of angiotensin II (Fig. 1.15). Juxtaglomerular apparatus is deeply innervated.

During hypoxia or following haemorrhage, release of red blood cells from the bone-marrow in the circulation is increased. But on the other hand, when the cell volume is increased, RBC release from the bone-marrow is decreased through decrease of erythropoiesis. It is known that under hypoxic state or following haemorrhage a hormone **erythropoietin**—glycoprotein in nature, is formed in

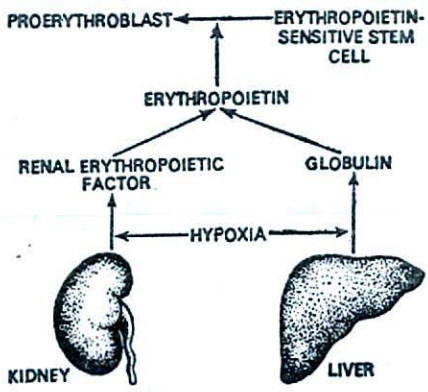


Fig. 1.16. Schematic representation of the role of kidney in erythropoiesis.

the blood by the interaction of renal erythropoietic factor (REF) or erythrogenin with the plasma globulin (Fig. 1.16). It is observed that this renal erythropoietic factor is only secreted from kidneys of dogs. But in other animals (rats and rabbits) and also in human beings this substance may be secreted even in absence of kidneys. The erythropoietin which is known as a hormone and having molecular weight of about 25,000-40,000, causes the certain stem cells (erythropoietin-sensitive stem cells) in the bone marrow to be converted to **proerythroblast.** It is claimed that the action of erythropoietin is apparently mediated through the stimulation of mRNA synthesis. The blood level of erythropoietin thus plays an important part in the control of erythropoiesis.

The **REF or erythrogenin** is known to be the secretion of juxtaglomerular cells. Its production is increased by hypoxia, cobalt salts and androgens. Cobalt salt stimulates the production of erythropoietin by causing degranulation of the epithelioid cells.

Juxtaglomerular cells are granular epithelioid cells situated in the media of the preglomerular portion of the afferent and occasionally of the efferent arterioles and also in the adjacent connective tissue. Granulation in the juxtaglomerular cells is related with the presence of secretable renin. Also it is observed that flourescent antirenin antibodies localise in the juxtaglomerular cells. These two are evidences to suggest that the juxtaglomerular cells are the source of renin. Renin secretion is determined by the degree of stretch of the afferent glomerulus and also by the Na-concentration of the macula densa cells.

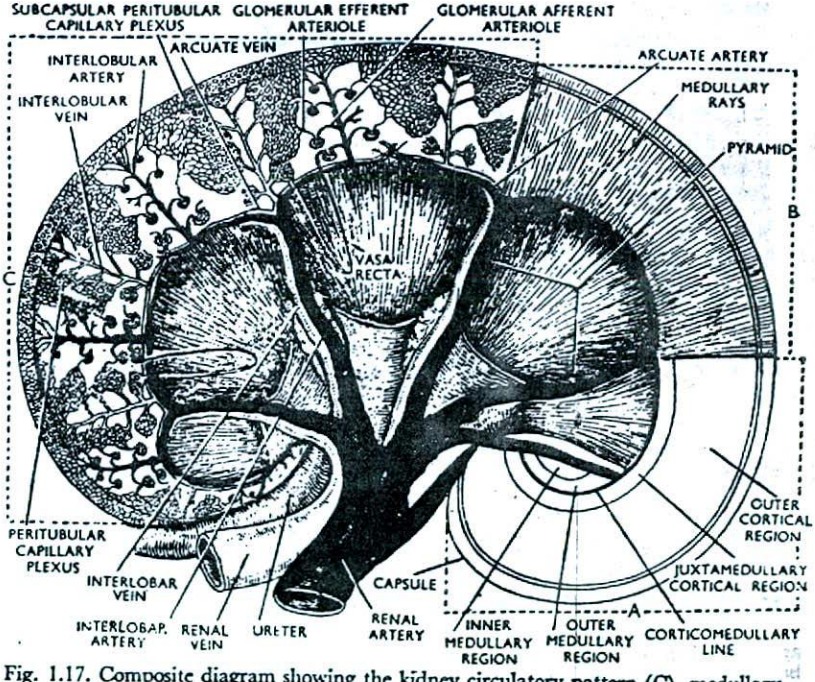


Fig. 1.17. Composite diagram showing the kidney circulatory pattern (C), medullary rays and pyramid (B), and different zones of the kidney (A).

Macula densa is a modified epithelial cell in the portion of the distal convoluted tubule lying in contact with the afferent glomerular vessel of the same nephron. Macula densa cell does not possess the basement membrane (Fig. 1.5) and possess Golgi apparatus which lies between the nucleus of the epithelial cell and the outer border of the cell. Towards the glomerular side of the tubule, the cells are taller and thinner (Fig. 1.4).

'Lacis cell' is known as Polkissen (polar cushion) cell, Goormaghtigh's cell, pseudo-Meissnerian cell. It is a cell mass formed mainly by the agranular or occasional granular cells. These cells lies in close contact with the macula densa cells and also within the vascular pole formed by the afferent and efferent glomerular vessels.

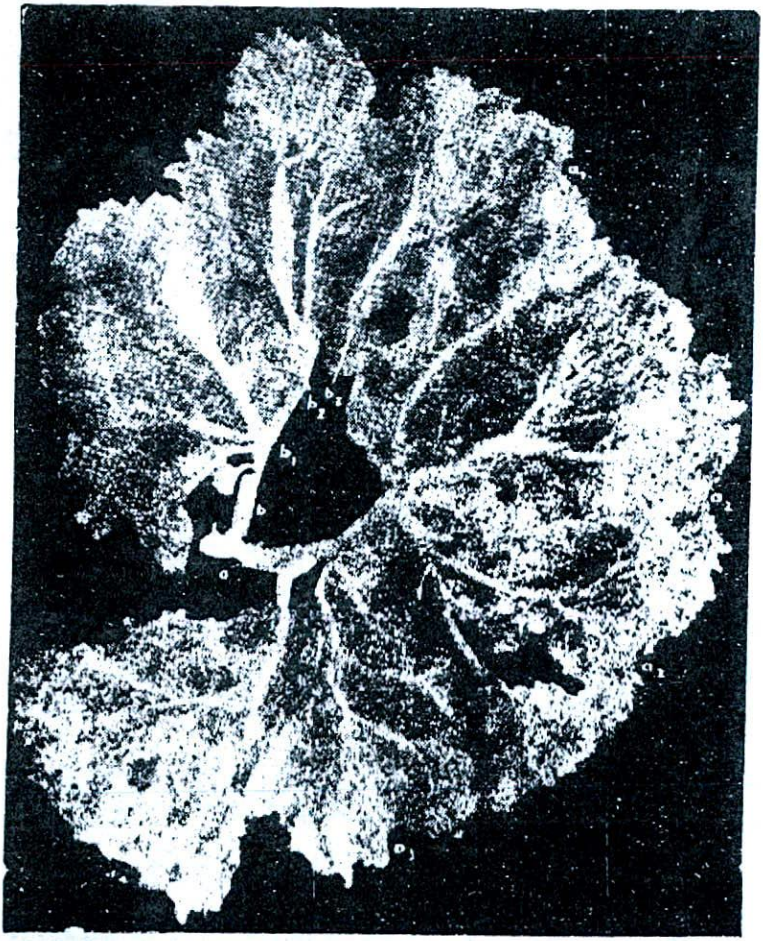


Fig. 1.18. Corrosion specimen of kidney showing branching arrangement of the renal artery. (Mag. × 5). 1 = trunk of renal artery; a_1 = anterior division; a = apical branch; a_2 = upper middle branch; a_3 = lower middle branch; a_4 = lower branch; b = posterior division; b_1, b_2 & b_3 = showing respectively upper, middle and lower branches of the posterior divisions. *By courtesy of Dr. A.K. Datta, M.B.B.S., M.Sc. Med.).*

RENAL CIRCULATION

The renal arteries arise nearly at right angle from the sides of the abdominal aortta. Upon or just before entering the hilus of the kidney the renal artery (70%) on each side divides into an anterior and a posterior division. The primary branches of the division supply the five renal vascular segments (anterior, apical, upper middle, lower middle, lower and posterior). These primary branches are called segmental arteries (Fig. 1.18). Usually these segmental arteries are end arteries.

Each segmental artery divides into lobar branches, one for each renal pyramid (Fig 1.17). Those branches which pass between renal pyramids are known as interlobar (straight) arteries. Each interlobar artery gives off branches which run across the bases of the pyramids and are called arcuate (arciform) arteries. There is no communication between these arcuate arteries (Fig. 1.19). These arteries again give off small branches called small interlobular arteries which run radially through the cortex towards the renal surface.

In the case of superficial cortical glomeruli, the interlobular artery breaks up into a number of arterioles, most of which one forms an afferent vessel to the glomerulus. Just before entering the glomerulus, the afferent arterioles are found to contain numerous juxtaglomerular cells. Each afferent arteriole devides into about 50 capillaries which stay close together to form the glomerulus which lies within the cortex of the kidney. This capillary tuft reunites and forms the efferent arteriole. This vessel again breaks up into a second set of capillary network which twins round the different parts of the corresponding renal tubule (peritubular network) (Fig 1.17). Ludwig has described that the afferent vessels (aglomerular arterioles, probably the result of previous glomerular degeneration) in the corticomedullary zone without forming the glomerular tuft may sometimes join directly the medullary peritubular capillaries as by-pass (**Ludwig shunt**). This by-pass may have some functional importance during emergency. This is very infrequent in normal kidneys of dog, cat and man. The afferent vessel is short and wide, while the efferent vessel is thin and long. This arrangement makes the blood pressure in the glomeruli relatively higher—making it more suitable for filtration. Moreover, the afferent vessel rises directly from the interlobular artery at an angle



Fig. 1.19. Arteriogram on coronal section of kidney showing absence of arcuate arteries. *By courtesy of Dr. A.K. Datta, M.B.B.S. M. Sc. (Med.).*

advantageous for the free flow of blood. Since superficial cortical glomeruli constitute 85% of the total number, the major part of renal circulation normally passes through them.

In the case of juxtamedullary glomeruli, circulatory pecularities (Fig. 1.20) are as follows: (1) There is no disparity between afferent and efferent vessels, even the efferent arteriole may be larger. (2) The afferent vessel though large yet arises at an angle not suitable for free flow of the blood stream. Hence, normally they have little work to do. Very little blood passes through them. But in time of stress a large quantity of blood may be shunted through them. (3) The efferent vessel breaks up into a number of straight vessels—the vasa recta, which for the most parts do not join the peritubular network but descends closely applied to the descending and ascending loops of Henle and to the collecting ducts and drain almost directly into the capillary venous plexus **(Trueta shunt).** These are known as descending vasa vecta. Thus the medulla gets blood supply mostly from the vasa recta originating from the efferent arterioles of the juxtamedullary glomeruli. Blood from the capillary venous plexus in the medulla drain into the arcuate or interlobular veins via ascending vasa vecta. In the outer medulla both ascending and descending vasa vecta are grouped into vascular bundles within which they are closely apposed to each other. This close relationship of ascending and descending vasa vecta with each other and with the surrounding duct system provides the structural basis for diffusional exchanges between outflowing and inflowing blood (counter-current exchange and multiplier system).

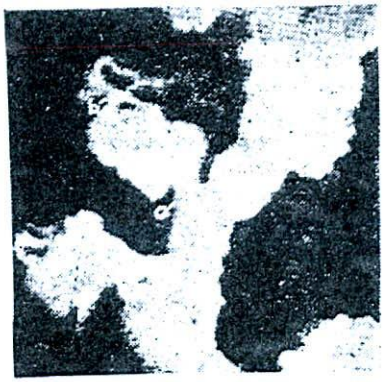


Fig. 1.20. Microphotograph of the glomeruli. (Mag. × 45). a= afferent glomerular vessel; b= efferent golmerular vessel. *By courtesy of Dr. A. K. Datta, M.B.B.S., M.Sc. (Med.).*

The venous return of the kidneys starts in a venous plexus in the cortex where all the capillaries drain. From this plexus blood passes through the **interlobular veins** which accompany the corresponding arteries. The interlobular veins unite to form the large **arcuate (arciform) veins.** In the medulla *straight radially* arranged veins known as **venulae rectae** directly open into the arcuate veins. The arcuate veins fuse to form **interlobar veins** which ultimately join the renal vein. Some venous blood passes through the **venae stellatae** under the capsule and joins the **perirenal veins.**

Peculiarities of renal circulation. From the above, the peculiarities of renal circulation may be summarised as follows:

1. Almost all blood that passes through the kidney has to pass through the glomerular tuft.

2. *Renal circulation is a portal system.* The blood has to pass through double capillary network—at first through the glomerular capillaries and then through the peritubular capillaries. So, almost all blood that reaches

the tubule has to cross the glomerular tuft. These two capillary systems serve two different functions: (*i*) The glomerular tuft filters. (*ii*) The tubular tuft reabsorbs.

3. *Renal blood pressure is comparatively high.* This is due to two reasons: (*a*) The renal artery is short and wide, and arises directly from the aorta. It divides into a small number of wide branches. Owing to this arrangement, blood enters the kidneys at a comparatively high pressure. (*b*) The afferent glomerular vessel is wider and shorter than the efferent vessel. Due to this, glomerular pressure remains fairly high and is about three to four times more than the capillary pressure elsewhere. It is about 75 mm Hg (same as the diastolic pressure of the subject). This high glomerular pressure is very suitable for filtration.

4. *Rate of blood supply to the kidney is comparatively high.* About 1,200—1,300 ml of blood (about 25-30% of cardiac output) pass through the two kidneys per minute in a man weiging about 70 kg at rest and the plasma flow is 600 ml per minute as is determined by para-amino-hippuric clearence test. The total quantity of blood in the human body may circulate through the kidneys in four to five minutes.

5. There are two circulations in the kidney—the *greater* and the *lesser*. The greater circulation carries 85% of blood and first passes through the superficial cortical glomeruli, then through the peritubular network and finally joins the renal vein. The lesser circulation carries only 15% of blood normally and passes through the juxtamedullary glomeruli. The efferent glomerular vessels, after a short straight course, **vasa recta,** join (mostly) the renal vein directly and join partly the peritubular network. Under abnormal conditions it may act as a 'shunt' —*Trueta shunt.*

6. Extraglomerular vessels of Ludwig—though not of much importance normally—may serve important functions in chronic kidney disease where the glomeruli are blocked.

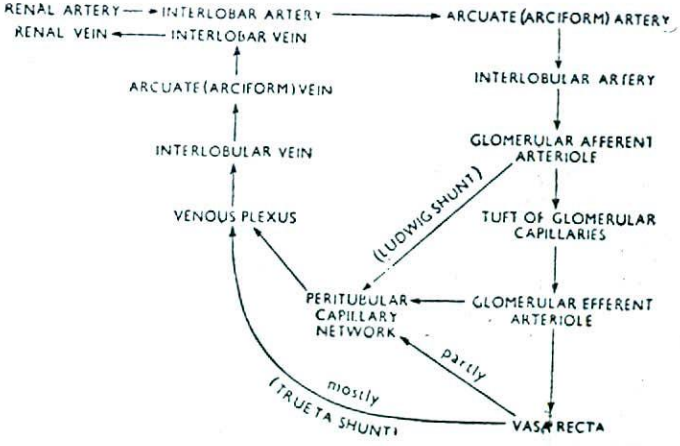


Fig. 1.21. Schematic representation of the anatomical organisation of the renal circulation.

7. In man and animal under basal condition, renal blood flow is not altered in denervated or innervated kidney. This shows that there is no neurogenic vascular tone in kidney under basal state.

8. Neurogenic vasodilatation is also non-existent and vasoconstriction can only be produced by stimulating the sympathetic nerve. Neurogenic vasodilatation in renal blood vessels can be produced by stimulation of the receptors in the carotid sinus and aortic arch in condition having pre-existing vasomotor tone due to hypoxia or by any reason.

The anatomy of renal circulation including its peculiarities in cortical and juxtamedullary regions has been presented schematically in Fig. 1.21.

Lymphatic supply. An abundant lymphatic supply of the ktdney drins via the thoracic duct into the venous circulation inthe thorox.

Nerve supply. The kidneys are supplied mainly by the sympathetic but there are some parasympathetic fibres also. The sympathetic come mainly from the 10th to 12th thoracic segments and the parasympathetic from the vagus. The sympathetic carries vasoconstrictor and afferent fibres. The autonomic fibres also supply the tubular cells and reabsorption of sodium is probably influenced by these nerves.

NORMAL RENAL BLOOD FLOW

The blood flow is much greater in the renal cortex than in the renal medulla.

In a resting state and with a normal arterial blood pressure about 1,200-1,300 ml of blood or 25-30% of total cardiac output passes through both human kidneys per minute.

Blood flow per gram of kidney tissue has been observed to be 4 ml per minute, but the distribution pattern of blood to the different parts of the kidneys is not similar and varies from area to area. In the kidneys there are two capillary beds united in series. These are the glomerular capillaries and the peritubular capillaries. These capillary beds are separated by vasa efferentia. The **vasa afferentia** (*preglomerular*) and **vasa efferentia** (*postglomerular*) behave functionally and anatomically like *arterioles*. Main pressure drops in the kidneys are observed in these vascular beds. Pressure gradients in the renal vascular beds have been observed in Fig. 1.22

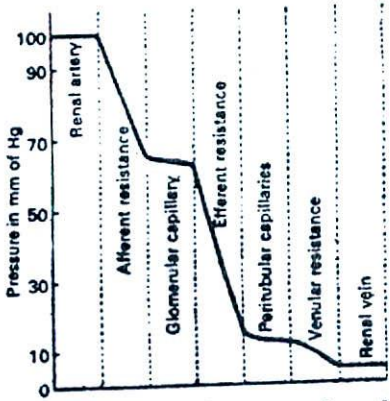


Fig. 1.22 Graphical representation of pressure gradients in renal circulation. The areas of major pressure change are afferent arterioles and efferent arterioles.

Blood flow rate in the cortex is higher than that in the medulla. Blood flow values obtained in the unanaesthetised dog are 4·5-5 ml/g/minute in the cortex, 1·25-1·50 ml/g/minute in the *outer* medulla and 0·15-0·2 ml/g/minute in the *inner* medulla. This lower blood flow rate in the medulla is possibly due to (*i*) unusual length of the *vasa recta* and (*ii*) increase of blood viscosity in the medulla caused by the transmembranous shunting of water from the descending limb to the ascending limb of the *vasa recta*.

Autoregulation of renal blood flow. Within the physiological limit kidney has the peculiarity of maintaining the normal blood flow under any conditions. This self-controlling mechanism of blood flow is known as *autoregulation*. Mostly all the vascular beds follow the haemodynamic principle with the exception of renal bed, which behaves indifferently. In the renal bed if the pressure is increased then the flow is also increased in response to pressure up to 90 mm Hg and further increase of pressure up to 250 mm Hg will have little effect in renal plasma flow (Fig. 1.23). But if the pressure is increased further above 250 mm Hg, then the regulation may fail. **Glomerular filtration rate** (GFR) varies less than the **renal plasma flow** (RPF). In an average sized man the GFR is about 125 ml per minute. But fall of systemic blood pressure below 90 mm Hg drops the GFR very sharply (Fig. 1.24). This autoregulation is only present in the cortex. Extrinsic reflex mechanism is non-existent and it is observed in isolated as well as in denervated kidneys.

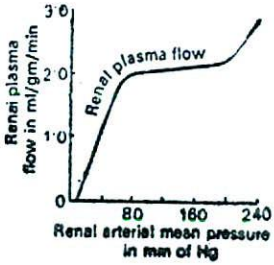


Fig. 1.23. Graphical tracing shows the autoregulation of RPF.

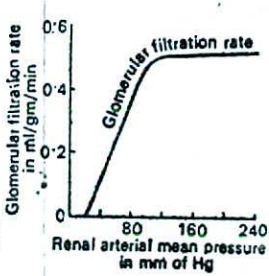


Fig. 1.24. Graphical tracing shows the autoregulation of GFR.

Mechanism of autoregulation in the kidney is inconclusive though several theories have been postulated in explaining the peculiar behaviour of the kidney vessels.

(*a*) **Myogenic theory.** According to this theory, the smooth muscles which present in the preglomerular blood vessels are capable of reacting to distention by shortening during elevation of perfusion pressure. Thus the preglomerular vascular tone is increased due to this myogenic response to increased arterial blood pressure. This reactivity is abolished after paralysing the smooth muscles by potassium cyanide, papaverine and by high concentration of procaine.

(*b*) **Intrarenal reflex.** It has been suggested that the intrarenal reflexes are the possible mechanism in autoregulation and the use of ganglioplegic and sympatholytic agents may eliminate this mechanism. Both the intrarenal neurogenic component (axon reflex) and smooth muscles of the preglomerular blood vessel may play an important role in autoregulation.

(*c*) **Cell separation theory or Viscosity theory.** It has been claimed that with the increase of pressure, the viscosity of the blood in the cortical region mostly in the distal part of the interlobular arteries is greatly increased due to higher haematocrit value. Because in a large blood vessel, erythrocytes remain in the axis and the smaller branches get blood mostly devoid of erythrocytes and thus the same are perfused by cell-free plasma. This is known as plasma skimming or cell separation. This cell separation occurs unusually in the afferent glomerular vessels and this is depending mostly upon the increased perfusion pressure. So with the increase of

pressure, resistance likely the viscosity in the interlobular arteries as well as in the cortex is increased greatly due to greater accumulation of red cells and thus the constancy in the flow is maintained. However if the kidney is perfused with cell-free plasma, then the autoregulation does occur, which goes against the hypothesis.

(*d*) **Intrarenal tissue pressure theory.** It has been observed by inserting a 24-gauge needle into the renal tissue that with the increase of perfusion pressure, the tissue pressure is increased disproportionately with creating a resistance to flow. This increased tissue pressure creates a clamping effect over the renal blood vessels to flow and thus a constant blood flow is maintained.

(*e*) **Intrarenal Na-feedback theory.** In this theory, importance has been given to the macula densa cells in the regulation of renin secretion from the glomerular afferent arterioles. If it is supposed that there is no autoregulation in the kidney, then with the increase of blood pressure, renal blood flow as well as the glomerular filtration rate (GFR) will be increased. Due to increased glomerular filtration rate, distal convoluted tubule will have greater Na-load which stimulates the liberation of renin from the juxtaglomerular cells. The renal blood flow as well as the glomerular filtration rate will be decreased due to renin-induced-cortical-preglomerular vasoconstriction. So, the Na-load in the distal convoluted tubule at the juxtaglomerular region may be the determinant of renal autoregulation. The intrarenal Na-feedback theory can be described schematically in Fig. 1.25.

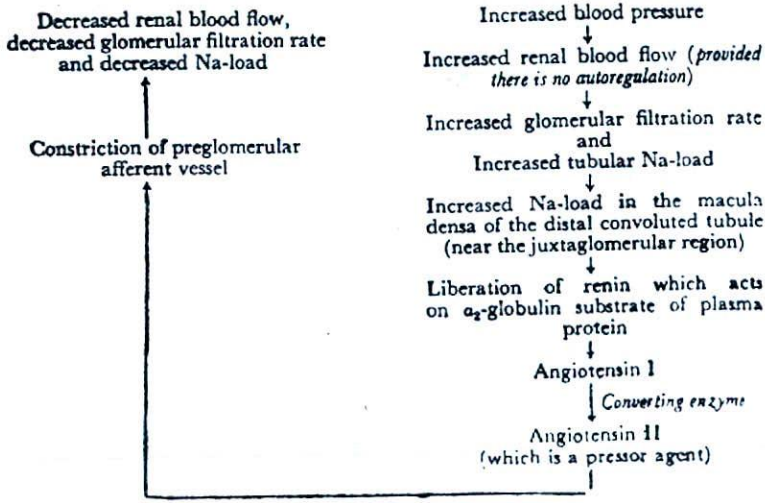


Fig. 1.25. Schematic representation showing the importance of macula densa in the autoregulation of renal blood flow through the Na-feedback theory.

Nervous control. Though the kidney has got both sympathetic and parasympathetic nerve supply yet its significance under resting basal state is very poorly understood. Under resting and recumbent positions, the renal

blood flow in the denervated kidney does not differ from that of the innervated kidney. Besides this, neurogenic vasodilatation is non-existent under resting state, but vasoconstriction can be induced by hypoxia or sympathetic nerve stimulation.

Pomeranz and others (1968) have observed vasodilatation in the outer medulla with simultaneous vasoconstriction in the outer cortical peritubular capillaries following mild stimulation of the splanchnic nerve. Though the cortical and medullary blood vessels behave differentially in response to mild stimulation of the splanchnic nerve yet the total blood flow to the kidney remains unaltered. But Aukland (1968) has observed profound decrease of renal blood flow in both the cortex and outer medulla following strong stimulation of the splanchnic nerve or administration of high dose of adrenaline (epinephrine).

Other **factors which may modify the renal circulatory haemodynamics** are:

Exercise, posture and central blood volume. Renal blood flow is decreased during exercise. *Exercise* in recumbent position has got no effect on renal blood flow but if the position is changed from recumbent to upright position then the circulation may be altered. For this reason renal blood flow remains unaltered in dog while running, because in dog, *posture* is not apparently changed. It has been observed that during upright posture *central blood volume* is reduced and this may reflexly produce vasoconstriction in the renal vascular bed. On the contrary, if the central blood volume is increased by negative pressure breathing, instead of renal vasodilatation, diuresis occurs. This diuretic effect has been claimed to be the reflex inhibition of secretion of antidiuretic hormone (ADH) through the stimulation of stretch receptors situated at the left atrial wall by increased central blood volume.

Hypoxia, hypercapnia and acidosis. With *mild hypoxia,* there may be a slight renal vasodilatation due to reactive hyperaemia but if the hypoxia is severe and prolonged then there may be profound vasoconstriction. This vasoconstrictor response during severe hypoxia has been claimed to be reflex chemoreceptor effect from the carotid body and aortic body. Because denervation either of the chemoreceptor or of the kidney fails to alter the renal haemodynamics.

Hypercapnia and *acidosis* also reduce renal blood flow. This effect has been described to be centrally mediated neurogenic action rather than local action, because this response is abolished following denervation of the kidney.

Clamping of the renal artery. During partial clamping of the renal artery, pressor substances may be formed due to liberation of renin from the juxtaglomerular cells only to maintain the renal haemodynamics. This formation of pressor substances may produce *systemic hypertension* (*renal hypertension*). It has been argued that renin secretion is an antihypotensive function of the kidney. Because it is the inherent protective mechanism of the cortical glomerular vessels to maintain the normal pressure and flow as well during circulatory insufficiency due to partial occlusion. Explanation is that, due to partial clamping, perfusion pressure in the afferent glomerular vessels falls which increases liberation of renin. This will raise the systemic blood pressure with the formation of angio-

tensin II and subsequently the glomerular blood flow will be resumed through increased systemic pressure.

Hypothermia. At the initial stage of hypothermia and when the body is trying to maintain its body temperature by shivering, a slight increase of renal blood flow can be observed. But this effect can be abolished, if the shivering is checked by administration of *d*-tubocurarine. But with gradual progress of hypothermia the renal blood flow begins to reduce. This decrease of renal blood flow is not clearly understood though the viscosity of blood is increased greatly due to cooling.

Hormones. Catecholamines constrict renal blood vessels. *Adrenaline* (*epinephrine*) and *noradrenaline* (*norepinephrine*) in small doses have a less effect on the affcrent than the efferent arterioles. They have got constrictor effect on the renal blood vessels either given intravenously or directly into the renal artery. *Pitressin* in a physiological dose with antidiuretic effect has got no effect on renal blood flow. But in higher doses it may produce vasoconstriction. *Serotonin* (*5-Hydroxytryptamine*) has got peculiar effect on renal circulation. If it is infused directly into the renal artery in a dosage of 10 μg to 100 μg per minute then it increases the vascular resistance (Emanuel and Others, 1959) through vasoconstriction. This effect is observed in both denervated and innervated kidneys. On the other hand, if the serotonin is administered intravenously then it produces renal hyperaemia with a striking antidiuretic effect. This renal hyperaemia is reflex in origin.

Other pharmacological agents. Ephedrine, phenylpropanolamine, hydroxyamphetamine when injected intravenously have got no constrictor effect but if administered directly into the renal artery, then they produce vasoconstriction. Apresoline (Hydralazine), a drug used to treat high blood pressure, lowers the systemic blood pressure by reducing the vascular resistance, but increases the renal blood flow. Xanthine group of drugs like caffeine and theophylline have got effect on renal circulation. It increases the glomerular filtration rate. High protein diet increases renal blood flow. Bacterial pyrogen increases renal blood flow.

Anaesthetic agents. It has been pointed out by many that anaesthetic agents have got effects on renal plasma flow, glomerular filtration rate, etc. During light anaesthesia, there may be a redistribution of blood from splanchnic beds to the skin and muscles of the extremities. So under such state the kidney is also affected. But during deep and sustained anaesthesia, renal blood flow is decreased all throughout.

Renin and Angiotensin

Ischaemic kidney produces **hypertension.** Such kidney liberates a substance—**renin.** It is produced in the cortex of the kidney (juxtaglomerular cells of the afferent glomerular vessels and also other components of the juxtaglomerular apparatus). Possibly stretch or other receptors, present in these cells when stimulated, are reponsible for elevated renin secretion. This response takes place in denervated as well as in transplanted kidneys.

Stimuli, *viz.* shock, low sodium intake and intrathoracic concentration of the inferior vena cava increase the granularity of the juxtaglomerular apparatus, while hypertension, DOCA and high salt diet decrease it. It is also suggested that a stimulus for renin production is a decrease in intramural tension of the wall of the afferent glomerular

arteriole, so that a decrease in renal perfusion results in increased renin production and conversely.

The mechanism of the release of renin is still a complicated one and requires further study. It has been discussed earlier (*vide* page 1-208) that increased Na-load due to increased blood pressure and glomerular filtration rate (GFR) in the macula densa may stimulate the release of renin (Goormaghtigh). Renin release is also dependent upon sympathetic nerve activity as observed following renal nerve stimulation (Vander, 1965). Adrenaline (epinephrine) and noradrenaline (norepinephrine) also stimulate the release of renin.

Vasopressin, aldosterone and angiotensin II have got inhibiting effects on renin release. These activities are claimed to be the feedback inhibition in normal physiological condition. Increased blood volume has also got similar role. Possible mechanisms of the release of renin-angiotensin and its subsequent relation with other bodily processes have been presented schematically in Fig. 1.26.

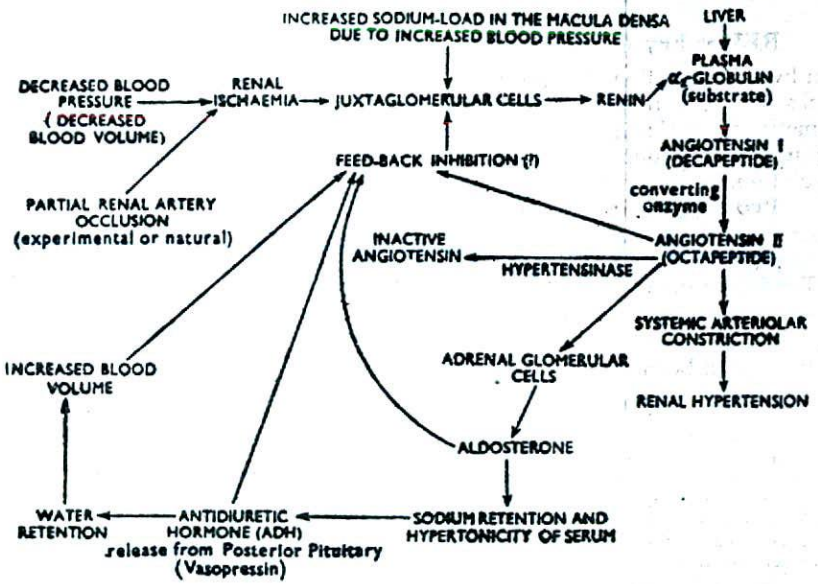


Fig. 1.26. Schematic representation of probable mechanisms of the release of renin-angiotensin and its subsequent relation with other bodily processes.

Renin is a proteolytic enzyme and interacts with a normal plasma α_2-globulin (angiotensinogen or hypertensinogen) and forms angiotensin I (Fig. 1.26). **Angiotensin I** (decapeptide) is an inactive compound. Plasma enzyme (converting enzyme) interacts with angiotensin I and forms angiotensin II (octapeptide). Amino acid sequences of angiotensin I and II have been presented in Fig. 1.27. **Angiotensin II**(formerly known as hypertensin or angiotonin) constricts blood vessels and raises systemic blood pressure. It also stimulates the secretion of aldosterone

from the adrenal cortex. It has been suggested that the secretion of aldosterone through angiotensin II is primarily dependent upon adrenocorticotrophic hormone (ACTH) level in blood. Angiotensinase or hypertensinase, present in many tissues, breaks down angiotensin II into inactive angiotensin.

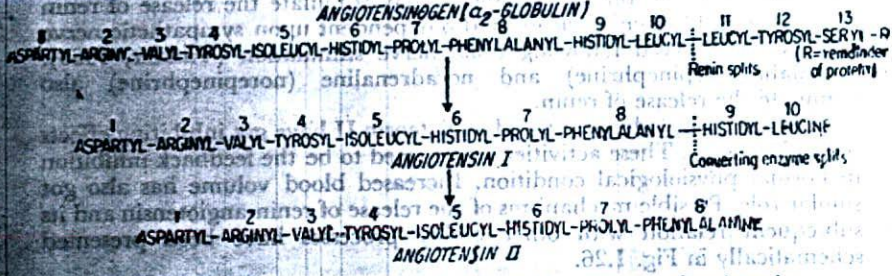


Fig. 1.27. Schematic representation of amino acid sequences of angiotensins.

REF or Erythrogenin and Erythropoietin (*vide* pages 1-12 & 1-13.)

In hypoxia, renal erythropoietin factor (REF) is secreted from glomerular cells and it is related to the formation of erythropoietin. This erythropoietin is concerned with the regulation of normal erythropoiesis. It is not at all concerned with blood pressure regulation or aldosterone secretion.

Prostaglandins. In the kidneys primary protaglandins cause an increase in renal blood flow and vasodilation.

Kininogen. It produced by the kidneys has an anti-hypertensive effect and regulates blood pressure.

Insulin and glucagon. They are destroyed within the kidneys.

The kidneys also play a vital role acting as a receptor organs for parathyroid hormones, androgen and vasopressin.

MEASUREMENT OF RENAL BLOOD FLOW

It can be measured in animlas (1) by **venous-sunt technique** or (2) by **Fick principle.**

Venous-shunt technique. A cannula is inserted in the left ovarian vein (which joins the left renal vein), the renal vein is occluded for a brief period, venous blood from left kidney is shunted along the ovarian vein and is directly measured by a volume recorder. This method can be adopted for measuring the venous flow in any part of the body where two veins join to form a common vein.

Fick principle. Let P and V be the concentrations in mg%, of a particular constituent (*C*) in the plasma of renal arterial and renal venous blood respectively. Let Um be the output in mg of the same substance (*C*) in the urine per minute. So that 100 ml of arterial plasma enter kidney with P, leave with V and lose P—V.

P—V is, therefore, excreted from 100 ml of renal plasma flow.

$\therefore$ Um will be excreted from $\frac{100}{P-V} \times Um$ = ml of renal plasma flow per minute.

Thus renal plasma flow per minute is known. From the haematocrit reading, the total blood flow can be calculated.

In man, renal vein puncture is not practicable. This principle, therefore, can only be used if the degree of 'extraction' is constant and is known. The term **extraction** indicates the ratio (P—V)/P and represents that fraction of the arterial plasma concentration (of a constituent) which is excreted by the kidney. If the extraction is complete and none of the constituent (*C*) escapes in the renal vein, V becomes 0. Consequently,

the formula for renal plasma flow becomes (100/P) × Um. That is, only arterial blood and urine need be analysed. **Diodrast (Diodone)** and such other organic iodine compounds fulfil this condition and may be used for this purpose. When it is injected into the blood to produce an iodine concentration not exceeding 5 mg (even up to 15 mg), it is completely extracted by the kidney. After injecting the requisite quantity, the concentration in the arterial blood and the minute output in the urine are measured. From these data the renal blood flow in man can be calculated. With this method the human renal blood flow comes to about 900-1,300 ml (plasma 450-700 ml) per minute.

FUNCTIONS OF KIDNEY AND GLOMERULUS

Functions of kidney

1. *It excretes waste products, especially the nitrogenous and sulphur-containing end products of protein metabolism.*
2. *It helps to maintain the normal hydrogen-ion concentration of body fluids and electrolytes.*
3. *It helps to maintain water balance of the body and thereby plasma volume.*
4. *It helps to maintain the optimum concentration of certain constituents of blood (by the process of selective reabsorption).*
5. *It eliminates drugs and various toxic substances from the body.*
6. *It manufactures certain new substances—ammonia, hippuric acid and inorganic phosphates. Ammonia helps in preserving acid-base equilibrium.*
7. *It helps in maintaining the osmotic pressures in blood and tissues.*
8. *It helps in the regulation of blood pressure during hypoxia in condition of emergency through the liberation of renin from the juxtaglomerular apparatus.*
9. *It helps in the regulation of erythropoiesis through the formation of erythropoietin by REF secreted from the glomerular cells.*
10. *It plays an important role in vitamin D metabolism.*

Functions of glomerulus*

A fine filter *(millipore filter)* can separate the red cells from the plasma (blood), yet the process is a simple filtration. Still finer process is ultrafiltration by which colloidal materials, e.g., proteins and fats can be removed from solution. *The glomeruli act as ultrafilters. The process of filtration in the glomerulus is a passive process and never an active one. They filter all the constituents of plasma excepting the colloids* (i.e., proteins and fats). The facts upon which this conclusion is based are briefly summarised below:

1. *The effective filtration pressure of the glomerular capillaries.*
2. *The amount of fluid formed must be directly proportional to the quantity of blood flowing through the kidneys per unit time.*
3. *The capsular fluid must have the same composition as the plasma, excepting its colloids.*
4. *Actual filtering pores must be present in the filtering membrane.*

Each one of these conditions is found to be satisfied by the glomerulus.

Evidences for them are briefly summarised below :

Effective filtration pressure. The glomerular hydrostatic (capillary) pressure averages about 75 mm Hg. The colloidal osmotic pressure of plasma proteins averages only about 30 mm Hg. The hydrostatic pressure in Bowman's capsule (intracapsular hydrostatic pressure) is about 20 mm Hg (interstitial pressure, 10 mm Hg and intratubular fluid

*To be accurate, the term 'Malpighian body' should be used instead of 'glomerulus'.

pressure, 10 mm Hg). Of these three factors, blood pressure is the motive force for filtration. The other two oppose the process of filtration. So, the net or *effective filtration pressure* is about 25 mm Hg and this is the force upon which filtration depends (Fig. 1.28). It has been proved by the experiment in which the pressure in the capsular space is artificially raised to the same height as the effective filtration pressure, when formation of filtrate is found to cease. It is also obseraed by the fact that a rise of glomerular pressure increases, whereas a fall of pressure diminishes the amount of capsular fluid formed. On the other hand, when the concentration of plasma proteins is lowered (such as, by intravenous saline injections) the colloidal osmotic pressure is reduced increasing the effectiae filtration pressure and thereby increasing the formation of capsular filtrate.

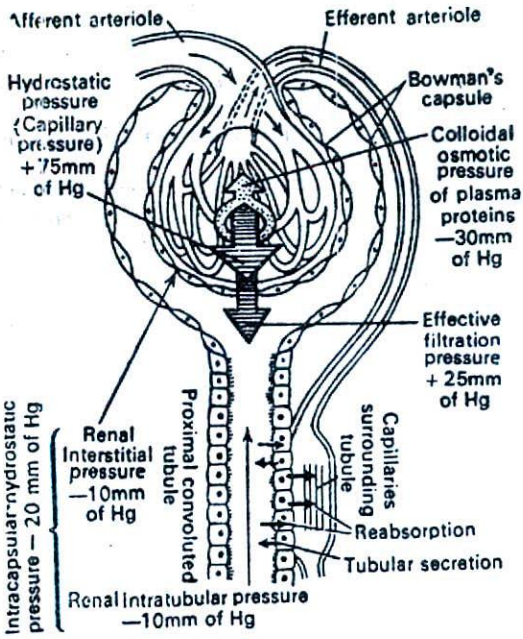


Fig. 1.28. Diagram showing the factors controlling the net or effective filtration pressure (15 mm Hg) within the glomerulus.

Effective filtration pressure may be expressed thus:

EFP=GCP—(GOP+CHP)

where

EFP=*effective or net filtration pressure,*

GCP=*glomerular capillary pressure,*

GOP=*glomerular osmotic pressure,*

CHP=*capsular hydrostatic pressure.*

Composition of the capsular filtrate by micropuncture techniques. The most *direct evidence* has been supplied by the experiments of Richards and his associates. These observers have succeeded in introducing a fine quartz pipette into Bowman's capsule of the amphibian (frog) kidney and collected fluid directly from the capsular space (Fig. 1.29). By microanalysis it was found to be similar to blood plasma without the colloid, i.e., a protein-free fluid obtained. For instance, the crystalloid concensration, osmotic pressure, pH, electrical conductivity, etc., were all same.

Presence of filtering pores in the filtering bed of the glomerules: *Filtering pores* are actually present in the capillary endothelium and capsular epithelium. Their diameters can be measured by injecting substances with known molecular weight and size, and watching their appearance in the urine. If the injected substance be found in the

urine, obviously it has passed through the filter bed. So, the size of the filtering pores is bigger than the size of the molecule. With such experiments, it is seen that *serum albumin* (molecular weight 70,000, size 6-7 millimicrons) cannot pass. *Serum globulin* (mol. wt. 170,000) and *fibrinogen* having still bigger molecule also fail to pass. But *haemoglobin* (mol. wt. 68,000) can freely pass out. Gelatin, Bence Jones proteins, egg albumin (mol. wt. 35,000 and size about 4 millimicrons), being smaller than haemoglobin, easily pass through. This proves that the size of the filtering pores is such as will allow the molecules with less than 70,000 mol. wt. to pass out, but not the bigger ones. Serum albumin thus lies on the border line. Normally a very small amount of serum protein (protein per cent less than 0·03) is present in the glomerular fluid and is reabsorbed in the renal tubules. Electron micrograph has revealed that the diameter of the filtering pores of the capillary endothelium and capsular epithelium are about 50-100 nm and 25 nm respectively. In anoxia, heart failure, and other pathological conditions, where the membrane becomes damaged, the filtering pores enlarge in size, so that serum albumin, passes out in the largest amounts and appears in the urine. *This is one of the causes of* **albuminuria.**

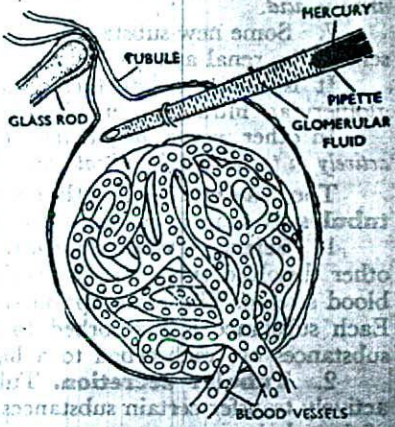


Fig. 1.29. Illustrating Richards' method of obtaining a sample of the fluid from Bowman's capsule.

All the above evidences go to prove that glomeruli act as **ultrafilters.** It has been shown that 1,200-1,300 ml of blood, i.e., about 660 (770) ml of plasma passes through the kidneys per minute. Out of this, 120 ml of filtrate is formed by the glomeruli per minute. In 24 hours the total volume of glomerular filtrate is about **170 litres. The term filtration fraction** means the ratio between the volume of glomerular filtrate and the plasma flow per minute. Here it is 120/660 (700) = 0·17 (0·18). *This ratio indicates the efficiency of the filter bed.*

Functions of renal tubules

It is known that the capsular filtrate has the same composition as plasma excepting the colloids. When this fluid is compared to the fully formed urine, certain remarkable differences are noticed. The differences are briefly summariesed below:

1. *The total volume of urine in 24 hours is much less than the amount of glomerular filtrate* formed during the same time. It is known that about 170 litres of filtrate are formed by the glomeruli in 24 hours, whereas only 1·5 litres of urine are excreted per day.

2. *Some substances are present in the glomerular filtrate but are practically absent in the urine,* for instance, glucose and bicarbonates.

3. *The solid constituents are much more concentrated in urine than in the glomerular fluid* (i.e., in plasma).

4. *All the solids do not undergo the same degree of concentration.* Each one of them has a different concentration in the urine.

5. *The total quantity of some solid substances* in the urine is much more than that of glomerular filtrate.

6. *Glomerular filtrate is alkaline in reaction* (same as plasma) but *the urine is acid.*

7. Some new substances are present in the urine which are not present in the renal artery.

It is obvious that these changes must have taken place in the glomerular filtrate when the latter passes down the tubules.

In other words, *the function of the tubules is to bring about these changes actively in the glomerular filtrate and thus convert the latter into fully formed urine.*

The **modern conception about the functions of the renal tubules** is that it performs the following *three functions:*

1. **Selective reabsorption.** The renal tubules reabsorb water and other dissolved substances from the lumen of the tubule back into the blood stream. The reabsorption is differential and purposefully selective. Each substance is reabsorbed to a particular degree. The more useful substances are reabsorbed to a higher degree than the less useful ones.

2. **Tubular secretion.** Tubules not only reabsorb but can also actively transfer certain substances from the blood stream into the lumen of the tubules.

3. **Formation of some new substances.** The tubular epithelium can also form certain new substances such as ammonia, inorganic phosphate, etc.

Methods of study of tubular functions

The tubular function has been studied by (1) analysis of the composition of the fluid withdrawn from the tubules with micropipettes by the micropuncture technique (Fig. 1.30) and (2) stop-flow method.



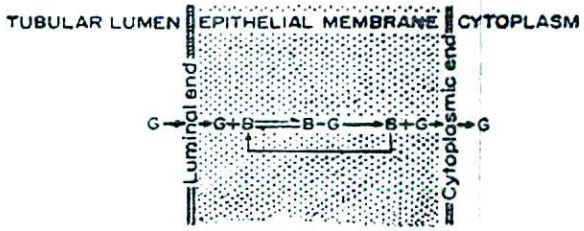
Fig. 1.30. Showing Richards' method of collecting samples of fluid from different parts of the tubule by insertion of micropipettes. P and P' = micropipettes.

I. SELECTIVE REABSORPTION

Protein. Normally a small amount of protein that is filtered into glomerular filtrate, is reabsorbed through the brush border of the proximal tubular epithelium by the process of *pinocytosis.* [The protein is adsorbed on the membranes which engulf it, forming a pinocytic vesicle. Hydrolytic enzymes, elaborated by the lysosomes present inside the vesicle, digest the protein and evenly distribute the amino acids liberated.]

Glucose. Under normal condition glucose is completely reabsorbed in the first half of the proximal tubules. It is evidenced with micropuncture technique after adding *glucose* to the perfusing fluid of the proximal tubule, that this portion has reabsorptive capacity for glucose as the quantity of glucose in the filtrate is diminishing gradually. But when the glucose was added to the distal tubule, it is evidenced that this part of the renal tubule

has got no capacity for glucose reabsorption as the whole amount of glucose is appearing in the urine. In this portion of renal tubule the concentration of glucose increases only due to reabsorption of water. The amount absorbed increases as the concentration of glucose in the plasma is raised. Glucose absorption is inhibited by phloridzin, but unaffected by insulin. Approximately 100 mg of glucose are filtered per minute. Of this only a small fraction is excreted in urine. Evidently, the transport of glucose is effected against a concentration gradient and, since glucose carries no electrical charge, its transport must be an active process. Fructose, galactose and some of the pentoses are also actively reabsorbed.



B=carrier, G=glucose.

Fig. 1.31. Schematic representation of the possible mechanism of reabsorption of glucose in the renal tubule.

Regarding the **mechanism of reabsorption of glucose,** no direct evidence has yet been obtained. A more acceptable description was made by Shannon (1939). He has suggested that a *carrier substance* is present at the luminal wall of the tubular epithelium at the proximal end. The amount of these carrier substances is fixed and limited. At the luminal surface of the apical membrane, the carrier (B) combines with glucose (G) of the tubular fluid to form a reversible carrier-glucose (G—B) complex which then migrates towards the cytoplasmic end of the membrane and splits up. The free glucose is then delivered to the cytoplasm. This free carrier again goes back to its original position to combine with another molecule of glucose (Fig. 1.31).

The reabsorption rate of glucose depends on the availability of the carrier. This limitation of the capacity of tubular cells to reabsorb glucose is termed as Tm for glucose or Tm_G in short. So the glucose reabsorptive mechanism is a Tm limited one, The average value for man is 375 mg/minute/1·73 square metre of body surface area and for woman is 300 mg/ minute/1·73 square metre of body surface area. If the glucose concentration of the filtrate is lower than this value, the total amount of glucose is reabsorbed. Under hyperglycaemic state

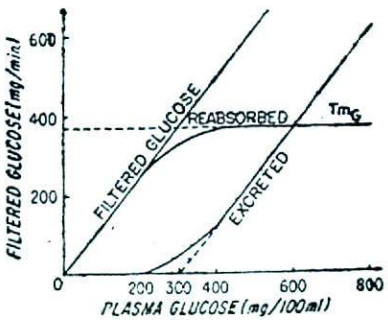


Fig. 1.32. Relative rates of glucose filtration, reabsorption and excretion in human kidney (diagrammatic).

and also in higher glucose concentration in glomerular filtrate (GF) than the Tm_G, the capacity of the carrier system fails to reabsorb glucose completely, and so the excess glucose appears in the urine (Glycosuria) (Fig. 1.32). This is often observed when the venom blood-glucose level exceeds the threshold value (180 mg%) (which corrosponds to an arterial level of 200 mg%). It is suggested that not all of the 2 million nephrons in the kidneys have exactly same transfer maximum glucose (Tm_G) or filtration rate; in some, Tm_G is exceeded at low levels of plasma glucose (P_G). Or some glucose excapes reabsorption when the amount filtered is below the Tm_G, because the reactions involved in glucose transport are not completely irreversible. This deviation is called **splay.**

Water. Out of 170 litres of water filtered by the glomeruli per day, 168·5 litres are reabsorbed in the renal tubules. Only 1·5 litres are excreted as urine. The reabsorption of water occurs in the proximal, distal and collecting tubules.

The normal osmolality (Fig. 1.33) of plasma is about 280 milliosmol/litre and is maintained by the kidney's ability to excrete water and sodium. The proximal tubule has got high water permeability. About

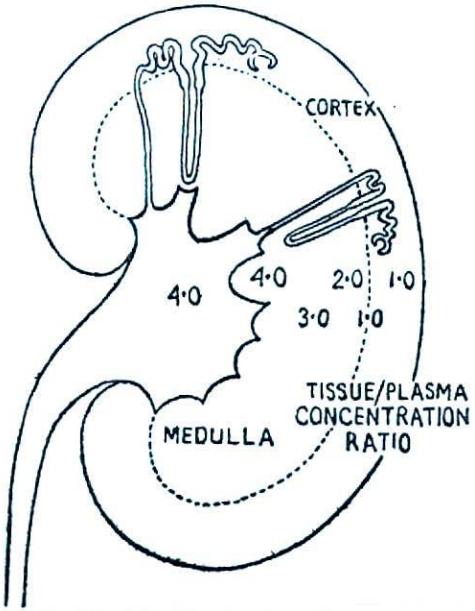


Fig. 1.33. The mechanism of osmolar concentration of urine at the depth of the kidney.
After Janaieson and Kay's Text Book of Surgical Physiology.

two-thirds to seven-eights of water of the glomerular filtrate are reabsorbed in the proximal tubule. *Active* reabsorption of *sodium* along with *passive* reabsorption of *water* takes place in the proximal tubule. Here water and electrolytes are reabsorbed as an *isosmotic* solution and do not play any

part in the concentration or dilution process. This is called **obligatory water reabsorption.** In the proximal portion of renal tubule, the sodium as well as potassium are reabsorbed actively but chloride reabsorption is a *passive* process (Fig. 1.34). Water is reabsorbed passively at osmotically equivalent rates. So the tubular fluid leaving the proximal tubule is *isotonic*.

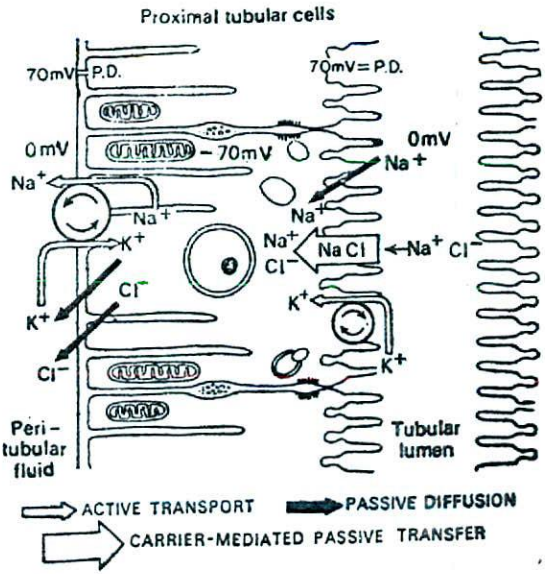


Fig. 1.34. Schematic representation of ion exchange in the first convoluted tubular cells (diagrammatic).

The fluid in the descending limb of the loop of Henle maintains the same osmotic pressure as the interstitial fluid, and H_2O and Na^+ pass by diffusion into and from the interstitium respectively. The ascending limb of the loop of Henle is impermeable to H_2O and it is there that sodium is pumped out actively into the interstitium so raising the osmolality and providing a hyperosmolar medium which allows the loop to act as a countercurrent multiplier system. There is active reabsorption of sodium and as a result the tubular fluid becomes dilute and *hypotonic*.

The distal portion of the renal tubule does the function of reabsorption of water and ions in the following manners: (*i*) The epithelial cells of this part can establish a relatively high ion concentration gradient between the blood and tubular fluid which is altered with the change of the blood content of ions and controlled by *mineralocorticoids* of the adrenal cortex. (*ii*) This portion can also establish relatively high osmolar concentration gradients between blood plasma and tubular fluid which is altered with the percentage of body fluid (water) content. (*iii*) Water permeability through the epithelium of the distal portion of the renal tubule is controlled by the circulating antidiuretic hormone (ADH)

level secreted by the posterior pituitary gland. The secretion of this hormone (ADH) is controlled by water content of the body. In addition the ADH may stimulate the pumping of sodium in the loop of Henle.

However, in summary it may be stated that the reabsorption of water at proximal tubule, loop of Henle and distal tubule, is a passive process which is determined by the osmotic forces created by the reabsorption of ions.

When the fluid passes into the collecting ducts, which are permeable to H_2O, this passes through the duct walls with the osmotic gradient into the medullary interstitium. It is here the ADH has its effect in enhancing the movement of H_2O so producing a hyperosmolar urine.

The facts that first observed by Walker and his co-workers (1941), suggested that (*i*) more salts (ions) than water are reabsorbed in the loop of Henle as hypotonic fluid is entering into the distal tubule from the loop of Henle (Wirz, 1956). (*ii*) Under conditions of hydropenia, water is reabsorbed quickly across the tubular epithelium, i.e., the tubular epithelium becomes highly permeable to water. (*iii*) The urine is not concentrated in the distal tubule but in the collecting ducts.

In the distal tubule **facultative water reabsorption** occurs and is regulated (Fig. 1.35) by the antidiuretic hormone (ADH). It increaess the permeability of the distal tubule to water. There is active reabsorption of sodium and chloride in the distal tubule and the tubular fluid becomes isotonic. The isotonic fluid enters the collecting tubule and is more concentrated (*hyperosmotic*) here due to further reabsorption of water.

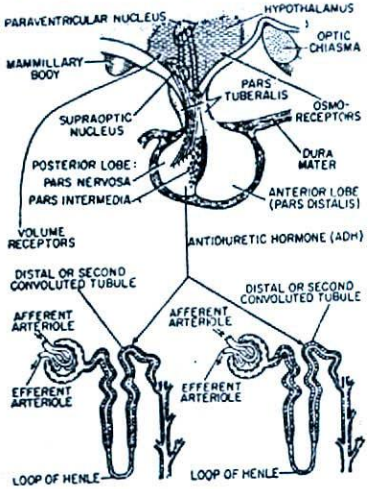


Fig. 1.35. Diagrammatic representation showing the regulation of secretion of antidiuretic hormone and its action on renal tubules.

So the process of reabsorption of water may be summed up in the following way:

(*a*) *In the proximal tubule two-thirds to seven-eighths of the water are reabsorbed.* This is called 'obligatory water reabsorption'—*a passive process.*

(*b*) *In the distal tubule water is reabsorbed with the help of ADH and the tubular fluid that leaves the distal tubule is isotonic.* Distal tubular reabsorption is called 'facultative water reabsorption'—an *active process.*

(*c*) *In the collecting ducts the reabsorption of hyperosmotic fluid occurs.*

Since reabsorption has to work against the gradually rising osmotic pressure, it is obvious that a point will come where these two opposite forces will exactly equalise and further reabsorption will cease. In other words, there is a maximum limit beyond which the urine cannot be concentrated. The solid constituents of urine, therefore, require a certain minimum amount of water for excretion. This is called the *minimum volume* or **obligatory volume.**

Antidiuretic hormone (ADH) is an octapeptide and is produced in the supra-optic and paraventricular nuclei of the hypothalamus from which it is transported through the hypothalamico-hypophyseal tract to the neurohypophysis, where the ADH is stored.

The secretion of ADH from the posterior lobe of the pituitary gland is controlled by the hypothalamus. The original concept (Verney, 1958) of control of ADH was that osmoreceptors *alone,* situated in the hypothalamic region, were responsible for the release of ADH. Hypothalamus receives impulses from the osmoreceptor cells supplied by the internal carotid artery and from volume receptors in the thorax. Increased osmotic pressure in the blood or extracellular fluid stimulates the osmoreceptors, which in its turn increases the intensity of impulse to the hypothalamus. This impulse leads to increased secretion of ADH. It has been shown by Gauer and Henry (1963) that the distention of the left atrium in the experimental subjects by a balloon causes diuresis. They have also suggested that impulse from the stretch receptors in the left atrium has been carried by the vagus and has inhibited the release of ADH, Shu'ayb, Moran and Zimmerman have supported this hypothesis by direct measurement of ADH in similar experiments.

Increase in blood volume through the volume receptors produces opposite effect, i.e., inhibit ADH secretion (Fig. 1.35). In a disease called **diabetes insipidus** there is elimination of large quantity of water due to lack of secretion of ADH. ADH causes increased release of an enzyme *hyaluronidase* from the collecting ducts. This enzyme depolymerises intercellular mucopolysaccharides which are the cementing substances and thus responsible for increased passage of water through the tubules.

Countercurrent multiplication theory of urine concentration. The different phases through which the urine becomes **hypertonic** in relation to the body fluids have been studied by Wirz and his associates (1951) and later by Bray (1960). It is a complex process and has got close relation with the anatomical distribution of the tubules along with the Na-concentration and different depths from the cortex towards the medulla of the kidney (Fig. 1.36). The loop of Henle along with blood vessels passes from the corticomedullary junction to the medulla and again returns towards the cortex and thus simulates a **hairpin countercurrent arrangement.**

The glomerular filtrate has a concentration same as blood plasma and although about 80% of the filtrate is reabsorbed in the proximal tubule, yet the remaining 20% enters into the descending loop of Henle in an **isotonic state.** So as the *isotonic fluid* passes through the descending limb, there is *passive diffusion of sodium* into the tubule from the surrounding hypertonic tissue fluid and becomes **hypertonic.** Now this *hypertonic fluid* enters into the ascending limb and gradually becomes **hypotonic** due to active transport of sodium from the tubule to the surrounding tissue and also due impermeability of this portion of the tubule to water. So this hypotonic fluid is entering into the distal convoluted tubule where the antidiuretic

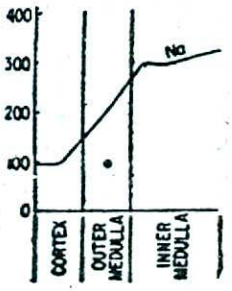


Fig. 1.36. Graphical representation of concentration of sodium in slices of the cortex and of the outer and inner regions of the medulla in the hydropenic animal.

hormone (ADH) increases the permeability to water of the distal convoluted tubular epithelium and the hypotonic fluid again attains isotonic state. Now this isotonic fluid passing through the collecting tubule becomes hpertonic due to the ionic and water exchange in between the tubular fluid and the hypertonic medullary tissue fluid. And thus the hypertonic urine is formed and passes through the ureter (Figs 1.37B & 1.38).

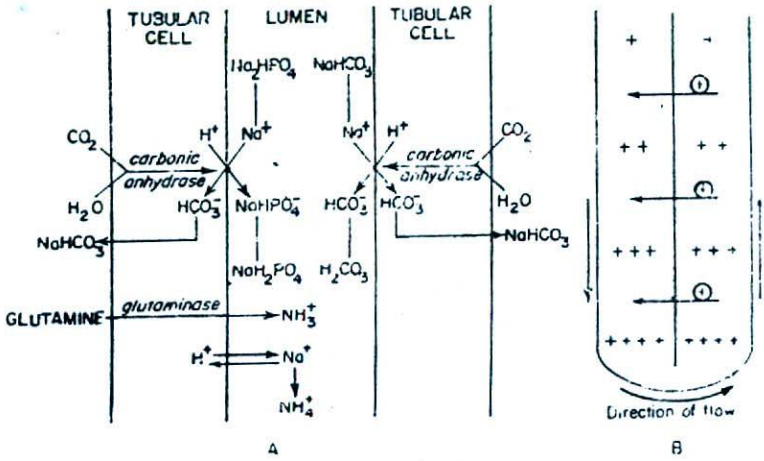


Fig. 1.37. Diagram *A* illustrating the ionic movements across the tubular cell concerned in the excretion of H_s^+ and conservation of cation. The Na^+CO_3 and Na^+HPO_4 shown have been filtered through the glomerulus. Diagram *B* illustrating mechanism of a countercurrent multiplier. The transfer of a single ion at each site indicated results in a gain of three ions at the tip of the loop, although the osmotic gradient across which each ion has to pass is only unity.

Countercurrent exchange theory for the vasa recta (Berliner and his associates, 1958). It is a passive process and depends on the diffusion of solutes and water in both the directions across the permeable walls of the vasa recta. As the descending limb of the vasa recta gradually enters dip into the medulla, water diffuses out from, and osmotically active particles diffuse into, the blood vessel. In the ascending loop, the diffusion process is just in opposite direction and thus isotonic blood is leaving the medulla (Fig. 1.38). The countercurrent exchange reduces the rate of dissipation and hence reduces the rate at which the countercurrent multiplier must pump Na^+ to maintain any given gradient.

Sodium and Chloride. Sodium is absorbed along with chloride. There is active transport of Cl^- in the thick-walled ascendinglimb of Henle's loop. Out of 560 g of Na^+ filtered by the glomeruli per day 490 g are reabsorbed in the proximal tubule and 65 g are reabsorbed in the distal tubule and 5 g are excreted in the urine. Reabsorption of Na^+ in the tubules is an active process and is due to the activity of the cells of the proximal tubule, the ascending limb of the loop of Henle and the distal tubule (Figs. 1.34, 1.38 & 1.39). But in the descending limb of Henle's loop the sodium

movement is just in the reverse direction, i.e., sodium enters into the

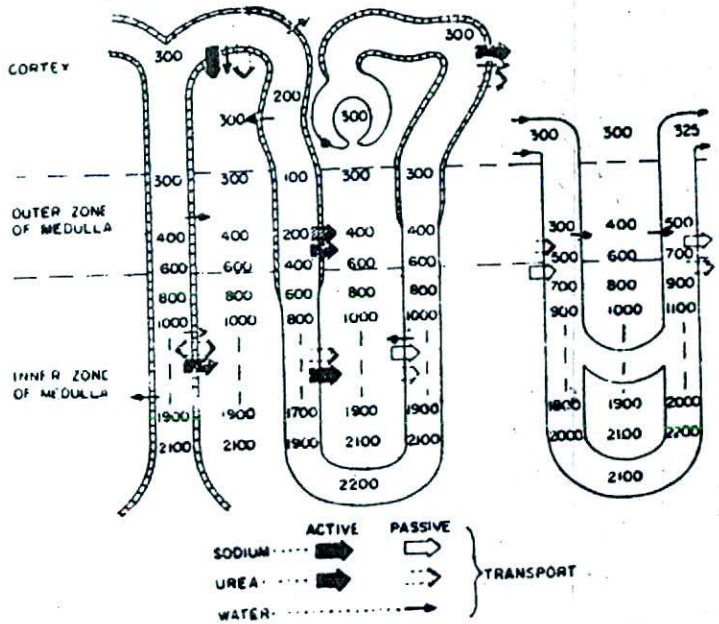


Fig. 1.38. Diagram illustrating the countercurrent mechanism as it is believed to operate in a nephron with a long loop and in the vasa recta (represent on the right). The numbers represent hypothetic osmolality values. No quantitative significance is to be attached to the number of arrows and only net movements are indicated.

tubular lumen passively through the process of diffusion. Reabsorption of water follows passively due to active reabsorption of sodium in the tubule. The reabsorption is influenced by *aldosterone,* the adrenal cortical hormone. Aldosterone release is controlled by blood volume, a decrease of blood volume causes an increase in hormone secretion and thus increased retention of sodium occurs. Renin secreted from juxtaglomerular apparatus causes increased formation of angiotensin II, which possibly controls aldosterone secretion. As sodium is actively absorbed by tubular cells, it can be inhibited by chemical agents like mercury. The reabsorption of chloride in the renal tubules is also a passive process which works with the electrochemical gradient (Figs. 1.34 & 139).

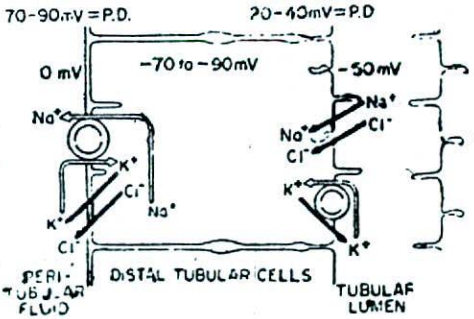


Fig. 1.39. Schematic representation of ion transport in the second convoluted tubular cells (diagrammatic).

Potassium. About 80-95% of the potassium filtered is reabsorbed in the proximal tubule and a specific active transport process is involved in it. The secretion of potassium takes place in the second convoluted tubule. Reabsorption of sodium ions and secretion of potassium ions are simultaneous processes. About 75% of urinary potassium is accounting from the process of secretion. The secretion of potassium is augmented during *alkalosis*.

Bicarbonate. Bicarbonate is completely reabsorbed in the renal tubule. pH of the fluid collected from the proximal tubule is alkaline in reaction. In the lumen of the tubule HCO^-_3 combines with H^+ which diffuses from the tubular epithelial cells in exchange of reabsortption of Na^+.* H_2CO_3 is formed which yields CO_2 and H_2O. CO_2 diffuses into the tubular cells and with the help of carbonic anhydrase (CA) forms H_2CO_3. The cell wall at the luminal side is not permeable to HCO^-_3 ion. Na^+ which in separately absorbed, is transferred to the blood capillaries together with HCO^-_3 from the tubular cells. During alkalosis, less amount of H^+ ion is present for exchange with sodium and $NaHCO_3$ is excreted in urine. During acidosis on the other hand more CO_2 is present and the amount of H_2CO_3 formed inside the tubular cells under the influence of carbonic anhydrase is increased (Figs. 1.40 & 1.41).

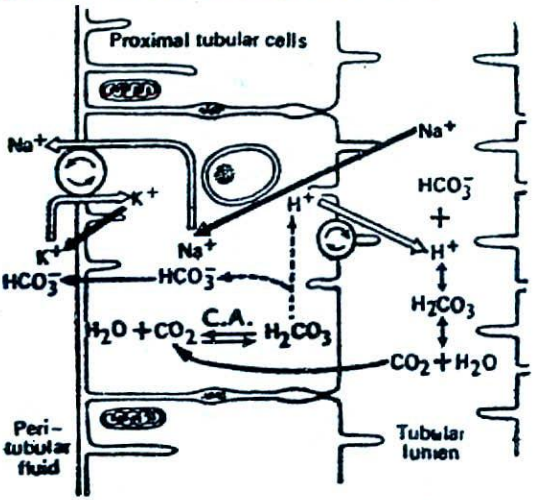


Fig. 1.40. Schematic representation of bicarbonate reabsorption in the first convoluted tubular cells (diagrammatic).

The renal threshold of bicarbonate is 28 mM/l in man. This value is influenced by the following four factors: (*i*) CO_2 tension in the arterial blood, (*ii*) potassium store in the body, (*iii*) chloride level in the blood, and (*iv*) amount of secretion of adrenal cortical hormones. The bicarbonate reabsorption increases with the increment of CO_2 in the blood, and depletion of potassium or chloride and *vice versa*. The bicarbonate reabsorptive mechanism is certainly affected by the secretion of adrenal cortical hormones though the mechanism of action is not known. Hypersecretion of mineralocorticoids and glucocorticoids causes metabolic acidosis along with increased bicarbonate reabsorption.

Phosphate. Reabsorption of phosphate takes place in the proximal tubule. Phosphate reabsorption is an active process. The transport mecha-

***Acidification of urine.** The tubular cells synthesise and secrete H-ions in exchange of Na-ions which diffuse into the tubular cells. H-ions are responsible for making the urine acid.

nism is influenced by a number of factors. Parathyroid hormone depresses the transport mechanism. Acidosis increases excretion of phosphate. The mechanism of reabsorption of the inorganic phosphates resembles in many aspects with that of glucose. The differences are: (*i*) the kidney regulates the plasma phosphate concentration as slight alteration of plasma phos-

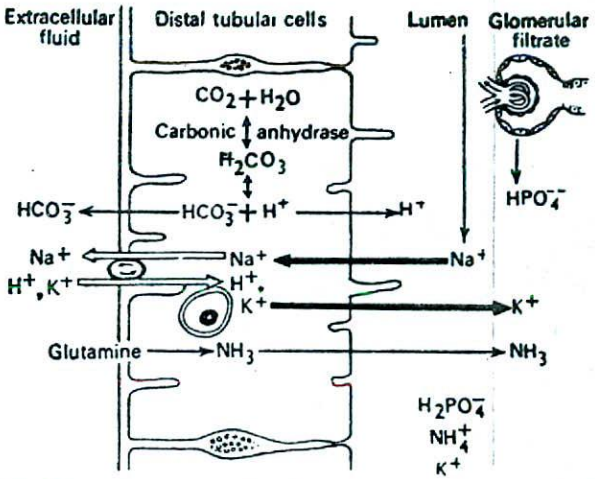


Fig. 1.41. Schematic representation of transport of bicarbonate and sodium by the second convoluted tubular cells (diagrammatic).

phase content alters the rate of phosphate excretion, (*ii*) the absorptive capacity of the tubular epithelium is much more variable and influenced by body store of ions and also by adrenal cortical and parathyroid hormones but in case of glucose, the absorptive capacity is remarkably stable.

Reabsorption of other substances like sulphate, uric acid, ascorbic acid, β-hydroxybutyric acid, ketone bodies aceto-acetic acid, creatine and some amino acids also occur in the tubules. The mechanism of reabsorption of sulphate in the renal tubule is in resemblance with that of phosphate and is also an active process. The reabsorption of amino acids is more or less complete in renal tubules and is controlled by the plasma concentration of the same and ultimately negligible quantities are excreted. Creatine is reabsorbed completely from the renal filtrate. But reabsorption of creatine is completely blocked by saturation of the reabsorptive mechanism by *glycine* and *alanine* which indicates that these three substances may be reabsorbed through a single mechanism.

II. TUBULAR SECRETION

Although selective reabsorption is the main function of the renal tubules but the tubules also secrete some substances. Tubular secretion is an active process carried out by the tubular cells. Various -etheral sulphates, steroid and other glucuronides, and 5-hydroxyindoleacetic acid

which are produced normally in the body are secreted by the tubules. In some fishes there is no glomerulus in the kidneys but the urine contains chloride, creatinine, uric acid, water, creatine, magnesium, potassium, sulphate, urea, etc. As there is no filtration due to lack of glomeruli, these substances must be the secretory products of the tubules. In man certain substances, e.g., phenol red, Diodrast (Diodone), penicillin, para-amino hippuric acid, (PAH) etc., are actively transferred by the tubules from the blood stream into the lumen of the tubules. Potassium, creatinine and hydrogen ion are also secreted by the tubules. Normally reabsorption of potassium is complete in the proximal tubules. Studies with radioactive potassium shows that potassium present in the urine is the secretory product of the tubules. When Na^+ ion is reabsorbed in the tubules, potassium and hydrogen ion are at the same time secreted by the tubules. When reabsorption of Na^+ is increased by the hormone aldosterone, K^+ is secreted in larger amounts. On the other hand, when the secretion of H^+ ion increases, that of potassium is decreased. EDTA (ethylenediaminetetraacetic acid) is also secreted. PAH reduces the secretion of 18- and 3-glucuronide derivatives of aldosterone. Up to a range of 6 mg PAH/100 ml of plasma, the rate of filtration, secretion and excretion of PAH changes proportionately. But about 10 mg/100 ml, the secretion of PAH is maintaining a constant value, i.e., independent of plasma concentration. The Tm value for PAH secretion is about 80 mg/minute/1·73 square metre of body surface area under normal condition (Fig. 1.42).

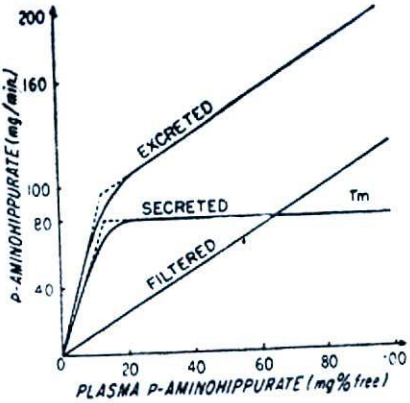


Fig. 1.42. Graphical representation of relative filtration, secretion and excretion of PAH by the kidney as functions of plasma concentration (diagrammatic).

Determination of tubular secretory or excretory power

Like selective reabsorption, tubular secretion or excretion also depends upon the vital activity of the epithelium. The maximum power of the tubules to excrete substances (e.g., PAH) can be determined and is called **Tm** or **Tubular maximum.** The term PAH Tm means the maximum power of the tubule to excrete it. This may be determined by injecting PAH and thereby raising its concentration in the plasma well above that level, up to which complete extraction is possible; urinary PAH excretion (Um) is noted; the amount of PAH filtered (F) is calculated from the plasma PAH concentration and the volume of glomerular filtrate formed (Inulin clearance value), viz., Um—F=Tm. The Tm *value is related to the number of functioning tubules and their excretory efficiency.* A decrease in the Tm represents decrease in the number of tubules or their efficiency or both.

III. FORMATION OF SOME NEW SUBSTANCES

1. **Formation of ammonia.** The cells of the renal tubules contain deaminases (amino acid oxidases) which can produce ammonia by the deamination of *amino acids*. This is proved by the facts that (1) renal vein contains greater amount of ammonia than renal artery and (2) experiments with ^{15}N-labelled amino acids also produce the same isotopic ammonium salts. About 60% of ammonia is formed from *glutamine* (Fig. 1.43). The rest is formed from *glycine, alanine, leucine* and *aspartic acid*.

It is said that urinary ammonia is mainly produced in the kidney.

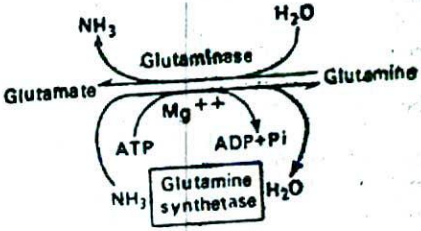


Fig. 1.43. Schematic representation of glutamine synthetase reaction.

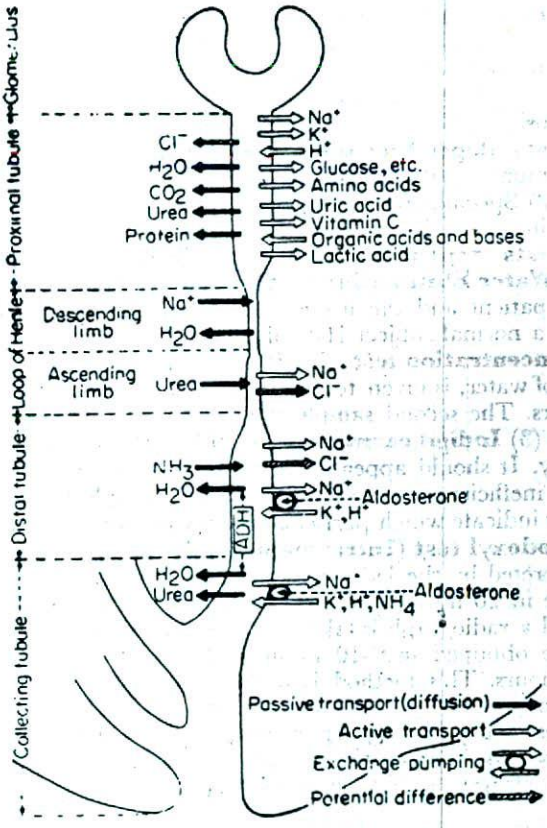


Fig. 144. Diagrammatic representation of the tubular reabsorption and secretion in the course of urine formation.

The ammonia, thus formed, is passed out into the lumen of the tubules where it combines with the acid radicles and liberates the fixed bases (e. g., Na^+, K^+, etc.).These bases are reabsorbed to maintain the alkali reserve. The amount of ammonia formation markedly increases during acidosis. This is an important way by which kidneys help to maintain a constant blood reaction.

2. The **tubules can synthesise hippuric acid** by combining benzoic acid with glycine.

3. **Formation of inorganic phosphates.** Part of the inorganic phosphates eliminated by the kidneys is manufactured in the tubules. The enzyme phosphatase hydrolyses organic phosphates (hexose phosphate) and liberates inorganic phosphate.

Role of renal tubules in the formation of urine has been summarised diagrammatically in Fig. 1.43.

RENAL FUNCTION TESTS

I. **Tests depending upon blood analysis only.** (1) Estimation of nitrogenous constituents, to find nitrogen retention if any, e.g., urea, blood urea nitrogen (BUN), nonprotein nitrogen (NPN), uric acid, creatinine, etc. (2) Estimation of cholesterol and albumin/globulin ratio (Nephrosis).

II. **Tests depending upon urine analysis only.** (1) Volume, reaction, ammonia coefficient, concentration of normal constituents (e.g., urea, etc.). (2) Specific gravity test. (3) Presence of abnormal constituents (e.g., albumin, casts, blood cells, etc.).

III. **Tests depending upon the elimination of some substances.** (1) **Water Elimination test**—568 ml (a pint) of water is given to a fasting patient and the urine is collected and measured at hourly intervals. In a normal subject 568 ml should be excreted in three hours. (2) **Urea concentration test**—Bladder is emptied and 15 g of urea, in about 142 g of water, is given to the subject. Urine is collectes after one and two hours. The second sample should have a urea concentration of 2% or more. (3) **Indigo carmine test**—0·1 g of the dye is injected intramuscularly. It should appear in the urine in 6-8 minutes. Any delay means renal inefficiency. Excretion is usually complete by 12-24 hours. This test may indicate which particular kidney is wrong if ureteric catheter is used. (4) **Iodoxyl test (Intravenous pyelography)**—This compound is rapidly excreted by the kidney and is opaque to X-ray. About 15 g of the substance in 20 ml of a 10% solution of invert sugar, is given intravenously, and a radiograph is taken. In normal persons, a distinct pyelogram will be obtained in 2-10 minutes. In renal deficiency it may be delayed for hours. This method is useful in demonstrating the size and shape of kidney, renal pelvis, calyces, ureters, presence of stone, etc.

IV. **Tests depending upon both blood and urine analysis (Clearance tests).** The best test for renal function are the renal clearance tests. Plasma clearance of a substance (χ) can be calculated by the formula:

$$\text{Plasma clearance of } \chi \text{ (ml/minute)} = \frac{\text{concentration of } \chi \text{ per ml of urine} \times \text{quanlity of urine (ml/minute)}}{\text{concentration of } \chi \text{ per ml of plasma}}$$

It should always be remembered that clearance value of x is the volume of plasma completely cleared of χ and not the quantity of χ (chi) that is cleared from plasma. This is an index for renal efficiency.

Three types of clearance values can be obtained according to the nature of the substance used: (1) When the substance used is filtered by the glomeruli and is neither reabsorbed nor excreted by the tubules, its clearance value is equal to the volume of glomerular filtrate. This applies for inulin. Actually, glomerular filtrate can be measured by inulin clerance test (125 ml). (2) When the substance is filtered by the glomeruli but is reabsorbed by the tubules, its clearance value is less than the volume of glomerular filtrate, i.e. inulin clerance. This is true for urea clearance (maximum clerance—Cm 75 ml, standard clearance—Cs 54 ml). The more is the degree of reabsorption, the less will be the clearance value. (3) When the substance is filtered by the glomeruli, as well as excreted by the tubules its clearance is more than the glomerular filtrate. This is true for creatinine (170 ml). If a substance is completely cleared from the plasma, its clearance value is equal to the renal plasma flow. This is true for Diodrast (iodopyracetate) or PAH.

The following clearance tests are commonly used:

1. **Inulin clearance (A measure of Glomerular Filtration Rate).** This inulin clearence test is performed to estimate the glomerular filtration rate. Any substance may be regarded suitable for estimating glomerular filtration rate if it possesses the following four physiological properties: (i) It is freely filtrable through the renal corpuscular filtrating membrane (ii) It is biologically inert, neither reabsorbed nor secreted by the tubules. (iii) It is non-toxic and does not alter renal function. (iv) It is easily and accurately estimable. The clearance of such substance will be equal to the glomerular filtration rate. The principle and procedure is as follows: 10 g of inulin, dissolved in 100 ml of normal saline, is given intravenously at the rate of 10 ml per minute. Since inulin is filtered by glomeruli and is neither reabsorbed nor excreted by the tubules, clearance value will measure the rate of glomerular filtration.

Calculation Inulin clearance can be calculated from the formula:

$$C_{In} = \frac{U_{In} \times V}{P_{In}} \text{ ml/minute,}$$

where U_{In} = inulin concentration in mg per 1·0 of urine; V = volume of urine in ml per minute; and P_{In} = concentration of inulin in mg per 1·0 ml of plasma; C_{In} = inulin clearance in ml per minute.

Normally inulin clearance is 125 ml per minute.

Inulin, a polymer of fructose with mol. wt. of 5,200 that is found in dahlia tubers.

2. **Urea clearance test** (Van Slyke)

Procedure. Two one-hourly samples of urine are collected. Blood is collected at the end of first hour and its urea content (mg%) is estimated. The urine samples are measured and their urea concentrations separately estimated (mg%). The minute output of urine is calculated from these data.

Calculation. (A) **Maximum clearance**. If the minute output be 2 ml or more, the result is called maximum clearance (Cm). The formula for it is as follows:

$\frac{U_u \times V}{P_u}$, where U_u = urine urea in mg per ml; V = volume of urine in ml per minute; P_u = urea in mg per ml of plasma.

In normal human adults, the value is relatively constant and averages 15 ml per minute. The result is usually expressed as percentage of the clearance, as follows:

For Cm 75 ml is taken as the 100% efficiency.

$\therefore$ Cm $\times \frac{100}{75}$ i.e., Cm $\times$ 1·33% will give the percentage efficiency for maximum clearance. For instance, if the Cm of a normal subject is found to be 50 ml, the renal efficiency will be 50 $\times$ 1·33, i.e., 66·5%.

(B) **Standard clearance.** If the minute output of urine be less than 2 ml, the value is named as standard clearance (Cs). For it, the following formula is used:

$$\frac{U_u \times V}{P_u}$$

The normal range of Cs is 40-65 ml (average 54 ml). To express as percentage of normal, Cs is to be multiplied by 100/54, i.e., 1·85. For example, if the Cs of a subject is found to be 50, the renal efficiency will be 50 $\times$ 18·5, i.e., 92·5%.

This test, according to Van Slyke, is a reliable method for estimating renal efficiency. In a person with high protein diet or who injected urea, the plasma concentration of urea (P_u) increases and the same time the rate of excretion of urea ($U_u \times V$) also increases in direct proportion. So the ratio $\frac{U_u \times V}{P_u}$ remains unaltered. Thus the urea clearence value is independent of plasma urea concentration and the rate of urea concentration. The urea clearance value varies proportionately with the filtration rate. In renal disease, the urea clearance value is reduced. In severe congestive failure, dehydration, shock and cirrhosis with ascites, the urea clearance value is reduced.

The plasma clearance of some important substances used for determination renal function are shown below:

TABLE 1.1

Substance	Plasma clearance per minute	Used as a measure of
Inulin	125	Glomerular filtration rate
Diodrast	560	Plasma flow and blood flow through the kidneys
PAH	585	Do
Urea	75	Overall renal efficiency
Creatinine	140	Do

VOLUME AND CHARACTERISTICS OF URINE

1. **Volume.** Quantity of urine formed in 24 hours in an adult normal individual varies from 600 ml to 2500 ml. Normally it depeends upon (a) water intake, (b) diet, (c) environmental temperature, (d) mental state, and (e) physical conditions of the subject. About half as much urine is formed during sleep as during activity.

There is a special relationship in between the skin and the kidneys where excretion of water is appreciably made by these two organs. Thus perspiration has got inverse relation with the formation of urine.

Substances that stimulate the formation of urine are termed as **diuretics.** Tea, coffee, alcoholic beverages and also nitrogenous end products have got diuretic effects. Low threshold substances like urea, sulphate and phosphate resulting from protein metabolism retain water in the tubules to keep those materials in solution. For this reason after high protein diet, urine volume is increased. High threshold substances like glucose, amino acids, etc., also produce diuresis when present in the tubule still in excess after reabsorption. Because these substances require water for keeping themselves in solution. For the same reason, diabetes is always accompanied with diuresis.

Table 1. 2 summarises mechanism of action of some of the drugs commonly used in medical practice as diuretics.

TABLE 1.2

MECHANISM OF ACTION OF SOME DIURETICS

Drugs	Mechanism of action
Mannitol and Glucose	Produces osmotic diuresis.
Organic salts of mercury	Inhibit Na^+ and Cl^- reabsorption beyond the proximal tubule; inhibit K^+ secretion.
Carbonic anhydrase inhibitors—acetazolamide (Diamox)	Decrease H^+ secretion with resultant increase in excretion of K^+ and Na^+
Thiazides	Inhibit Cl^- reabsorption in the distal portion of loop of Henle and proximal portion of the distal tubule.
Furosemide, Ethacrynic acid	Inhibit Cl^- reabsorption in the loop of Henle.

2. **Colour.** Normal colour of the urine is pale-yellow or amber and it is mainly dependent upon the presence of pigment, **urochrome.** This colour also varies with the quantity and concentration of the urine voided. In fever, urine becomes dark-yellow or brownish. If vitamin riboflavin is taken then it is excreted through the urine causing its colour yellow. In liver disease bile pigment may give the urine green, brown or deep-

yellow. Blood and haemoglobin colours the urine smoky to red, Homogentisic acid and methaemoglobin may give urine a dark-brown colour.

3. **Reaction.** Normal freshly voided urine is usually clear and acid in reaction with a pH value as low as 4·5 and as high 8·2. The mean pH of the normal mixed 24 hour urine is about 6·0. The urine becomes alkaline on standing because of conversion urea to ammonia and loss of CO_2 in air. It may also be alkaline after excessive vomiting, at least at the early stage and after meals due to H^+ secretion in the stomach (alkaline tide). When the protein intake is high, the urine is acid. Because, excess phosphate and sulphate are produced in the catabolism of protein.

4. **Specific gravity.** In normal urine specific gravity varies between 1·01 to 1·05 and may be subject to wide flutuation. As a result of excessive water intake, specific gravity may fall to 1·003 and on the other hand may rise to 1·040 or higher because of haemoconcentration due to excessive perspiration. The specific gravity of urine is directly proportional to the solute content and varies inversely with the volume.

5. **Turbidity.** Usually freshly voided urine is transparent but alkaline urine on standing may become cloudy due to precipitation of calcium phosphate. In pathological condition the urine may be turbid due to presence of mucoid, nucleoprotein, epithelial cells, pus cells, etc.

6. **Odour.** The colour of normal urine is faintly aromatic and is due to presence of number of volatile organic substances. Sometimes, the odour of urine may be atributed to a neutral ill-smelling substance—**urinod** (C_6H_8O). After ingestion of asparagus, urine may have a characteristic odour due to presence of methyl parcaptan (CH_3SH). In diabetes, urine gives a sweetish odour but in extreme condition of the diabetes when excessive ketosis occurs, urine has got the characteristic odour of acetone. Normal urine on standing gives an ammoniacal odour because of the conversion of urea to ammonia.

7. **Osmotic pressure.** Osmotic pressure of the urine is much above that of blood plasma. The depression of freezing point Δ of plasma is only 0·56°C., whereas that of the urine varies between 0·87°C and 2·71°C.

On keeping, various changes may be seen in a sample of urine. For instance—(a) A cloud of mucus may develop consisting of nucleoproteins derived from the epithelium of the bladder and urinary passages. (b) The reaction becomes alkaline due to ammoniacal decomposition. Ammonia is formed from urea by the action of an organism, known as Micrococcus ureae. (c) The originally clear urine may become turbid. This is due to precipitation of phosphates in the alkaline urine or may be due to growth of bacteria. (d) The pale-yellow colour of the urine becomes deeper due to the oxidation of urobilinogen (colourless) into urobilin (coloured) by air.

Heating a sample of urine, as in clinical examination, may bring about three changes: (*a*) A turbidity may develop. This may be due to the deposition of phosphates or coagulation of albumin if present. On heating, CO_2 is driven off and urine becomes less acid or alkaline. This causes precipitation of dissolved phosphates. Addition of a few drops of acetic acid redissolves this precipitate. But coagulated albumin cannot be dissolved with weak acid. Here, the cloud usually becomes thicker due to additional acid coagulation. (*b*) A pre-existing turbidity may disappear and the turbid urine may become clear. This is due to the dissolution of uric acid and urate crystals favoured by the alkaline reaction of the urine caused by boiling. (*c*) A precipitate may appear when the urine is gradually heated (at about 55°C.) but near about the boiling point (between 80°C. and 90°C.) the precipitate disappears. On cooling such a specimen of urine reverse changes are seen. This is due to the presence of certain types of proteoses, such as the *Bence Jones proteose.*

COMPOSITION OF URINE

Normal constituents of urine (*vide* table 1.3 in page 1-47)

Origins of the most of organic and inorganic constituents of urine have been discussed in the chapter of metabolism and here some of the additional relevant facts of different constituents are given below:

A. **Organic constituents** (*vide* table1.3 in page 1-47)

1. **Urea.** It constitutes about half of the total urinary solid and is the principal end product of protein metabolism. In human beings, it repesents about 80-90% of the total urinary nitrogen. About 25-30 g of urea are excreted per 24 hours. Generally, the quantity of urea excreted is proportional to the total protein metabolism including food protein and tissue protein undergoing catabolism. In fever, diabetes or in excessive adrenocortical activity, urea excretion is increased due to increased protein catabolism. In liver diseases, such as acute yellow atrophy and cirrhosis, production of urea is greatly decreased and naturally the excretion is decreased. In case of acidosis, the amount of urea excreted is considerably reduced because amino acid nitrogen is diverted in the formation of ammonia. In nephritis, excretion of urea may be decreased because ability of the kidney to excrete urea is severely impaired.

2. **Ammonia.** It is the second and most important nitrogenous constituent. Ordinarily there is very little ammonia in the freshly voided urine. It is about 2·5 to 4·5% of the total urinary nitrogen and in average 0·7 g is excreted per day.

In severe nephritis, urinary ammonia is greatly decreased because capacity of the kidney to form ammonia is impaired. But in cystitis, urinary ammonia is greatly increased due to excessive hydrolysis of urea by the bacteria in the bladder. Besides this, if the urine is stored without preservative then the urinary urea may be converted to ammonia by bacteria.

3. **Uric acid.** It is the end product of the purine metabolism in the body. About 0·7 g uric acid is excreted through the urine per 24 hours. It is derived both from the dietary nucleoprotein and from the breakdown of cellular nucleoprotein. Uric acid is very slightly soluble in H_2O but soluble salts with alkali. Excretion of uric acid is increased in leukaemia, severe liver diseases and in various stages of gout.

4. **Creatinine and Creatine.** Creatinine is the product of the breakdown of creatine. The amount of creatinine excreted through the urine by an adult individual is about 1·2 to 1·7 g per 24 hours. Excretion of creatinine per 24 hours is practically constant in the subject with creatinine-free diet. **Creatinine coefficient** may be defined as the ratio between the amount excreted in 24 hours and the body weight in kilogram. It is commonly 20 to 26 mg per kg per 24 hours in normal man and 14 to 22 mg per kg in normal woman per 24 hours.

Creatine is present in the urine of children and in much smaller amounts in a normal adult men. It is observed that normal males excrete about 6% of the total creatinine output of creatine (60-150 mg/day). In females, this amount is higher than that of in males. Excretion of creatine is increased in pregnancy and is decreased in hypothyroidism. In pathological conditions namely starvation, impaired carlobydrate metabolim, hyperthyroidism and certain myopathies creatinuria is also found.

5. **Oxalate.** Normal urine contains about 10-30 mg of oxalate per 24 hours. Though some quantity of oxalic acid comes from the metabolism of glycine and ascorbic acid, major portion of oxalic acid comes from the diet such as asparagus, spinach. Excretion of oxalic acid is increased in diabetes, in certain liver diseases. In normal urine, sometimes oxaluric acid is present in traces. This acid is a combination of oxalic acid and urea. Upon hydrolysis oxaluric acid breaks up into oxalic acid and urea.

6. **Amino acids.** In adults about 150-200 mg of amino acids are excreted through the urine in 24 hours. All the naturally occurring amino acids are excreted through the urine in small amounts although its renal threshold is quite high. In liver diseases and also in poisoning with carbon tetrachlorides and chloroform, amino acid excretion is greatly increased.

7. **Hippuric acid.** It is chemically benzoyl glycine. It is the detoxication products of benzoic acid with glycine. The quantity of hippuric acid excreted through the urine is about 0·7 g (ranges about 0·1 to 1.0 g).

8. **Allantoin.** It is derived from partial oxidation of uric acid and present almost in all mammals. In human beings, it is present in very small amount.

9. **Vitamins, hormones and enzymes** are also excreted in normal urine. In adults 15-50 mg of ascorbic acid are excreted per 24 hours. Metabolic degradation, products of adrenocortical hormones are excreted through the normal urine of both males and females.

B. **Inorganic constituents** (*vide* table 1.3 in page 768)

1. **Chloride.** Next to urea, it is the chief solid constituent of urine. Generally, 6-9 g per 24 hours as chloride and 10-15 g as sodium chloride are excreted through the urine. Chlorides are mainly excreted as sodium chloride. Excretion of chloride is mostly dependent upon the diet. In fever, certain stages of nephritis, diarrhoea and vomiting, chloride excretion is greatly reduced. In excessive perspiration, chloride excretion may be greatly reduced.

2. **Phosphate.** The amount of phosphate excreted through the urine varies widely and it depends largely upon the diet. It is normally excreted 0·8-1·3 g of P per day. Urine phosphates are combination of Na^+ and K^+ phosphates as well as calcium and magnesium phosphates.

Urinary phosphate comes largely from the breakdown of phospholipids, nucleoprotein, nucleotides and phosphoprotein of the diet and tissues. *Phosphaturia* is a condition where urine contains a crystalline precipitate of magnesium ammonium phosphate. This occurs due to decreased acidity of the urine. Kidney and bladder stones are the cause of precipitation of the insoluble inorganic phosphates. In certain *bone* diseases (*renal tubular rickets, osteomalacia* and *periosteosis*), excretion of phosphorus is increased. In *hyperparathyroidism* its excretion is increased whereas in hypoparathyroidism the same is decreased. In *pregnancy*, phosphorus excretion is decreased due to excess utilisation of maternal phosphate for the growth of the foetus.

3. **Sulphates.** Urinary sulphates are derived mainly from the metabolic degradation of sulphur-containing amino acids—methionine, cystine and cysteine. The quantity of excretion of sulphate depends upon the protein consumption and the breakdown of tissue protein. The urinary sulphates are present in the urine in three forms: (*i*) *inorganic sulphur* (*sulphate*), (*ii*) *ethereal* (*conjugated*) *sulphate* and (*iii*) *neutral sulphur*.

The inorganic sulphate constitutes about greater portion (85-95%) of urinary sulphur. It is excreted about 0·7-1·0 g per 24 hours.

The ethereal sulphate is excreted about 0·06 to 0·12 g per day. It comprises of the sodium and potassium salts of sulphuric acid ester of phenols such as indoxyl, skatoxyl, phenol and cresol.

The neutral sulphur is excreted about 0·08 to 0·16 g per 24 hours through the urine and is comprised of heterogeneous mixture of sulphur compounds. Neutral sulphate can be determined as the difference between the total sulphur and the sum of the sulphate sulphur and etheral sulpher.

4. **Minerals.** The four cations—Na^+, K^+, Ca^{++} and Mg^{++} are present in the urine. The quantity of sodium is excreted through the urine normally ranges from 4-5 g per 24 hours. Urinary potassium is about 2·5 to 3·0 g per day and rises when the intake is increased or in presence of excessive tissue catabolism. Potassium and sodium ratio is about 3: 5. In Addison's disease (hypofunctioning of adrenal cortex) sodium excretion is increased and potassium excretion is decreased.

Calcium and magnesium are practically excreted through the faeces and very little amount is excreted through the urine. Daily excretion of calcium is about 0·1 to 0·3 g and of magnesium is about 0·1 to 0.2 g. The excretion of these two ions are dependent upon the nature of diet.

Iodine, arsenic and lead are also excreted.

TABLE 1.3

NORMAL AND ABNORMAL CONSTITUENTS OF URINE

Normal constituents of urine		Abnormal constituents of urine
A. Organic constituents		
1. Nitrogen (total)	25-35 g	1. Protein
2. Urea	25-30 g	(*a*) Albumin
3. Creatine	60-150 g (appx.)	(*b*) Globulin
4. Creatinine	1·4 g (1·2-1·7 g)	(*c*) Bence Jones proteins
5. Ammonia	0·7 g (0·3-1·0 g)	2. Sugar
6. Uric acid	0·7 g (0·5-0·8 g)	(*a*) Glucose
7. Hippuric acid	0·1-1·0 g	(*b*) Fructose
8. Oxalic acid	10-30 mg	(*c*) Galactose
9. Amino acids (Amino acid nitrogen)	150-200 mg	(*d*) Lactose
10. Allantoin	Small quantity	(*e*) Pentose
11. Vitamins, hormones and enzymes	Small quantity	3. Ketone bodies
B. Inorganic constiuents	(per 24 hours)	4. Indican
1. Chloride	6-9 g	5. Blood
Chloride as NaCl	10-15 g	6. Pigments
2. Phosphate as P	0·8-1·3 g	(*a*) Bile pigments
3. Sulphate (total sulphur)	0·8-1·4 g (average 1·0 g)	(*b*) Urochromogen
4. Potassium	2·5-3·0 g	(*c*) Porphyrin
5. Sodium	4-5 g	(*d*) Melanin
6. Calcium	0·1-0·3 g	7. Casts
7. Magnesium	0·1-0·2 g	8. Calculi
8. Iodine	50-250 μg	9. Pus
9. Arsenic	50 μg	10 Hormones
10. Lead	50 μg	

Abnormal constituents of urine (*vide* table in page 1-47)

1. **Protein.** Normally very little protein is excreted through the urine and is not more than 20-80 mg per 24 hours. But in abnormal condition as much as 20 g of protein are excreted through the urine.

Proteinuria (Albuminuria) is the condition where albumin and globulin are frequently present in abnormally high concentration in the urine. Besides these, nucleoprotein, fibrin, myoglobin, haemoglobin, proteoses, peptones and Bence Jones proteins are present in the urine. Proteinuria is of two types: (*i*) *physiological* and (*ii*) *pathological* (acidental). In physiological proteinuria, less than 0·5% protein is present and this may occur due to severe exercise, high protein meal, pregnancy, etc. Pathological proteinuria is of three types: (*a*) *pre-renal* in which primary causes are the factors operating before the kidney is reached, (*b*) *renal,* where kidneys are involved primarily (*i*) causing filtration of increased amount of protein through the *leaky* glomeruli **(glomerular proteinuria)** and (*ii*) failure of proximal tubular function of reabsorption of α_1- and β-globulins and hence excretion through the urine **(tubular proteinuria)** and (*c*) *post-renal,* where destructive lesions occur in lower urinary tract. In pathological proteinuria along with protein, casts are found in the urine. Casts are always accompanied by proreinuria. Casts are definite evidence of renal lesions and these are either (*i*) epithelial casts shed from the tubules, (*ii*) coarse granular casts and (*iii*) waxy casts. Casts are generally composed of (*i*) albuminous material, (*ii*) degenerated tubule cells, (*iii*) red blood cells and (*iv*) pus cells.

Nephritis is the condition which represents a diffuse inflammation of the glomeruli and is always associated with urinary albumin, casts, haemoglobin, etc. In glomerulonephritis, glomeruli are characterised by inflammation along with secondary changes in the tubule.

Nephrosis or degenerative nephritis is always characterised by degenerative changes in the tubules and also in the glomeruli both. Nephrosis is always associated with albuminuria, haematuria (blood in the urine), oedema, hypertension and anuria.

Nephrosclerosis is the condition where there are pathological changes in the glomeruli as well as marked arteriosclerosis of the arteries and veins of the kidney.

Bence Jones protein. It is considered as a low-molecular weight-globulin and may occur in the urine of patients with multiple myeloma, leukaemia (rarely), Hodgkin's disease and also in lymphosarcoma. The Bence Jones proteins have got a peculiar solubility. These proteins are precipitated out if the urine is heated at 50-60°C. but redissolve again almost completely if the urine is heated further at 100°C. The precipitation reappears on cooling.

2. **Glucose.** In normal urine very negligible amount of glucose is present in the urine and it is clinically insignificant. About 140 mg per 24 hours are excreted through the urine. Abnormal excretion of glucose through the urine is called **glycosuria.** In diabetes mellitus, excessive glucose is excreted through the urine. About 10% or more glucose is excreted through the urine. The is associated with the increased blood sugar levels exceeding the threshold level.

3. **Other sugars.** (*i*) **Fructose—Fructosuria** is a condition when excess fructose is excreted through the urine. It is observed in severe cases

of diabetes mellitus in which fructose is excreted along with glucose. (*ii*) **Galactose—Galactosuria** is a condition in which galactose is excreted through the urine of nursing infants. (*iii*) **Lactose**—It is frequently present in urine **(lactosuria)** of lactating mother as because the lactose may frequently come from the mammary gland in the general circulation. Since lactose as such is not utilised by the tissue, it is excreted. (*iv*) **Pentose —Pentosuria** is the condition in which transient excretion of pentose is observed through the urine. Congenital pentosuria is a benign genetic defect which is characterised by inability to metabolise L-xylulose.

4. **Ketone bodies.** In normal individual 3-15 mg of ketone bodies are excreted through the urine per 24 hours. In diabetes, starvation, pregnancy and ether anaesthesia, excessive ketone bodies are excreted. The ketone bodies come from the excessive oxidation of fatty acids.

5. **Indican.** It is indoxyl potassium sulphate and is formed from indole. Indole is formed in the large intestine due to putrefaction of protein food. Indole is absorbed in the blood and being toxic to the body, is detoxified in the liver with the formation of indican, the less toxic and excretable substances. In normal urine very little amount of indican is formed but in abnormal condition when excessive putrefaction of proteins occurs, excess indican is excreted through the urine.

6. **Blood.** In cases of acture inflammation of the kidney blood may be present in the urine (haematuria) which may be the result of a lesion in the kidney or urinary tract (e.g. after trauma in the urinary tract). In tuberculosis, cancer and renal stone, haematuria is frequently observed.

7. **Pigments.** A number of pigments is found in the urine. These are urochromogen, bilirubin, porphyrine and melanin. Urochrome gives a normal colour of the urine. This urochrome comes from haemoglobin through series of reactions. In tuberculosis, *urochromogen* is excreted through the urine instead of urochrome.

Bilirubin is excreted through the urine in obstructive jaundice when bile is reabsorbed from the biliary tract into the blood stream. Bile pigment makes the urine a greenish-yellow or golden-brown colour. In chronic malaria, wasting diseases, melanin is excreted through the urine.

8. **Calculi and Casts.** Mineral salts may precipitate and form calculi or stones. These stones may be formed in any part of the kidney tubules. These calculi or stones may be present in the urine.

In some abnormal conditions, kidney tubules become lined with substances that harden or form a cast inside the tube. These casts are excreted through the urine. Nature of casts has already been discussed (page 1-48).

9. **Pus.** Pus cells often are formed in the urine in suppurative condition of the urinary system.

10. **Hormones.** Urinary excretions of different adrenal steroid hormones and gonadal hormones are altered considerably in different physiological and pathological conditions. Urinary neutral 17-ketosteroids are the reflection of the androgenic function of the subject. In adrenocortical carcinoma, hyperplasia of the cortex and testicular tumours, excretion of urinary 17-ketosteroids are tremendously increased. Excretion of 17-ketosteroids is decreased greatly in Addison's disease, pituitary dwarfism, Simmond's disease, etc. Pituitary gonadotrophins and placental gonadotrophins are also excreted through the urine in different physiopathological conditions of the organ.

Excretion of human chorionic gonadotrophin (HCG) is increased greatly in certain stages of pregnancy and in chorionepitheliomas and hydatidiform moles.

FACTORS AFFECTING FORMATION OF URINE

1. **Water intake.** When large quantities of water (1-2 litres) be taken diuresis starts after a latent period of about 15-30 minutes. The flow becomes maximum in the second hour, when the output may be as high as 1,300 ml per hour (resting 50 ml per hour). Then it declines and comes back to normal in about three hours' time. Even 5 litres of water drunk during two hours may be completely excreted by the kidney in 4-5 hours. Rise of blood volume and the consequent dilution of plasma and the lowering of the osmotic pressure are very slight. Because, water passes out into the tissues almost as rapidly as it is absorbed from the intestine. As diuresis proceeds the water is slowly drawn in.

As the quantity of urine rises, its specific gravity falls and may go down to 1·003. Total quantity of NaCl and urea excreted rises slightly, but their concentration is very low. This increases loss of salts is compensated by reduced rate of excretion following diuresis. So, the total solid loss per day is same. On the whole, during water diuresis a selective increase of water excretion takes place. The increased loss of solids is only incidental.

Although plasma becomes slightly diluted and blood volume increases to a little extent, yet these factors do not directly influence diuresis. Because, diuresis starts not immediately but a few minutes after the maximum dilution of blood takes place. Also during diuresis, no increase in the renal circulation or in the rate of glomerular filtration (until the volume of urine exceeds 900 ml per hour) is found to take place. *Consequently, this diuresis is due to decreased reabsorption of water by the renal tubules.* It is believed that dilution of blood, however small, reduces the secretion of antidiuretic hormone of the posterior pituitary (through hypothalamus) and thereby reduces reabsorption of water.

2. **Intravenous saline injection.** If a large volume of saline is given intravenously, diuresis starts after a latent period of a few minutes. It becomes maximum in the second hour and then gradually falls. The cause is chiefly decreased tubular reabsorption. Dilution of plasma proteins and consequent fall of colloidal osmotic pressure, may be an additional factor in this case.

3. **Drinking saline solutions.** *Isotonic salt solution* (similar to Locke's solution) does not give the same result as water drinking. When about 1 litre is taken urine volume may not rise at all. When about 3 litres are taken in an hour, moderate degree of diuresis takes place, the maximum rate being only 300 ml per hour. But the output remains above normal (above 100 ml per hour) for more than 24 hours. Considerable dilution of plasma proteins takes place, as is proved by the fact that haemoglobin concentration may fall by 10%. But in spite of this dilution comparatively light rise of urine volume takes place. But when water is drunk or when saline is injected intravenously, considerable diuresis occurs. It seems, therefore, that *saline is retained in the body when given by mouth or rectum but not when given intravenously.* It has been suggested that kidney can tolerate much increase of fluid content provided no change in the electrolyte concentration (as after drinking saline) takes place. But it cannot tolerate even smaller increase of fluid content accompanied by dilution of the electrolyte content of plasma (as in water drinking). It is a curious fact that isotonic KCl solution (1·3%) when given by mouth is not retained at all. It is eliminated as rapidly as urea and other waste products.

4. **Effects of salts.** (*a*) *Increased salt intake.* Experimentally, it has been shown that after ingestion of 28 g of NaCl, flow of urine was increased to 120 ml per hour. The maximum concentration of NaCl in urine was found between the third and the twelfth hour, being about 3·4% (normal 1%). On the whole, it is found that rate of salt excretion is comparatively slower. Consequently, after intake of salt, considerable amount of water has to be taken to dilute the retained salt and thus to maintain optimum osmotic pressure. The excess fluid and salt are slowly excreted in the course of few days.

(*b*) *Deprivation of salt.* This can be produced in man by giving a salt-free diet or by increasing the salt loss by inducing profuse sweating. In such cases, it is found that at first both plasma Cl^- level and Cl^- excretion in the urine progressively fall. Later on Cl^- excretion practically ceases due to complete reabsorption. At this stage the level of plasma Cl^- rises to some extent and remains only slightly below normal.

Under such conditions, it is found that *kidney function is seriously disturbed* although blood pressure remains unaltered. Glomerular filtration is decreased by 30%, urea clearance is decreased from 40-80% of normal, blood urea increases and a state of uraemia

develops. The decreased rate of glomerular filtration may be one cause in producing this uraemia. Water intake does not induce the normal diuresis in such cases.

5. **Effect of water deprivation.** (*a*) *In adults*—The renal circulation remains unchanged. There is no decrease in plasma volume and no haemoconcentration. Because, fluid is drawn from the tissue spaces. Body weight decreases by about 3-5 kg. The volume of glomerular filtrate is reduced by 20% and the volume of urine per hour is reduced to 30-40 ml. At this rate of output (30 ml per hour), urea, creatinine, phosphate and other nitrogenous and non-nitrogenous solids in urine become concentrated to the maximum. It means that unless the urine volume is increased, larger amounts of these constiuents cannot be eliminated. On the other hand, if urine volume is further reduced, total solid excretion diminishes, so that they accumulate in the blood leading to uraemic symptoms. (*b*) *In children*—Effects of water deprivation are more disastrous for the children. Because, at birth the kidney is not functionally developed, as is proved by the fact that infant urine is hypotonic (and not hypetronic as in adults). Beeause, the kidneys cannot concentrate the urine. Hence, more water is required to excrete a given amount of solid. Comparatively, a small quantity of fluid is available in the body to be out as urine, as with diarrhoea or vomiting, and consequently there is a retention of urea and other nitrogenous constiuents producing uraemia, rapidly. Hence, in children, suffering from diarrhoea, vomiting, etc., the fluid intake should be kept high.

6. **Effects of exercise.** It always reduces urine volume. The initial effects are not due to adrenaline secretion or renal vasoconstriction. Emotional states also produce similar results. It is suggested that both exercise and emotion, acting upon the hypothalamo-pituitary mechanism, increase the secretion of antidiuretic hormone and thus urine output is reduced. After severe exercise the urine volume is further reduced and becomes more acid in reaction.

REACTION OF URINE

The reaction of urine is generally acid throughout the greater part of the day. The normal range of pH of urine is 7·5-5·0, the average being 5·3. After a meal the human urine may be alkaline. This phenomenon is known as *alkaline tide*. It is believed to be due to relative increase of alkaline radicles in blood caused by the passage of large amount of HCl in the gastric juice. Increased respiration due to loss of CO_2 causes alkaline urine. In herbivorous animals and in others after a diet containing an excess of fruits and vegetables the urine becomes alkaline. Organic acids (e.g., tartarate and citrate) present in the above food are oxidised to carbonate. Rice, meat or a highly fatty diet produces acid urine. Urinary acidity also occurs during exercise due to increased production of lactic acid and in diabetic ketosis.

Total amount of acids eliminated per day varies from 600-700 ml of N/10 acid, of which about 400 ml is excreted as ammonium salts (not titratable) and the rest 300 ml is in the form of titratable acidity. The **pH** of the urine may be determined by **indicators** or by **titration** or by **hydrogen electrode.** Owing to the buffering action of phosphates, the titratable acidity of urine is always higher than is suggested by its H^+ ion concentration.

For all practical purposes any alteration of the reaction of urine reflects faithfully the tendency of blood reaction. In acidosis, it becomes more acid, in alkalosis, it becomes alkaline. The explicit purpose is to maintain the body reaction constant. The mechanism by which kidneys regulate the blood reaction and consequently after the reaction of urine is described below.

MECHANISM OF REGULATION OF BLOOD REACTION BY THE KIDNEYS

Maintenance of blood reaction to neutrality is an essential condition for life. Various factors take part in this regulation in which kidneys have

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the main role. During acidosis, the acidity of urine might be 1,000 times more than plasma. Kidneys regulate the blood reaction in the following five ways:

1. **Bicarbonate mechanism.** The epithelial cells of kidney tubules (proximal, distal and collecting one) secrete hydrogen ion into tubular fluids and change the reaction of the urine accordingly. Bicarbonate usually in combination with Na^+ is present in glomerular filtrate, but it is absent from the normal urine due to complete reabsorption. Na^+ is absorbed by the tubular cells in exchange of H^+ which is secreted by them. The entry of Na^+ ions into the proximal tubular epithelium is a passive process as the movement is only diffusion down a concentration gradient. But on the contrary, the hydrogen ion moves in the reverse direction with an active secretory pump system (Rector and his coworkers, 1965) (Fig. 1.40). The H^+ combines with bicarbonate ion to form carbonic acid. The carbonic acid breaks up into CO_2 and H_2O, the CO_2 diffuses into the tubular cells. Inside the cell, this CO_2 unites with water to form carbonic acid again, the reaction is catalised by the enzyme, *carbonic anhydrase*. The carbonic acid dissociates into bicarbonate ion and hydrogen ion, the latter is secreted into the tubular lumen. If enough hydrogen ions are present, almost all the bicarbonate filtered by the glomerulus are reabsorbed. The net result of this mechanism is reabsorption of Na^+ and bicarbonate of the tubular fluid into blood capillaries in exchange of H^+ ion.

The factors affecting bicarbonate transport are as follows:

(*a*) **Changes in the carbon dioxide tension (pCO_2) of the arterial blood**—Increased pCO_2 in the arterial blood causes significant increment in bicarbonate reabsorption.

(*b*) **Variations in the body store of potassium**—The intracellular concentration of the potassium, and not of the plasma is the factor that controls the bicarbonate reabsorption. Cooke, Darrow and others have shown that when excess potassium was infused, potassium rapidly enters into the cell in exchange of H^+ ion. The H^+ ions leaving the cells are buffered by bicarbonate of extracellular fluid and the plasma bicarbonate content is reduced. So in the renal tubular epithelium gives up less H^+ ion and thereby less bicarbonate is reabsorbed.

(*c*) **Variations in plasma level of chloride**—Increase or decrease of chloride concentration in plasma causes decrease or increase of bicarbonate concentration respectively. When the chloride excess is excreted or the chloride deficit is replenished, the plasma level of bicarbonate rapidly returns to normal.

(*d*) **Variation in the secretion of the adrenal cortical hormones**—The hormones of the adrenal cortex have some role in bicarbonate reabsorption but the actual mechanism is not known. In **Cushing's syndrome** and in hyperaldosteronism, the plasma bicarbonate concentration is increased which indicates that increased glucocorticoids and mineralocorticoids produce alkalosis associated with augmented bicarbonate reabsorption.

2. **Phosphate mechanism.** Both disodium hydrogen phosphate and monosodium dihydrogen phosphate are present in the plasma. The pH of the urine is determined by the ratio of disodium hydrogen phosphate to the monosodium dihydrogen phosphate. In plasma the concentration of the disodium hydrogen phosphate (alkaline phosphate) exceeds that of the

monosodium dihydrogen phosphate (acid phosphate) and the ratio is 4 : 1. But in the urine the concentration of the monosodium dihydrogen phosphate exceeds that of the disodium hydrogen phosphate and the ratio becomes 9 : 1. The kidneys naturally eliminate more acid phosphate and retain the basic phosphate as far as possible. This is mainly done by altering the excretion of alkaline and acid phosphates. In acidosis, more acid phosphates are eliminated. In alkalosis alkaline phosphate are excreted in excess. In this way the constant ratio between the two phosphates in blood is maintained and the blood reaction is kept constant. The possible theories for phosphate reabsorption along with excretion are shown in Figs. 1.45, 1.46 & 1.47.

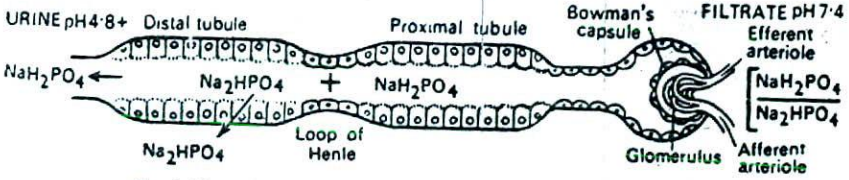


Fig. 1.45. Diagram explaining the phosphate reabsorption theory.

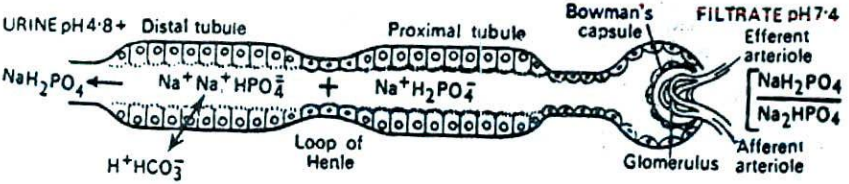


Fig. 1.46. Diagram explaining the tubular ion exchange theory.

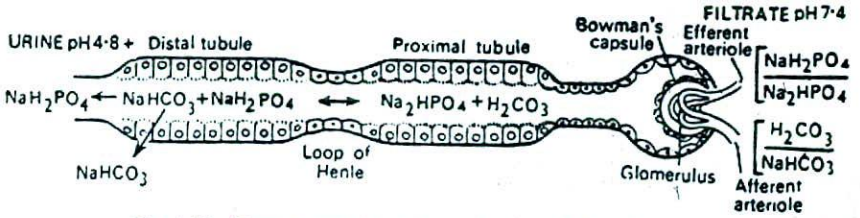


Fig. 1.47. Diagram explaining the carbonic acid filtration theory.

During excretion of large amounts of acid the tubular cells also manufactures ammonia from the glutamine and other amino acids, and ammonium salts are formed and excreted.

3. **Ammonia mechanism.** It has been discussed earlier (*vide* page 1.39) that the cells of the renal tubules contain *deaminases* (amino acid oxidases) which can produce ammonia by the deamination of *amino acids*.

The ammonia, formed with the action of glutaminase on glutamine (60%) and also with other reactions (*vide* p. 1-40), is passed out into the lumen of the tubules where ammonia combines with the acid

radicles and thus spares the fixed bases (e.g., Na^+, K^+, etc.). These bases are reabsorbed to maintain the alkali reserve. During acidosis the amount of ammonia formation is markedly increased. The effect might be due to an increase in the renal enzyme, glutaminase or amino acid oxidase. Adrenal cortical hormone has some role in this adaptive mechanism also. This is an important way by which kidneys help to maintain a constant blood reaction. It has been reported that the ammonia first appears in the sample collected from the first part of the distal tubule and the concentration gradually increases along the passage of the fluid towards the collecting tubule (Walker, 1940). So it is evident that the ammonia mechanism for maintaining blood reaction constant takes place at the distal tubule of the nephron.

4. **Elimination of acids.** There are evidences that the kidney tubules can secrete H^+ ion to maintain the blood reaction. For the mechanism of secretion of H^+ ion, two theories have been suggested. Either molecular acid combines with titratable acids after secreted by the renal tubules, or the H^+ ion is exchanged against the cations across the tubular epithelium. The second theory has been supported by much evidences and is now mostly accepted one (Fig. 1.48). There are three major factors that

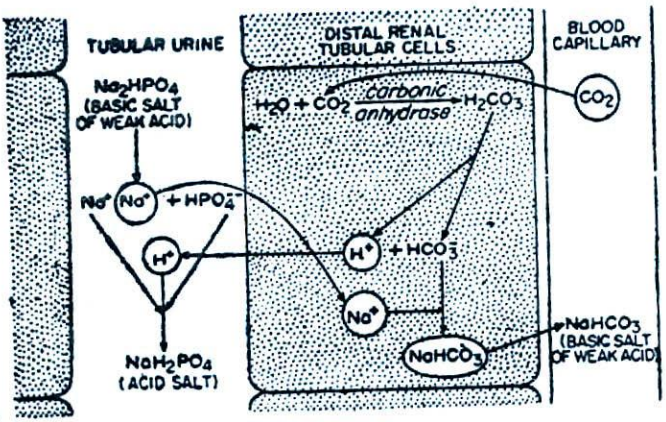


Fig. 1.48. Schematic representation of mechanism of formation of titratable acid by ion exchange in the distal renal tubular cells.

affect the rate of formation of titratable acids: (*i*) rate of excretion of the buffer, (*ii*) the pK′ of the buffer (Fig.1.49), and (*iii*) the degree of acidosis. From Fig. 1.49 it is evident that the rate of excretion of titratable acid progressively increases with the increasing quantities of buffer. Kisneys excrete directly some acids, such as uric acid, hippuric acid, the abnormal acids—like aceto-acetic acid, β-hydroxybutyric acid, glucuronic acid, homogentisic acid and so on. Although their acid value is not of much-practical importance, yet it is a distinct attempt on the part of the kidneys to maintain blood reaction.

5. **Elimination of alkalies.** Sodium bicarbonate, being a high threshold substance, is completely reabsorbed by the renal tubules. But in

alkalosis or when excess sodium bicarbonate is administered, it may be directly eliminated in the urine. Under such conditions, both bicarbonates and alkaline phosphates are found in the urine. One curious fact is that, presence of large amounts of chloride in the diet, diminishes the excretion of bicarbonates through the kidneys and therefore hampers the function of kidneys to combat alkalosis.

Although it is customary to say that urine reaction reflects the tendency of blood reaction, yet it seems that *preservation of an optimum saline concentration and crystalloid osmotic pressure is of greater importance than the maintenance of a constant H-ion concentration.* In order to attain this end, the normal pH level might have to be sacrificed. In excessive vomiting and diarrhoea,

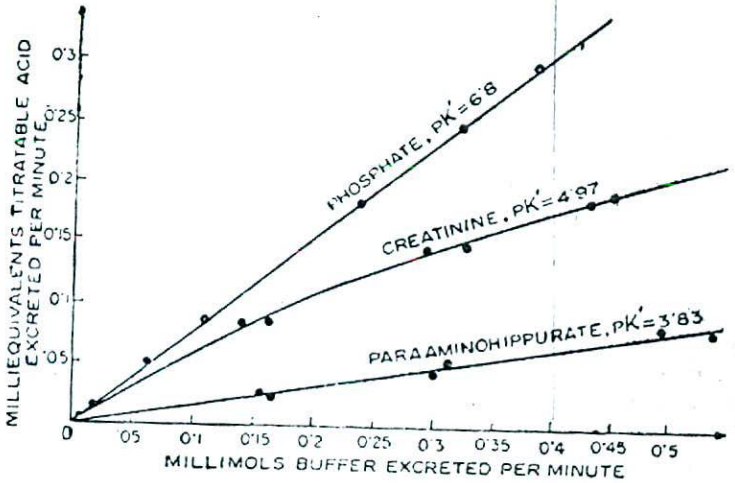


Fig. 1.49. Graphical representation of relationship of the rate of excretion of titratable acid to the rate of excretion of buffer and to pK′ of the buffer in an acidotic subject. Neutral sodium phosphate (having the highest pK), creatinine and sodium *p*-aminohippuric acid are infused at such rates as to cause equimolar increases in rates of excretion.

increased loss of chlorides occur, leading to a fall of plasma chlorides and consequently the osmotic pressure. The base left behind by the loss of Cl^-, combines with HCO_3^- to form more bicarbonates. These excess bicarbonates help to maintain the osmotic pressure of blood but, at the same time, cause alkalaemia. In such cases *acid urine* may be passed in spite of alkalosis. This shows that probably electrolyte balance and osmotic pressure are of more importance than a constant pH. Whenever there comes a clash between these two factors, kidneys will try to maintain the more essential, sacrificing the lesser one.

The role of the kidney in Acid-base Balance. In addition to carbonic acid, which is eliminated by the respiratory organs as CO_2, other acids which are not volatile are produced by metabolic processes. These include lactic and pyruvic acids and the most inorganic acids—hydrochloric, phosphoric and sulphuric. About 50 - 150 mEq of these inorganic acids are eliminated by the kidneys in a 24-hour period. It is of course necessary that these acids be pratically buffered with cation largerly sodium, but in the distal tubules of the kidneys some of the cation is reabsorbed (actually exchanged for hydrogen ion) and the pH of the urine is allowed to fall. This acidification

of the urine in the distal tubule is a valuable function of the kidney in conserving the reserves of cation in the body.

Another device used by the kidney to buffer acids and thus to conserve fixed base (cation) is the production of ammonia from amino acids. The ammonia is substituted for alkaline. Cation are the amounts of ammonia mobilised for this purpose may be markedly increased when the production of acid within the boby is in leasure (e.g. as in metabolic acidosis such as occurs as a resnet of the kitosis of uncontrolled diabetes)

When alkali is in excess, the kidney exeretes an alkaline urine to correct this imbalance (the details of the renal regulation of acid-base equilibrium are discussed elsewhere).

In kidney disease, glomerular and tubular damage results in considerable impairment of these important renal mechanisms for the regulation of acid-base balance.

GLYCOSURIA

Definition. *Glycosuria is a condition in which glucose is present in the urine in such quantities as will reduce Benedict's or Fehling's reagent.**

It is obvious that sugar may be present in the urine under two general conditions: (1) *When the blood sugar level goes above the renal threshold value of sugar,* i.e. 0·18%. (2) *When the degree of tubular reabsorption of sugar is deficient,* i.e. *where the renal threshold is low.*

All the different types of glycosuria can be put under these two groups: The first group is always attended with hyperglycaemia. In the second group, the blood sugar may be normal or even low. By the term **hyperglycaemia** is meant a condition, in which blood sugar rises above the maximum normal range, i.e. 0·12%. When this level goes beyond 0·18%, glycosuria takes place. So that hyperglycaemia between 0·12% and 0·18% is not attended with glycosuria. Thus glycosuria may be either due to hyperglycaemia or due to less tubular reabsorption or diminished renal threshold. These two groups are described below:

Glycosuria due to Hyperglycaemia

The following conditions give rise to hyperglycaemia which may lead to glycosuria:

1. **Alimentary glycosuria.** When a large carbohydrate diet is taken, blood sugar may rise and cause glycosuria. This condition does not seem to be a normal process. Because, hormonal control of carbohydrate metabolism is so efficient that a large amount of it can be taken as food without any appreciable variation in blood sugar level. Alimentary glycosuria, therefore, is only possible in those subjects in whom the power of sugar utilisation is deficient and subjects should be considered as early cases of diabetes.

2. **Nervous glycosuria.** Stimulation of the sympathetic nerves to the liver or of the splanchnic nerves, breaks down liver glycogen and produces hyperglycaemia, which may lead to glycosuria. Nervous stimulation mentioned above causes glycogenolysis directly, and is also responsible for increased liberation of adrenaline, which also activates glycogenolysis. Thus anything that stimulates sympathetic system, such as excitement, stress, etc., may produce glycosuria.

3. **Piqure glycosuria.** Certain injuries to the nervous system cause hyperglycaemia and glycosuria. Claude Bernard found that puncture of a

*Urine may also contain other reducing substances, such as uric acid, oxalates, glucuronic acid, lactose (in advanced pregnancy or in latating mothers), and these conditions should be carefully eliminated for the diagnosis of a case of glycosuria.

particular spot in the floor of the fourth ventricle of rabbits produces hyperglycaemia and glycosuria (Puncture diabetes). This glycosuria persists for 24 hours or more and is accompanied with marked hyperglycaemia. If the splanchnic nerves are divided beforehand, this experiment does not produce any hyperglycaemia or glycosuria. This indicates that the effects are brought about through the sympathetic nerves. It has been suggested that the experimental procedure stimulates a group of nerve cells at the floor of fourth ventricle which sends impulses through the splanchnic nerves to the adrenal medulla and liver. This centre can be reflexly affected by stimulation of many afferent nerves, such as vagus, and some other cranial and spinal nerves.

4. **Alloxan glycosuria.** When alloxan is injected to experimental animal, it produces necrosis of the β-cells of the islets of Langerhans. Due to deficiency of insulin, hyperglycaemia and thereby glycosuria occurs.

5. **Endocrine glycosuria.** Deranged function of a number of endocrine glands produces hyperglycaemia which may result in glycosuria. The important examples are as follows:

(*a*) **Pancreas** (Diabetes mellitus or Pancreatic diabetes). This has been fully dealt with in the chapters of Metabolism of Carbohydrates and Endocrines. In this condition the β-cells of the islets of Langerhans fail to secrete adequate amount of insulin. Lack of insulin produces hyperglycaemia and glycosuria.

(*b*) **Hyperthyroidism.** Hyperactivity of the thyroid is always attended with low *sugar tolerance,* hyperglycaemia and may be, glycosuria.

(*c*) **Adrenaline (Epinephrine).** Increased secretion of adrenaline stimulates synthesis of cyclic adenylic acid which activates inactive phosphorylase in hepatic and extrahepatic tissues. The active phosphorylase then causes breakdown of glycogen to glucose phosphate and then to glucose. The resultant effect is *hyperglycaemia* and ultimately *glycosuria.* Prolonged administration of adrenaline through subcutaneous route may increase the amount of liver glycogen by converting muscle glycogen into lactic acid and then lactic acid to liver glycogen. [*Vide Cori Cycle.*]

(*d*) **Anterior pituitary.** Hyperactivity of the anterior pituitary is also attended with hyperglycaemia and glycosuria (20-30% cases). This is supposed to be due to increased secretion of the growth or somatotrophic and adrenocorticotrophic hormones.

(*e*) **Adrenal cortex.** Hyperactivity of the adrenal cortex is believed to cause hyperglycaemia which may lead to glycosuria. Adrenal corticoid, e.g. cortisol, stimulates neoglucogenesis and produces hyperglycaemia and glycosuria and increased resistance to insulin.

(*f*) **Glucagon.** It is secreted by the α-cells of the islets of Langerhans. It also activates the inactive phosphorylase (only in liver) like that of adrenaline and thus stimulates glycogenolysis, producing hyperglycaemia and glycosuria.

In many clinical conditions glycosuria is found to take place. For instance—asphyxia, excited conditions, acute infective conditions, administration of anaesthetics, acute painful conditions, coma, etc., usually cause hyperglycaemia and often glycosuria. In all such conditions liver glycogen is found to be depleted. All these conditions are believed to act by causing sympathetic stimulation and thereby adrenaline secretio. There may also be an active inhibition of the β-cells of islets of Langerhans.

Glycosuria due to less tubular reabsorption

In the following conditions, renal reabsorption of sugar is defective. Blood surgar may be normal or low but still there is sugar in the urine.

1. **Renal glycosuria.** This is usually a developmental defect. The renal glycosuria is congenital and often demonstrated as familial. In one type the tubular maximum for tubular reabsorption (Tm_G) is reduced in the same line with the renal threshold. But in the other type there is no such relationship or any definite system. The cause for this irregularity in the second type may either be due to excessive glomerulotubular imbalance or to altered kinetics of the carrier system. It is probable that the **receptorcarrier mechanism,** which is responsible for the reabsorption of sugar by the renal tubule, fails to develop properly in this condition. This type of glycosuria is not attended with ketosis or the other ill effects generally found in diabetes mellitus. The man is otherwise completely healthy.

2. **Phloridzin glycosuria.** Phloridzin is a glucoside, found in the root of apple tree. When hydrolysed it gives *glucose* and *phloretin*. When phloridzin is administered subcutaneously it gives rise to intense glycosuria (the dose given to dogs is 1 g per day, in oil, subcutaneously).

Certain other glucosides, such as *arbutin* have similar effects. Phloridzin binds up strongly with membrane carrier preventing the glucose to attach with the membrane carrier and thus inhibits glucose reabsorption. Consequently, the renal threshold for sugar is abolished and no sugar is reabsorbed at all. So the Tm_G is minimum here. Glucose administered in this condition may be quantitatively recovered from urine. There is no hyperglycaemia here. The blood sugar is normal at the onset, but if the condition is prolonged, there may be hypoglycaemia. [So long as sufficient carbohydrate is given to compensate this loss of sugar, it does not cause any tissue destruction. But if the carbohydrate food be insufficient or the animal be starved a condition similar to diabetes mellitus develops. The fat depots are depleted, ketosis occurs, proteins break down and fully developed picture of pancreatic diabetes is found excepting the hyperglycaemia.] Phloridzin glycosuria is an accidental or an experimental condition. Although it has got no physiological importance yet phloridzin has been usefully employed in the study of carbohydrate metabolism.

3. **Diseases of the renal tubules.** In some cases of kidney disease, the tubules may be damaged, thus failing to reabsorb sugar. Consequently, sugar may be present in the urine.

4. **Due to heavy metal poisoning.** The heavy metals like lead, cadmium, mercury, etc., produces damage to the kidney cells thereby causing renal type of glycosuria.

5. **In pregnancy,** there is glycosuria due to lowering of renal threshold with the advancement of pregnancy.

From the above, it will be evident that glycosuria may take place under a variety of conditions. Investigation of a case of glycosuria is of immense importance for clinical purposes. *Sugar tolerance test* is of considerable value in this connection.

FACTORS CONTROLLING VOLUME OF URINE

The average volume of urine per day is 1,500 ml. But this volume is not a fixed quantity. It may increase or diminish considerably. There are

two principles on which urine volume will depend. One is the rate of glomerular filtration and the other is the degree of tubular reabsorption. Any factor, having influence on urine volume, will have to work on one or both of these two principles. The **factors that affect urine volume** may be briefly summarised as follows:

1. **Water intake.** Urine volume is directly proportional to the amount of water taken. If no food or drink is taken the urine volume diminishes to about 50 ml per hour. If two litres of water are drunk during 15 minures, the urine volume may rise to about 1,300 ml per hour (twenty-five times the normal). It has been shown that this effect is due to alteration of the rate of secretion of the antidiuretic hormone of the posterior pituitvry. Intravenous injection of saline produces similar effects. Drinking of tea or coffee increases urine volume as they contain diuretics.

2. **Elimination of water by other channels.** Urine volume is inversely proportional to the amount of water lost through other channels. For instance, diarrhoea, dysentery, cholera, excessive vomiting, etc., will all reduce the output of urine.

3. **Rate of renal circulation.** Urine volume is directly proportional to the degree of renal circulation. During sleep urine output is decreased. This is partly due to reduced renal circulation. Anything that improves renal circulation will increase urinary volume.

4. **Available filtration pressure.** Available filtration pressure is the resultant of many opposing forces (*vide* pages 1-25-1-26). Raised general blood pressure (as also increased blood volume—intravenous saline, etc.) increases filtration, and thereby urine volume. On the other hand, with fall of general blood pressure (as in shock, haemorrhage, heart failure, vasomotor failure, etc.) urine volume is reduced. Glomerular pressure may vary independent of general blood pressure. For instance, constriction of afferent arteriole (e.g., by adrenaline) will reduce glomerular pressure and reduce urine volume. On the other hand, dilatation of the afferent vessel (e.g., by caffeine) or constriction of the efferent vessel increases glomerular pressure and raises the amount of urine. Pressure in the ureter exerts an opposite effect. Rise of ureteric pressure, such as by a stone, reduces filtration and diminishes urine flow.

Colloidal osmotic pressure of plasma also affects urine volume. Reduction of colloidal osmotic pressure (such as by intravenous fluid administration or after ingestion of a large amount of water) increases filtration and thereby the volume of urine. On the other hand, increased concentration of plasma proteins (which may occur by excessive fluid loss through other channels) reduces urine volume.

5. **Number of active glomeruli.** It is obvious that, other factors remaining constant, amount of filtration will depend upon the number of active glomeruli. It is possible that during increased activity of kidney, a proportion of the inactive glomeruli will open up and help to increase the flow of urine. In frog, caffeine increases and adrenaline decreases the number of active glomeruli. Similar effects in mammals have not been proved beyond doubt. But still it is probable.

6. **Permeability of the filter bed.** Urine volume directly depends upon the permeability of the glomerular membrane. Anything that reduces the permeability reduces the urine volume.

7. **Degree of tubular reabsorption.** Normally, the renal tubules reabsorb water to about 90% from the capsular filtrate. The degree of reabsorption depends upon the antidiuretic hormone secreted by the posterior pituitary. This hormone increases the degree of reabsorption. In any condition, where the blood is more diluted (increased water intake, intravenous saline and so on) the secretion of this hormone is depressed, and therefore more water is allowed to pass out. In conditions of haemoconcentration more of this hormone is secreted, better tubular reabsorption takes place, resulting in less volume of urine. There is a pathological condition in which the secretion of this hormone is lacking (disease of the posterior pituitary or hypothalamus) and this may produce very large amount of dilute urine. This condition is known as *diabetes insipidus* where excretion of very large amounts of pale urine of low specific gravity and extreme thirst are caused.

Certain drugs, such as caffeine, mercurial diuretics, etc., reduces the power of absorption and increases the urine flow. In some types of kidney disease, in which the tubules degenerate, amount of urine increases due to failure of reabsorption.

8. **Amount of solids to be excreted by the kidney.** The osmotic pressure of the tubular contents work against reabsorption. In any condition therefore, where urinary solids increase in amount, the osmotic pressure will rise, reabsorption will be retarded and as such the volume of urine will rise. Some such conditions are as follows: (*a*) *Excess intake of salts.* (*b*) *Excess intake of sulphates, urea, etc.* (*c*) *Excess protein diet produces more urea,* hence, more urine flow. (*d*) *Thyroxine* stimulates metabolism, produces more metabolites and therefore, increases the amount of urine. (*e*) *Hypofunction of adrenal cortex* increases urine volume. It is partly due to associated salt loss and probably also due to reduced reabsorption of water by tubules. (*f*) In *diabetes mellitus* a large amount of sugar is present in the urine, This naturally increases the osmotic pressure and reduces reabsorption of water. It is due to this, that in diabetes, urine volume increases.

Various other factors may be mentioned which affect urine volume. But in all cases they will be found to work either by altering the rate of filtration or the rate of tubular reabsorption or both. On the whole it should be remembered that one function of kidney is to maintain the water balance of the body. In any condition where the water content of the body increases, urine volume will also rise. When the water content falls, volume of urine will be reduced. It must also be remembered that to eliminate the solid waste products a minimum amount of water must pass out. *Thus on the whole, the volume of urine represents either the inevitable minimum or the unnecessary excess. The regulating machinery is extremely efficient.*

Abnormal volume of urine. (1) **Nocturia,** early stage of kidney disease indicated by passage of more urine at night. (2) **Oliguria,** marked reduction of urine volume due to impairment of kidney function. (3) **Anuria,** complete suppression of urine flow due to severe kidney disease.

MICTURITION

The micturition is the process of accumulation of formed urine in the urinary bladder and evacuation of the same from the bladder from time to time, which are controlled by the nervous mechanism.

Structure of urinary bladder. Bladder *serves as a distensible reservoir for urine and to evacuate its contents at suitable intervals.* The urinary bladder

consists of two main parts: (1) the **body** and (2) the **trigone.** The body is a hollow sac of detrusor muscle, the interior is lined by layer of transitional epithelium which rests on lamina propria. The transitional epithelium

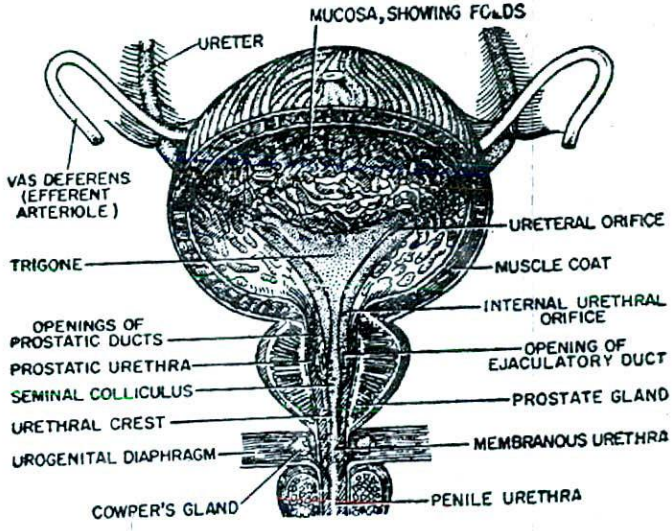


Fig. 1.50. Diagrammatic representation of the bladder to show the biadder wall, orifices of the ureters, urethra and related structures. The orifices of the urethra and ureters form the trigone. Also note that the ureters enter the bladder wall from the posterior and run vertically downwards.

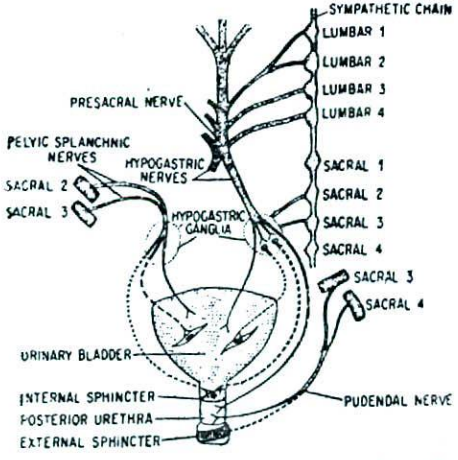


Fig. 1.51. Diagrammatic representation of the innervation of the bladder and the urethra in man.

of the innermost layer has got corrugations—rugae which are gradually flattened during filling of the bladder. During filling, the body of the bladder expands and the muscles contract during micturition reflex to evacuate it. The trigone is a small triangular region formed by connecting the openings of two ureters and the urethra. The *smooth* muscles surrounding the opening of the urethra form the *internal sphincter* of bladder. The muscles are tonically contracted till the pressure inside the bladder is raised high enough to open it. Distal to this the *striated* muscle of urogenital diaphragm forms the *external sphincter* of bladder. This muscle is also tonically contracted all the time excepting during micturition when it relaxes under reflex or voluntary control.

Nerve Supply of Bladder and Urethra is shown in table 1.4 and figure 1.51.

Efferent fibres (Motor)	Nerve Roots	Peripheral Nerves	Structures innervated	Functions
Somatic	S_3 and S_4	Pudic nerve	External sphincter and distal urethra	Control micturition (voluntary)
Sympathetic	T_{11} and T_{12} and L_1-L_4	Hypogastric nerves	Bladder and internal sphincter	Relax the bladder wall and constrict the internal sphincter
Parasympathetic	S_2-S_4	Nervi erigentes (Pelvic nerves)	Muscles of bladder (Detrusor) and internal sphincter	Contraction of the bladder and relaxation of the internal sphincter
Afferent (Sensory) fibres (concerned with pain and concious awareness of distension) from				Peripheral nerves
Bladder cavity Muscles of the bladder (Detrusor)				Hypogastric nerves Pelvic nerves
Urethra				Pudic nerves

MECHANISM OF FILLING OF BLADDER

Normally, bladder becomes filled up with urine coming from the two ureters. Peristaltic waves pass down the ureters from the renal pelvis to the bladder. With each such wave a jet of urine enters the bladder. The waves travel at a speed of 20-25 mm per second and with a frequency of 1-5 per minute. With each wave, urine enters the bladder and the intravesical pressure rises, which is followed by an immediate fall of pressure (nearly to the initial level) due to relaxation of the detrusor muscle. In this way, the bladder volume increases due to gradual relaxation of the detrusor muscle with the increased volume of urine accumulated in it, but without any appreciable rise of pressure (Laplace's law). This process continue until the urine volume (i.e., bladder volume) is about 400 ml beyond which the bladder wall fails to relax further and so the pressure rises up without any appreciable fall (Fig. 1.52). In this way, the bladder gadually fills up. *When about 350 to 400 ml of urine is collected the normal desire for micturition is felt.* By voluntary effort,

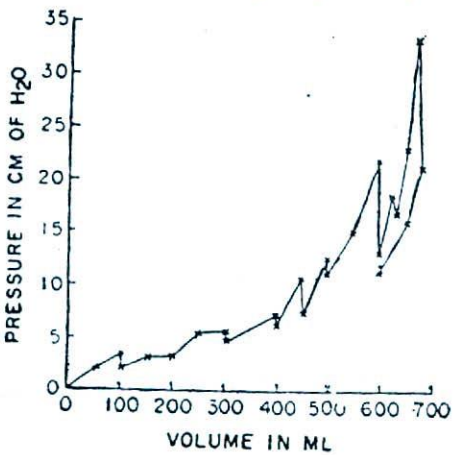


Fig. 1.52. Graphical representation of the pressure changes in the bladder during filling and emptying.

the onset of micturition can be delayed till a maximum of about 700-800 ml of urine accumulates in the bladder when it becomes urgent and painful. No further inhibition is possible beyond this stage and micturition will automatically begin. Under normal conditions, both the internal and external sphincters remain tonically contracted.

MECHANISM OF MICTURITION

The **act of micturition** involves the co-ordinated contraction of the smooth muscle of the bladder wall (detrusor muscle), abdominal wall and muscles of the pelvic floor, fixation of the chest wall and diaphragm, relaxation of the internal and external urethral sphincters. Accordingly, there are involvements of autonomic and voluntary activities.

The process of micturition can be studied by inserting catheter in the bladder, connecting it with a suitable manometer and studying the process under various conditions (Cystometrogram).

When the normal process of micturition is compared with the behaviour of a denervated bladder, the following facts are seen: In the denervated bladder the power of tone adaptation is lost and micturition starts much earlier than in a normal bladder. Although micturition starts yet the act is not complete. *Only partial emptying of bladder takes place and some residual urine is always left behind.* Whereas with normal bladder the power of tone adaptation is perfect, micturition starts much later (i.e., greater filling is allowed), and *the act of micturition is a complete process without any urine being left behind.*

This remarkable difference in the behaviour of normal and denervated bladders indicates that, under normal conditions, bladder does not behave simply as a hollow muscular organ, but that, nerves are necessary for its normal activity. In other words, *the normal act of micturition depends on the integrity of the nerves of bladder.* These considerations show that *micturition depends on nervous reflexes.*

In the denervated bladder, which acts simply as a muscular bag, only moderate filling raises the pressure to the adequate level causing contraction of the muscles and thereby starting micturition. When some quantity of urine is passed out, intravesical pressure falls below the critical level and further contraction ceases, till the requisite amount of urine accumulates again. In this way, always residual urine is left behind. But in normal bladder when micturition starts, intravesical pressure does not fall although fluid passess out. Because during the process, many sensory impluses arise from the bladder and the urethra and reflexly stimulate further contraction of the bladder until the act is complete.

Voluntary effort has enormous control over the process of micturition. Experimentally it has been shown that micturition can be inhibited for a long time or started much earlier by volitional effort. Volition can exert its influence both upon the sympathetic and parasympathetic supply of bladder and alter their activity. It is believed that in the normal micturition there is at first a voluntary removal of the constant inhibition upon the bladder, so that the lower centres are released. In this way micturition begins. When the bladder is not sufficiently filled, contraction of the bladder can be brought about by stimulating the pelvic visceral nerves by

volitional efforts. Moreover, raised intra-abdominal pressure caused by voluntary contraction of the abdominal muscle and that of the diaphragm, exerts pressure upon the bladder and mobilises micturition reflexes. In infants, due to non-myelination of the pyramidal tracts, the act of micturition is not under voluntary control. But since, the other centres are working properly the act, although involuntary, yet becomes complete.

Micturition reflex

As the bladder radius progressively increases with accumulation of urine coming from the ureters, the tension on the bladder wall increases. This tension on the vesical wall stimulates the proprioceptive end organs situated in the bladder wall which sends afferent impulses in the spinal reflex centre for micturition ($S_2 - S_4$), in the reflex centre for micturition in the brain stem (Pons?) and in the voluntary centre for micturition in the paracentral lobule in the cerebral cortex.

Normally the spinal reflex centre for micturition is inhibited by impulses from the brain stem centre even though the bladder is full. When an opportunity to empty the bladder is found, the inhibition of the higher centre to the spinal reflex centre is lifted and the micturition reflex begins. Parasympathetic efferent impulses from the spinal reflex centre to the detrusor muscle of the bladder wall. Contraction of the detrusor widens and shortens the posterior urethra resulting in passage of a bolus of urine into the posterior urethra. Urine in the posterior urethra stimulates the spinal centre which reflexly relaxes the external sphincter of the urethra and urine flows through the urethra. Micturition reflex is a "self-regenerative process" which means initial contraction of the bladder further stimulates the receptors to cause further increase in reflex contraction of the bladder. Thus a cycle starts which repeats again and again untill the bladder reaches a state of strong contraction. After some time the reflex begins to fatigue and the self-regenerative cycle ceased.

Centres of micturition. The central control of micturition lies at four levels: (1) **cortical,** (2) **hypothalamic,** (3) **brain stem,** and (4) **spinal.** The micturition is under the joint control of all these centres.

1. **Cortical centre.** The centre for control of the bladder is supposed to be present in the motor area of the cortex as well as in the upper part of the postcentral gyrus. The motor fibres arising from the cortex lie near the pyramidal tracts in the cord being mixed up with spinocerebellar fibres. Electrical stimulation of the premotor area raises the intravesical pressure which is followed by micturition. Bilateral lesions of the cortical areas (motor areas, 4 & 6) causes loss of voluntary control over the act of micturition. In other words, the voluntary holding up of urine is lost.

2. **Hypothalamic centre.** Beatty and Kerr observed the increased tone of the detrusor muscle after electrical stimulation of the anterior nuclei of the hypothalamus and the diminution of tone after stimulation of the posterior nuclei of the hypothalamus.

3. **Brain stem centre.** Section below the superior colliculus makes the bladder so excitable that micturition starts when only a few ml of urine being collected. Section below the inferior colliculus makes the bladder function reduced to the spinal state. The dominant centres for Barrington's first and second reflexes lie in the hind brain.

TABLE 1.5.

Summary of Barrington's micturition reflexes

NAME OF REFLEX	STIMULUS	AFFERENT NERVE	EFFERENT NERVE	CENTRE OF REFLEX	RESPONSE
First	Distention of bladder	Pelvic	Pelvic	Hind brain	Contraction of detrusor
Second	Fluid through urethra	Pudendal	Pelvic	Hind brain	Contraction of detrusor
Third	Distention of posterior urethra	Hypogastric	Hypogastric	Spinal cord	Contraction of detrusor
Fourth	Fluid through urethra	Pudendal	Pudendal	Spinal cord	Relaxation of urethra
Fifth	Distention of bladder	Pelvic	Pudendal	Spinal cord	Relaxation of urethra
Sixth	Distention of bladder	Pelvic	Pelvic	Spinal cord	Relaxation of posterior third of the urethra

4. **Spinal centres.** These centres remain in the second, third and fourth sacral segments. When these spinal centres are injured the act becomes involuntary and incomplete. These spinal centres can be excited reflexly by various types of sensory stimulation. The spinal centres are under inhibitory control of the cerebral cortex and midbrain. Irritation of the pelvic organs, as caused by intestinal worms in children, may give rise to reflex involuntary micturition. This is one of the commonest causes of nocturia in children. Voluntary micturition is abolished after lesion of the spinal cord above the sacral segments. The tone of the muscles of the bladder wall (detrusor) and of the sphincter is lost for a certain period. Reflex contraction of the detrusor muscle and relaxation of the sphincter muscle do not occur. But after some time the detrusor muscle regains some tone and minor contractions take place which is not sufficient to overcome the sphincter tone which has recovered earlier. One or two weeks later, the urethral resistance diminishes. Urine is collected in the bladder which is gradually overstretched causing a rise in the intravesical pressure. When this raised pressure overcomes the sphincter tone, a small quantity of urine dribbles out, leaving more urine in the bladder. This condition is called as **retention with overflow.**

From the above, it will be seen that the phenomenon of micturition involves a number of complex reflexes controlled by many centres. It is also interesting to find that both *somatic and autonomic nervous systems* are involved in the process. It is one of the few processes in the body which is almost equally under the dual control of somatic and autonomic nervous system.

EFFECTS OF LESION OF THE AUTONOMIC NERVES

1. **Effects of lesion of the afferent sympathetic and parasympathetic nerves.** There is loss of perception of pain and stretch sensibility of the bladder. The subject cannot feel the distention of the bladder, and as

a result urine accumulates, and when the intravesical pressure becomes high, the resistance of the sphincter is overcome and dribbling occurs. In

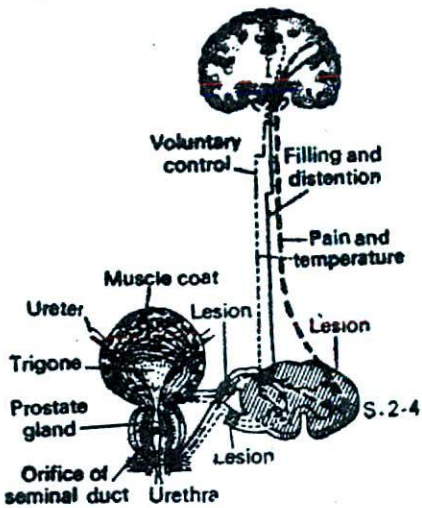


Fig. 1.53. Diagrammatic representation of a flaccid neurogenic bladder caused by a lesion of the sacral portion of the spinal cord or of the cauda equina.

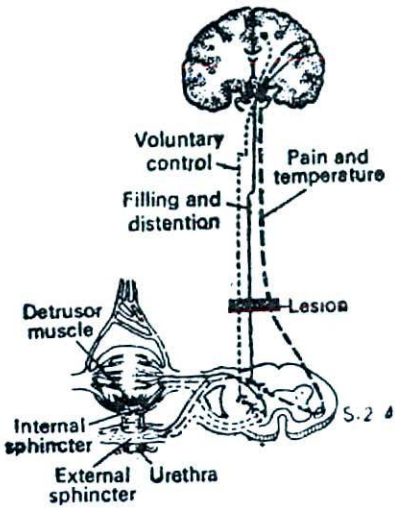


Fig. 1.54. Diagrammatic representation of a complete spastic neurogenic bladder caused by a more or less complete transection of the sacral spinal cord above S.2.

tabes dorsalis there is lesion of the posterior nerve roots in the lumbosacral region and similar changes are noticed.

2. **Effects of lesion of the efferent sympathetic nerves.** The internal sphincter, the trigone and the ureteric orifices will be relaxed. There may be rise in frequency of micturition at the initial stage. Later the internal sphincter regains its tone. Gradually normal function of the bladder is re-established.

3. **Effects of lesion of the efferent parasympathetic (sacral autonomic) nerves.** Voluntary micturition is almost abolished. The detrusor muscle becomes atonic. The bladder becomes flaccid neurogenic (Fig. 1.53). The tone of the internal sphincter rises. There is retention of urine. The intravesical pressure rises with volume and when it overcomes the resistance of the sphincter, the dribbling of urine occurs. But soon this condition disappears and the

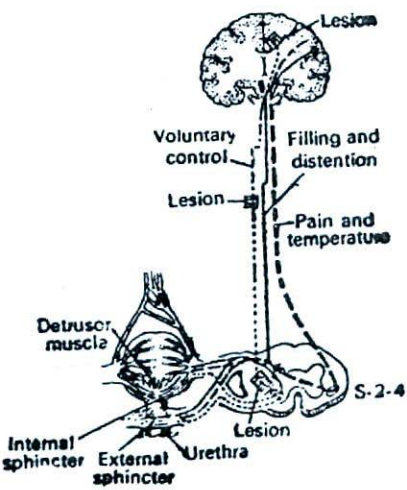


Fig. 1.55. Diagrammatic representation of an uninhibited neurogenic bladder caused by a lesion of the inhibitory centres of the cerebral cortex or pyramidal tracts.

bladder empties itself automatically hrough local nervous reflex. It is called an *isolated* bladder. The detrusor muscle contracts as soon as the intravesical pressure rises, but the contractions of the detrusor muscle are not strong and some residual urine always remains.

4. **Effects of complete transection of the spinal cord.** The bladder becomes complete spastic neurogenic (Fig. 1.54). The bladder capacity is diminished. There is increment in intravesical pressure, spasm of the external sphincter and involuntary contraction of detrusor muscle. Cerebral control is lacking. The bladder works in conjunction with its sacral reflex arc.

5. **Effects of incomplete lesions of the cerebral cortex or the pyramidal tracts.** The cerebral restraint becomes either weakened or abolished due to incomplete lesions of the cortex or the pyramidal (motor) tracts (Fig. 1.55). There may have frequent micturition, nocturia and uncontrollable urgency. These facts are also present in normal infants.

ARTIFICIAL KIDNEY

If the kidney fails to maintain its functions adequately then improvised device can be adapted so as to eliminate the incompatible substances of the body. This improvised artificial device is the artificial kidney. *It is based on the principle of dialysing out the incompatible substances from the blood.* The artificial kidney consists of a membrane through which incompatible substances are diffused out of the blood. This membrane allows all the constituents except the protein. The substance to be removed from the body is diffused out by adjusting the concentration gradient of dialysing fluid. For the operation of the artificial kidney, the arterial blood is passed through artificial kidney and the blood, after being filtered, is returned back to the body through the vein. For prevention of coagulation, heparin is always used.

VITAMINS AND KIDNEY

Like other organs the kidney is a very active organ for metabolism and many of the metabolic activities of the renal cortex, such as synthesis and hydrolysis of glutamine, deamination of amino acids and the synthesis of glucuronides are closely related to the excretory function of the kidney. As in other organs, the fundamental processes of anabolism and catabolism are same and the vitamin B complex acts as coenzymes of several enzymes that take part in some metabolic processes in the kidney. Vitamin C and different fat-soluble vitamins play much role in maintaining the integrity of cell membrane and other specific metabolic action of cells and organs.

Role of vitamins on metabolic and different functional changes in the kidney

(*a*) **Thiamine.** 2·8 μg of thiamine is present per gram fresh weight of kidney tissue. Thiamine plays an emense role on the different enzymatic processes of the kidney tissue. In deficiency of thiamine, transketolase activity is completely lost in the kidney but is revived partially within 24 hours if thiamine is administered. Adenosine deaminase activity of the kidney is depressed in deficiency of thiamine.

(*b*) **Riboflavin.** In deficiency of vitamin B_2, the enzyme activity is affected to a lesser degree in the kidney than in the liver.

(*c*) **Pyridoxine.** In vitamin B_6-deficient rats, the activity of the glutamate-pyruvate transaminase of the kidney is decreased to a greater extent than the activity of the glutamate-oxaloacetate transaminase.

Besides this, deficiency of vitamin B_6 may produce renal oxalate stone in rats. In rats, cats and monkey, vitamin B_6-deficiency is always associated with a marked excretion of oxalate through the urine. In human beings, if deficiency of B_6 is happened then oxaluria often occurs.

(*d*) **L-ascorbic acid.** Scorbutic guinea-pigs show decreased activity of alkaline phosphatase in the kidney. But glutamate-pyruvate transaminase activity is markedly increased in deficiency of vitamin C.

(*e*) **Vitamins A and E.** Vitamin A-deficiency in rats causes increase in alkaline phosphatase activity in the kidney. Alkaline phosphatase activity is significantly decreased in vitamin E-deficient rats. The activity of transamidinase is reduced in vitamin E-deficient rats.

Pathological changes in the kidney caused by vitamin deficiency

Deficiency of vitamin B complex is often related to the different pathological changes in the kidney.

(*a*) **Thiamine.** In thiamine deficiency marked hypertrophy in rat's kidney is often observed.

(*b*) **Riboflavin.** In riboflavin-deficient rats, weight of the kidneys is also increased. A lipoid degeneration of the proximal convoluted tubules of the kidney has also been reported in deficiency of riboflavin.

(*c*) **Vitamin B_{12}.** Vitamin B_{12}-deficiency shows little evidence of abnormalities in the low vitamin B_{12}-dietary rat's tissues, but female rats kept on B_{12}-deficient diet from before the time of mating until the end of gestation results degenerative changes of the brain, liver, heart and kidneys in their youngs. Kidneys of their new-born rats show retarded growth.

(*d*) **Nicotinic acid.** Deficiency of nicotinic acid causes severe tubular damage of the kidneys.

(*e*) **Vitamin A.** In vitamin A-deficient rats, desquamation of the renal tubular epithelium and enlargement of the distal convoluted tubules and collecting tubules are often encountered.

(*f*) **Vitamin E.** In chronic deficiency of vitamin E, the renal tubular epithelium becomes coarsely granular and receives a *honeycombed* contour.

INTEGUMENT

Skin

Skin acts as a protective covering for the body minimising loss of water from the body tissues. Various sensory nerve endings on the skin help to protect the body from injury by invoking appropriate response to noxious stimuli. The skin also plays an important role in temperature regulation.

Structure. Two main layers (*i*) Epidermis, (*ii*) Dermis. (Fig. 1.56)

Epidermis is the most superficial layer and is composed of stratified squamous type of epithelium. From outside inward stratified epithelium may be divided into 5 layers:

1. **Stratum Corneum** is most superficially placed. The cells are keratinised. The cell outlines are indistinct and the nuclei are absent. This layer is thickest at the sole and the palm and thinest at the lip. Hairs, loops, nails, feathers, scales, etc., are special outgrowth of this layer.

2. **Stratum Lucidum.** This is a thin more or less transparent layer 3 to 5 cells deep placed below the strutum corneum. The cell outlines are indistinct and the nuclei are absent. The cells contain droplets of 'eleidin' which is precursor of keratin.

3. **Stratum Granulosum** is situated below the stratum lucidum and consists of 3 to 5 layers of flattened polyhedral cells filled with keratohyalin granules which take a deep stain with haematoxylin.

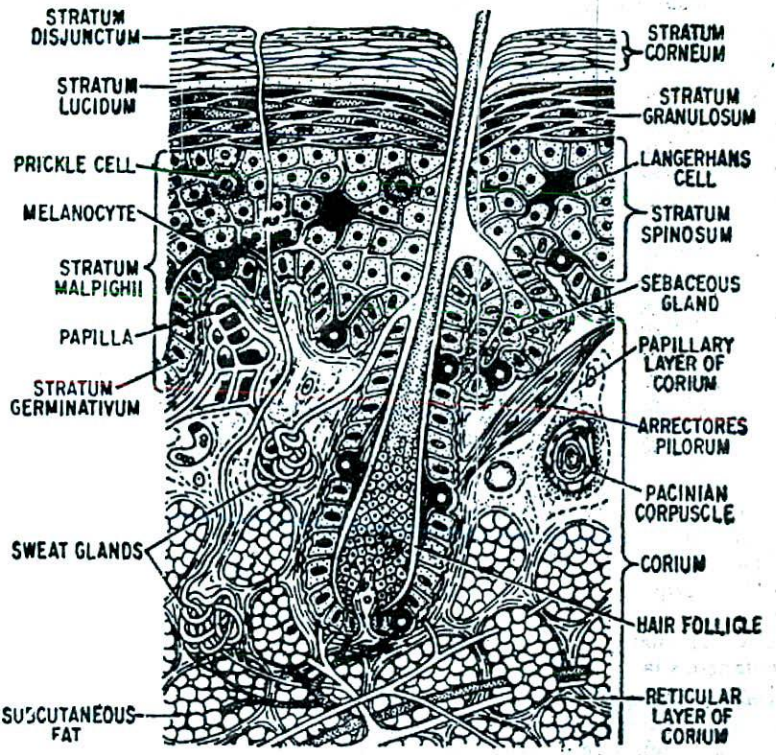


Fig. 1.56. Diagram shows section of skin.

4. **Stratum Spinosum.** This is a broad layer of variable thickness and is made up of polyhedral cells. The surface of these cells is apparently covered with minute spines, which interdigitate with similar spines of adjacent cells. These are consequently known as **"prickle cells".** As the cells move towards the surface, keratin is synthesised within them. Microscopic studies indicate that the prickle cells are in fact cytoplasmic protrusions and the branches from two cells actually do not have cytoplasmic continuity, but attached by well-developed cytoplasmic nodes called desmosomes. These cells are basophilic and are supported by a network of cytoplasmic fibrils. Scattered irregularly throughout this layer are branchedstar-shaped cells known as Langerhans cells demonstratable by appropriate technique. The functions of these cells are not known and they are capable of active synthesis of DNA.

5. **Stratum Germinativum** (Stratum Malpighii). This growing layer is composed of a single layer of columnar epithelium which has got transverse, thin, short cytoplasmic processes on its basal lamina by means of which they anchor the epithelium to the underlying dermins. These cuboidal to columnar cells with oblong nuclei, placed perpendicularly on the basement membrane, produce new cells to replace those of the above layers by the process of mitosis. Mitotic activity of the epidermis occurs in rhythmic diurnal cycles, the greatest activity in humans occuring during the hours of sleep. At the junction of the epidermis with the dermis there occur number of melanin-containing branched cells, known as **melanocytes*.** They send processes among the Malpighian cells and the melanin present in the deeper cells of the stratum Malpighii is produced by these melanocytes. Cytocrine secretion transfers the fully-formed melanin granules from melanocytes to the Malpighian cells. The ratio of melanocytes to basal *epidermal cells varies between* 1 *to* 4 *and* 1 *to* 10.

Epidermis of the body in general. Above characteristic features of the epidermis are mostly present in the palm and the sole. Epidermis in general, i.e. of other than soles and palms is thin and stratum Malpighii and stratum corneum are always present. Stratum corneum is also thin and just identifiable. Definite stratum leucidum is not seen.

Dermis (Cutis vera or true skin)

The true skin is made up of connective tissue and lies below the epidermal layer which it supports and binds to the underlying tissues. It is made up chiefly of collagenous and elastic fibres which provide it with a tensile strength equal to that of a thin steel wire. This layer is utilised for the production of leather after chemical processing. From the structural point of view the superficial part of the dermis is compact and forms the *papillary layer* because it sends innumerable finger-like projections (papillae) into the prickle cell layer of epidermis. The deeper part of the dermis is composed of rather loose connective tissue and is infiltrated with fat. This layer constitutes what is called *reticular layer* of dermis. The reticular layer of the dermis merges imperceptibly into the subcutaneous layer of fat.

Cells of the Dermis

1. Fibroblasts from which the fibrous tissue of the dermis develops.
2. Cells belonging to the reticulo-endothetilal system—which protects the body from invading bacteria. Some of these cells are loaded with melanin pigments and are known as Melanophores.
3. Besides the above two types of cells—dermis also contains other types of cells which are found in areolar tissue of other regions of the body.

Blood Vessels of the Dermis

Though the epidermis is devoid of blood vessels the dermis has got a luxuriant supply of capillary blood vessels which form a network from which "hairpin" loops supply the tip of the dermal papillae. The blood vessels play an important role in temperature regulation and have got rich vasomotor innervation.

There is also a well-organised lympatic system in the dermis.

* Now a days melanocyte is used instead of melanoblast. Melanoblast *is now used for such cells in embryonic life.*

Nerves of the Dermis

Besides the vasomotor nerves mentioned above the dermis is provided with sensory nerve endings of various types, which keep the individual informed about the surroundings.

Glands of the Dermis

The lower ends of the *sweat glands* reach deep part of the dermis and act as islands for re-growth of epidermis in case of injury or burns involving loss of epidermis.

Sebaceous glands located in the dermis open into the hairfollicles and secrete oily material called sebum.

NOTE: The ceruminous glands of the external auditory meatus and mammary glands are modified sweat glands.

Muscles of the Dermis (Corium)

(*a*) Arrectores pilorum—A small bundle of involuntary muscles attached to the hair in such a way that they cause the hair to stand on end.

(*b*) Tunica dartos and other involuntary muscles of the skin of the penis, nipple and areola are located deep in the dermis.

Pigmentation of the skin

The colour of the human skin is derived from a variety of chemical and physical properties associated with the skin structure. Five pigments are known to influence skin colour: (a) All individuals except *albinos* have some *melanin pigment* in their skin. *Melanin* is a yellow to black pigment which is found mainly in the stratum Malpighii, and is formed on a specific cell particle, the melanosome within the melanocytes. (Fig. 1.57) In man, melanosomes are uniformly elongated except red-haired individuals where they are spherical. During pregnancy, the pigmentation of the areola of the nipples increases. Melanin contributes colour quality to the skin and protects the organism from the ultra-violet ray. The stability of melanosomes after their incorporation into the cytoplasm of Malpighian cells along with their absolute increase in numbers is the main

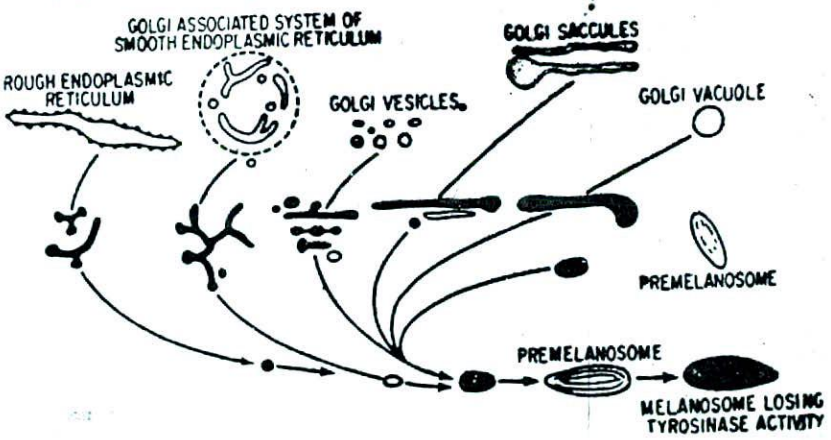


Fig. 1.57. Composite diagram shows the region in a melanocyte.

cause of the marked difference in the skin colour between black and white individuals. (b) *Melanoid is* supposed to be a degradation product of mel-

anin and is diffused through the epidermis. Melanoid has a different absorption band of visible light. (c) *Carotene* is a yellow-orange pigment and present in lipid-rich areas (i.e., the stratum corneum and the fat of the corium and subcutaneous tissue). Carotene adds the strong yellow component to skin colour of the woman in greater concentration than that of men. (d) *Oxyhaemoglobin* imparts a reddish hue to the skin colour and is evident to areas where there is rich arterial supply (i.e., face, neck, palms, soles and nipples). (e) *Reduced haemoglobin* contributes a bluish or purple character to skin colour and is more evident in lower areas of the trunk. Melanin concentration and skin thickness have a tendency to suppress the haemoglobinpigment colour component effects.

The distribution pattern and concentration of these pigments also influence the skin colour. Variations in the thickness of the skin may modify the skin colour. Subjects with thin epidermis have a ruddier colour complexion and with a thicker epidermis, look yellower. The thick epidermis is less transparent than the thin and the thin epidermis allows the colour of blood pigments to express their colour characteristics more readily. The light-scattering qualities of the skin may also act as a factor modifying skin colour. As the transparent stratum corneum scatters light slightly, the deeper layer appears bluer because of the scattering effect of light in the overlying coarser tissue layer where dark-pigment granules are commonly found. Pigmentation of the skin is supposed to protect the unerline tissue against the potentialy harmful effects of solar radiation.

Functions of the skin

1. **Protection.** *Stratum corneum* which is the outermost layer is horny and formed by the keratinised stratified epithelial cells resist the action of external agencies. It protects the internal individual injury and bacterial invasion. The nails (hoops, horns, etc., in animals) are also defensive appendages of the skin.

2. **Regulation of body temperature**

(a) *Cutaneous vasoconstriction* diverts the blood to the interior of the body and so diminishes heat loss. This is an important mechanism of protection against cold environment. Vasodilatation of the skin helps in elimination of heat from the body.

(b) *Sweating*—evaporation of sweat cools the body the latent heat of vaporisation being 0·56 calories/g of H_2O vaporised.

(c) *Hairs of the skin*—in lower animals entangles a layer of air in its meshes. This layer of stagnant air being poor conductor of heat intervenes between the warm air in contact with the skin and cdd atmospheric air and helps to preserve body temperature.

3. **General sensation.** The skin serves as the medium for receiving the general sensation. Touch, pain, temperature, etc., are subserved by the respective nerve endings present in the skin. The hair roots are richly supplied with nerves. Consequently, slight movement of the hair, such as by a blast of wind arouses sensation. In this way hairs help the sensory functions of the skin.

4. **Excretion.** Through sweat and insensible perspiration, salts and metabolites are excreted to some extent.

5. **Synthetic function.** Vitamin D is synthesised by ultra-violet rays of the sun acting upon the ergosterole present in the skin and subcutaneous tissue. For this reson exposure to the sun ensures supply of vitamin D.

6. **Secretion.** (a) *Sebum*—The sebaceous glands secrete a fatty substance which is rich in cholesterol, called sebum. It helps to keep the skin greasy and prevents drying. In cold climates the secretion is depressed and the skin becomes dry and scaly. (b) Sweat (described in detail below) which is the active secretion of sweat glands of skin plays a vital role in keeping the body cool in hot environment. (c) Milk, the secretion of the mammary glands, which are modified sweat glands. [In the toads, certain poisonous glands are present in the skin. They secrete a highly irritant fluid and in this way acts as a defensive weapon for the animal.]

7. **Absorption.** Waxy layer hinders water absorption through the skin. But the skin is not completely waterproof and on prolonged exposure to water, there is water absorption causing swelling of the stratum corneum. Lipids are easily permeable through the skin. Lipid-soluble substances like vitamins are easily absorbed through the skin.

8. **Water balance.** Formation and evaporation of sweat is an important factor in the regulation of water balance of the body.

9. **Acid-base equilibrium.** Sweat being acid in reaction, a good amount of acid is excreted through it. In acidosis it becomes more acid and in this way helps to maintain a constant reaction in the body fluids.

10. **Storage functions.** The dermis as well as the subcutaneous tissue can store (a) fats, (b) water, (c) salts, (d) glucose and such other substances.

It is found that when blood sugar level suddenly rises, considerable amount of sugar may be temporarily stored in the subcutaneous tissue and in the skin. As sugar is gradually used up, the skin sugar is slowly drawn in. The areolar tissue of the skin and subcutaneous tissue have great affinity for water and any excess of water in the body is stored mainly inside the skin and subcutaneous tissue. After haemorrhage the lost blood volume is quickly replenished by drawing fluid from the tissue and half of it comes from the skin. Similarly a large quantity of NaCl may remain stored in the skin. After a chloride-rich diet or after an intravenous saline injection, the heaviest load of NaCl is found in the skin and subcutaneous tissue. Whereas during salt deprivation, blood chlorides are maintained by drawing upon the chlorides, stored in the skin.

The subpapillary plexuses of the dermis can store up to about 1,000 ml of blood, which supplies muscles and other organs in times of emergency.

11. **Gaseous exchange.** Absorption of oxygen and excretion of CO_2 may go on to a considerable extent through the skin in those animals whose skin is thin and moist, e.g. forgs. It is said that it can be carried to such an extent that these animals may live even after the extirpation of the lungs or in the hibernating period when the lungs do not function. In man this effect is negligible. No oxygen is absorbed but a small amount of CO_2 is eliminated through the skin (probably it passes out being dissolved in the sweat).

12. Skin also exhibits signs of vitamin deficiency, malnutrition and advancement of aging (appearance of wrinkles on the skin).

Glands in the Skin

Sweat glands. Modified smooth muscle cells, known as myoepithelial cells invest the base of the glands and wind round their ducts in such a way that by their contraction they help in elimination of sweat.

There are about 3 million of active sweat glands in the body. They are devided into two groups: (1) Eccrine (2) Apocrine (Fig.1.58).

Eccrine sweat. The eccrine glands constitute the majority and are generally found throughout the surface. They are most numerous on the palms and soles, than on the head, but much less on the trunk and the extremities. In lower mammals they are relatively sparse being found mainly on hairless areas such as foot pads. They reach their peak of development in man where they may be 200-400/sq. cm of the skin surface. They are innervated by cholinergic sympathetic fibres whose discharge is altered primarily by changes in deep body temperature. The glands on palms and soles do not respond to temperature but secrete at times of emotional stress. They secrete dilute sweat-containing NaCl, urea, lactates, creatinine, uric acid, ammonia, amino acids, glucose, water-soluble vitamins B and C. NaCl content is variable. The sweat is not a simple filtrate of blood but the product of an active process though the composition depends on the blood constituents.

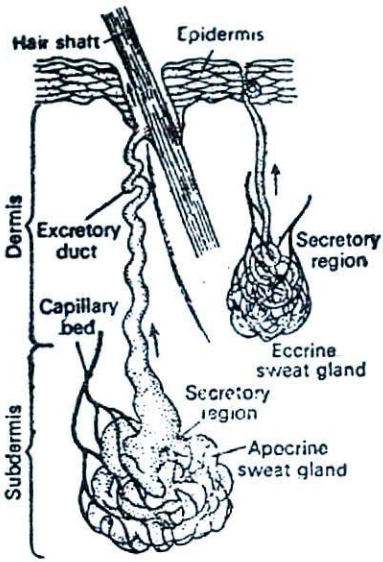


Fig. 1.58. Diagram shows the excretory duct, the tightly coiledsecretory region, and the vascular bed of eccrine and apocrine sweat glands.

Apocrine sweat*. The apocrine glands are larger sweat glands. They are derived from the hair follicles and include the ceruminal glands of the ear, those of the eyelid, and the mammary glands. The distribution of these large glands varies very much from individual to individual and from race to race and are found only in special regions, such as axilla, areola of the nipples, mons pubis, labia majora, etc. They are said to be, in many instances, of sexual significance and to become less so as we ascend the evolutionery scale. They respond to circulating adrenaline. They do not become active until puberty. Their secretion is viscid, milky and odourless at first. After puberty their secretions vary in composition and possess a characteristic odour. The odour is due to indoxyl. volatile fatty acids, hydroxy acids, ammonia, etc. Bacterial activity in the presence of the secretions contributes to the intensity and quality of the odour. The mammary glands which eject milk are forms of the apocrine sweat glands and an interesting study in evolution.

*According to Jenkin son's view, *apocrine* should be dropped to describe the sweat gland, because the original concecpt of formation of apocrine sweat by shedding the outer portion of secretory cells is now known to be incorret.

MECHANISM OF SECRETION OF SWEAT

Though the **eccrine** glands are supplied by the sympathetic fibres, yet adrenaline (epinephrine) has got no action on them. **Pilocarpine** which stimulates the parasympathetic fibres increases the flow of sweat and **atropine** which paralyses the parasympathetic endings, abolishes sweating. From these observations and from similar others, it is believed that acetylcholine is liberated at the nerve endings. Hence, although the fibres are automatically sympathetic, yet they are functionally cholinergic. Hilton has shown that the sweat secreted from the eccrine glands contains bradykinin-forming enzyme. This enzyme diffuses into the surrounding tissue and helps in forming bradykinin (Fig. 1.59). Bradykinin is a polypeptide and causes dilatation of the cutaneous blood vessels and blood vessels supplying the sweat glands. Injection has only very slight effect on this vasodilation.

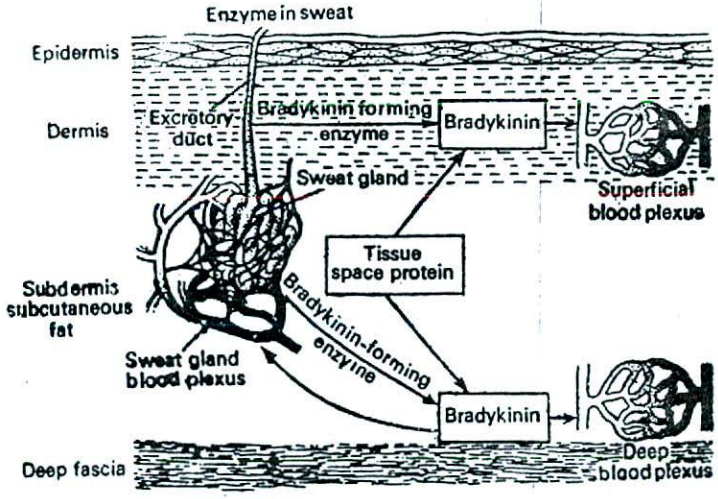


Fig. 1.59. Diagram showing the formation of bradykinin in human skin during body warming.

Different types of sweating

(1) **Insensible perspiration** which occurs even in cold climate amounts to 600 to 800 ml daily,

(2) **Thermal sweating** occurs in hot environmental temperature, the threshold being 28°C for man and 31°C for woman. As the environmental temperature rises sweating increases and may amount to 11 litre/day under extreme conditions. It is to be emphasised that when the ambient temperature is higher than body temperature sweating is the only method of keeping the body temperature normal, provided the humidity is low so that the sweat can evaporate.

(3) **Psychic sweating**—

(i) **Emotional (mental) sweating.** In the emotional conditions sweating occurs chiefly in the palms, soles and axilla, but it is also present at the head and neck and elsewhere. In the extreme emotional conditions

it may be more generalised (hyperhidrosis). Emotional (cold) sweating is due to impulses discharged from the higher centres, affecting the sweat centres directly (Fig. 1.60). The sweating that occurs under the emotional condition is probably under the control of the premotor area of the cerebral cortex.

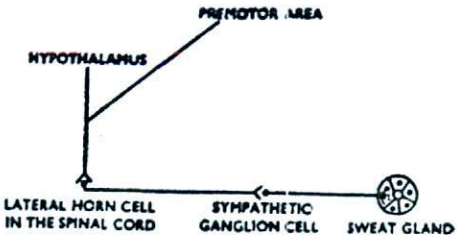


Fig. 1.60. Diagram shows the nervous path for regulation of sweat secretion.

(ii) **In muscular exercise,** the sweating both thermal and mental. Sweating is reduced by cold, which at the same time reduces cutaneous circulation. It is also reduced by dehydration, whether the result of deprivation of fluid intake or by sweating itself. The taking of a glass of cold water which dilutes the blood produces a profuse sweating.

(4) **In hot climates,** eating of spicy foods (e.g. capsicum or curry) stimulates sweating (**gustatory sweating**), because pain nerve endings in the mouth are stimulated. Hence reflex sweating occurs in the head and neck.

(5) **Owing to sympathetic activity,** nausea and vomiting, fainting, hypoglycaemia and asphyxia cause secretion of sweat.

Composition of sweat

Sweat mainly consists of secretions of the eccrine glands. It is the most dilute of all animal fluids. When freshly collected, it contains epithelial cells and some sebum. When filtered, it forms a clear colourless fluid. The human sweat has specific gravity of about 1·001—1·006, pH 3·8 to 6·5 and the average composition is as follows:

Water	99·221-99·742 g/100 ml
Solids	1·174-1·587 g/100 ml
Ash	0·144-0·566 g/100 ml
Creatinine	0·1-1·3 mg/100 ml
Urea	12-57 mg/100 ml
Lactic acid	285-336 mg/100 ml
Carbolic acid	2-8 mg/100 ml
Sugar (as glucose)	1-3 mg/100 ml
Uric acid	0·07-0·25 mg/100 ml
Ascorbic acid (as dehydroascorbic acid)	70·5 μg/100 ml
Total nitrogen	33·2 mg/100 ml
Non-protein nitorgen	27-64 mg/100 ml
Amino acid N	1·1-10·2 mg/100 ml
Ammonia N	5-9 mg/100 ml
Urea N	5-36 mg/100 ml
Calcium	1-8 mg/100 ml
Iodine	0·5-1·2 μg/100 ml
Iron	0·022-0·045 mg/100 ml
Chloride	36-468 mg/100 ml
Na^+	24-312 mg/100 ml
K^+	21-126 mg/100 ml
Sulphur	0·7-7·4 mg/100 ml
Copper	0·006 mg/100 ml
Amino acids (total)	43·62 mg/100 ml

It is to be noted that the only conspicuous constituent is **NaCl,** which varies between **0·2-0·5%.** Muscular exercise increases the salt concentration of sweat. Sweat secreted by clothed skin has a higher salt concentration than that of naked skin. When sweating is pro-

fuse the total elimination of NPN per hour may be as much as 0·5-1·0 g. Regarding salts a man may lose as much as 10 g of chlorides by profuse sweating in 3 hours.

Aldosterone, the secretion of adrenal cortex, reduces both the sodium and chloride ions in sweat and thus decreases their loss. Excessive sweating may cause increased secretion of aldosterone, and prevents depletion of salt reserves of the body. (Accomodation of sweat glands).

Urea has about the same concentration as in blood, but lactates seem to be either concentrated of actually formed by the sweat glands.

Sebaceous Glands

Sebum is the oily secretion of the sebaceous glands (Fig. 1.61). These glands are pear-shaped bodies opening into the root of the hair follicles. But where they are independent of hairs, their ducts open directly to the free surface of the skin (e.g. in gland penis, basal glands of the eyelids, etc.). Nicoll and Cortese (1972) have reviewed the current concepts on the ultrastructural anatomy and on the physiology of sebaceous gland cells. They have described the life cycle of sebaceous cells into three distinct cell types. These:

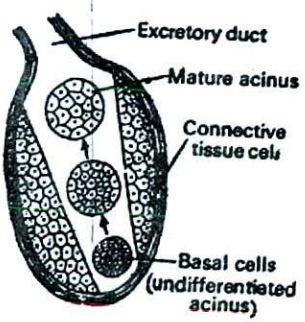


Fig. 1.61. Diagram showing the development of a sebaceous acinus.

(a) *The peripheral* cells which are containing ribosomes and are formed against the basement membrane that surrounds the acinus.

(b) *The partially differentiated cells,* which are actively synthesising and storing sebum droplets within the cells.

(c) *The fully differentiated cells,* which contain a multitude of tightly packed sebum vacuoles ready to be released upon rupture of the cell.

Cellular maturation and sebum lypogenesis represent a dynamic process. In the early stage of lipogenesis, glycogen, smooth endoplasmic reticulum and ribosomes predominate in the cytoplasm of cells. For the cellular maturation, numerous mitochondria along with smooth surface vesicles, ribosomes, glycogen and Golgi membranes fill cytoplasmic substance of the cells. As maturation of cells is completed, numerous lipid vacuoles, smooth membranes, and a minimal number of ribosomes and mitochondria appear within the cells. It is suggested more earlier by Rogers and Palay (1958) that smooth-surfaced endoplasmic reticulum is primarily involved in lipogenesis and mitochondria may play a role in producing energy. The sebum is thus formed in the cells of the gland and thereby the cells become impregnated with fat. These matured cells finally degenerate and break apart releasing the sebum to the excretory duct. The residue ultimately is coming out the skin surface through the hair root canal (Fig. 1.61). They are totally absent at the palms and soles. The sebaceous glands are very active during adolescence. When the secretion is not properly discharged, it lodges in the ducts as *whitehead.* The outer portion of the substance may be blackened by oxidation and then constitutes a *blackhead.* Formation of sebum is determined by alteration of vascularity of the skin.

Composition of sebum. Composition of sebum is not fully known. Sebum has a characteristic colour. Sebum is rich in fatty acids, stored

cholesterol, cholesterol esters, triglycerides, wax esters and other aliphatic components. This cholesterol has two additional advantages over ordinary fat. First, it can absorb about 100% of water and thus helps to keep the surface moist. Secondly, it is not attacked by bacteria and therefore does not become rancid. Irradiation of sebum give rise to vitamin D.

Control. There is no nervous control for the secretion of sebum. Hormonal regulation of sebaceous glands is well established. Experimental evidence suggests that excess administration of progesterone causes pronounced enlargement of cebaceous glands. This has given rise to the belief that in the female, acne is incited by progesterone formed by the corpus luteum of the ovary. But it is not ascertained whether the progesterone affects the sebaceous glands in physiological doses. Oestrogen is known to decrease the size of the sebaceous glands as well as to inhibit the formation of sebum in human. Current evidence suggests that sebum production is stimulated primarily by androgens secreted either from adrenal glands, testes or ovaries. In human males, testosterone is considered as the major cause of pubertal acne. Contraction of arrectores pilorum helps in the expulsion of sebum. These muscles contract by the application of cold, during excitement and in response to adrenaline.

Functions. Sebum has dual functions. It acts as a bacteriostatic agent and as a lubricant. It has also the property preventing damage of the epidermis during hot season and conservation of heat during cold.

Cerumen is a yellow, pasty substance resembling wax which is secreted by the modified sweat glands (ceruminal glands) located in the external auditory canal. An accumulation of cerumen deep in the auditory canal may interfere with hearing.

Repair of skin and skin grafting. When a certain area of the epidermis has been removed, repair is effected by growth from the Malpighian layer. In skin grafting, small pieces of healthy skin (including the deep layers of epidermis) are transplated on to the bare area. Each graft that takes serves as a centre from which the new epidermis spreads outwards, so that the bare area is quickly covered.

The special structures of the skin

1. **Nails** (Ungues). The nails from the protective covering on the dorsal surface of the terminal phalanges of the fingers and toes (Fig. 1.62) and are made up of horny plates. With continuous proliferation and differentiation of cells of the lower part of the matrix (*stratum germinativum*), the forming nail plate (*modified stratum corneum*) is pushed out of the groove and slowly advances over the dorsal surface of the digits towards the distal end. Component cells contain numerous cytoplasmic fibrils which are lost at the later stage as the cells become homogeneous, cornify and join the nail plate. The keratin of the nail is turned hard. The epidermis immediately beneath the nail plate constitutes the nail bed (*matrix*). The nail plate is contained within the nail groove and flanked by a skin fold, the nail wall (eponychium—modified stratum corneum). The nail bed is made up of the deeper layers of the epidermis and lacks sweat glands and hair follicles.

Functions. Protection, defence, in animals the nail helps in capturing the prey.

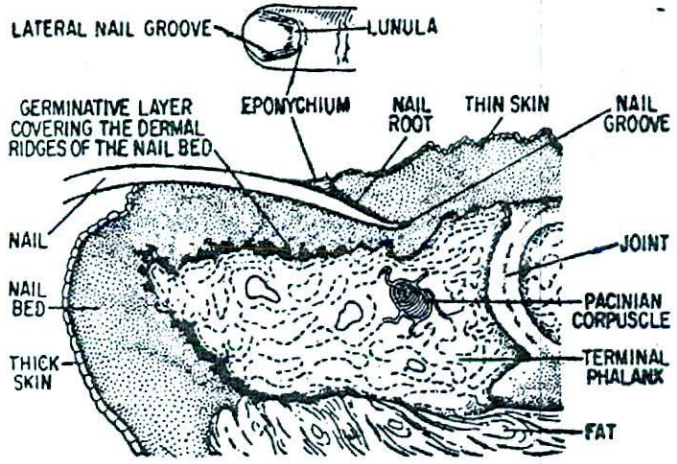


Fig. 1.62. A section of finger-tip through the nail fold, full term foetus, inset showing adult nail fold (diagrammatic).

2. **Hairs** (Pili). These are elastic keratinised threads which develop from the epidermis and extend downward into the subcutaneous tissue. They vary in length from 1 mm to 1,500 mm and in thickness 0·05 to 0·5 mm. The hairs are present all over the skin except for palms, soles and urogenital apertures. Each hair has a free shaft projected beyond the surface of the skin and a root embedded in the tubular hair follicle in the skin. The hair (Fig. 1.63) is composed of (a) *cuticle* is a single layer of scale-like cells which overlap. (b) *Cortex* is the middle portion of the hair.

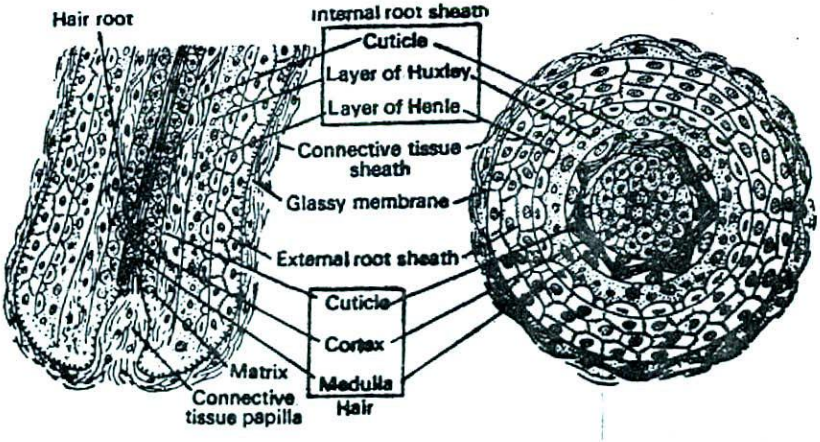


Fig. 163. Diagrammatic representation of a hair follicle in longitudinal section (left) and in transverse section (right).

It constitutes the main part of the shaft and is formed of elongated cells united to form flattened fibres. These fibres contain pigment granules in dark hair and air in white hair. (c) *Medulla* is the inner layer and is composed of rows of many-sided cells. These cells frequently contain air spaces. The hairs of the head and the fine hairs covering the surface of the body do not possess the medulla. The hair follicle has two parts: epidermal (*epithelial*) and dermal (*connective tissue*). The expanded lower part of the follicle is named as **hair bulb** which is indented at the basal end by a connective tissue papilla. Hairs have no blood vessels but receive nourishment from the blood vessels of the papilla. The follicle is associated into one or more sebaceous glands and a bundle of smooth muscle—**arrector pili**, contraction of which causes erecton of the hair which normally remains in an obtuse angle to the skin surface. Hairs grow from the papilla by multiplications of matrix cells which become elongated to form the fibres of fibrous part and when they are pushed to the surface, they become flattened and from the cuticle. Shedding of hairs is seasonal in some animals but not in man. The newly developed hair is longitudinal section (left) and in transverse section (right), present on the side of the shedding hair. Failure of replacement results to baldness, uncommon in the females. Baldness is related to presence of male sex hormone in the blood stream, but is not caused by it.

An accute inflammation of a hair follicle and its sebaceous gland gives rise to a boil due the entrance of staphylococci through the follicle.

Functions. (1) Presence of hair protects the body from the extreme temperature of the environment by acting as an insulator, especially in animals of cold countries. (2) Scalp hairs protects the head from mechanical injury as well as from heat, rays, etc. (3) The hair also does the tactile receptor function. (4) Hair serves a sexual function in promoting the evaporation of the apocrine sweat and the accompanying characteristic odour that goes along with it provides a sexual attraction for the lower animals.