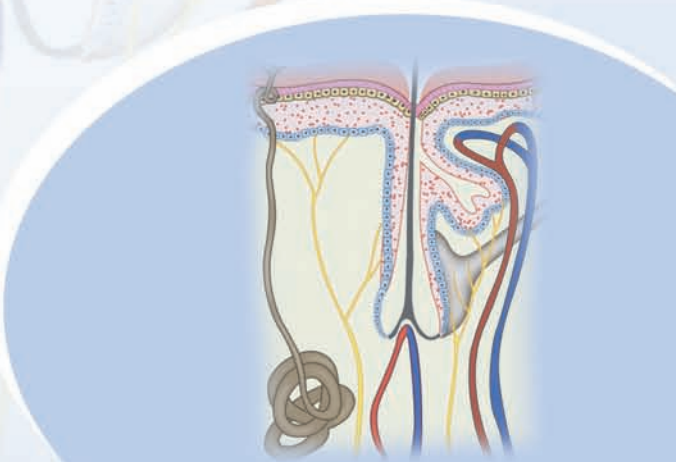
Section

5

Renal Physiology and Skin



Kidney

Chapter 48

INTRODUCTION

Excretion is the process by which the unwanted substances and metabolic wastes are eliminated from the body.

A large amount of waste materials and carbon di-oxide are produced in the tissues during metabolic process. In addition, residue of undigested food, heavy metals, drugs, toxic substances and pathogenic organisms like bacteria are also present in the body.

All these substances must be removed to keep the body in healthy condition. Various systems/organs in the body are involved in performing the excretory function, viz.

1. **Digestive system** excretes food residues in the form of feces. Some bacteria and toxic substances also are excreted through feces
2. **Lungs** remove carbon dioxide and water vapor
3. **Skin** excretes water, salts and some wastes. It also removes heat from the body
4. **Liver** excretes many substances like bile pigments, heavy metals, drugs, toxins, bacteria, etc. through bile.

Although various organs are involved in removal of wastes from the body, their excretory capacity is limited. But renal system or urinary system has maximum excretory capacity and so it plays a major role in homeostasis.

Renal system includes:

1. A pair of kidneys
2. Ureters
3. Urinary bladder
4. Urethra.

Kidneys produce the urine. Ureters transport the urine to urinary bladder. Urinary bladder stores the urine until it is voided (emptied). Urine is voided from bladder through urethra (Fig. 48.1).

FUNCTIONS OF KIDNEY

Kidneys perform several vital functions besides formation of urine. By excreting urine, kidneys play the principal role in homeostasis. Thus, the functions of kidney are:

1. ROLE IN HOMEOSTASIS

Primary function of kidneys is **homeostasis.** It is accomplished by the formation of urine. During the formation of urine, kidneys regulate various activities in the body, which are concerned with homeostasis such as:

i. *Excretion of Waste Products*

Kidneys excrete the unwanted waste products, which are formed during metabolic activities:

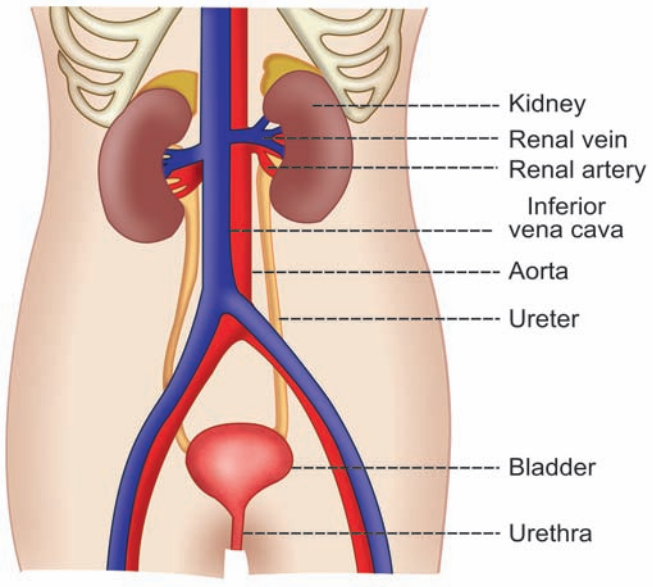


FIGURE 48.1: Urinary system

a. Urea (end product of amino acid metabolism)
b. Uric acid (end product of nucleic acid metabolism)
c. Creatinine (end product of metabolism in muscles)
d. Bilirubin (end product of hemoglobin degradation)
e. Products of metabolism of other substances.

Kidneys also excrete harmful foreign chemical substances such as toxins, drugs, heavy metals pesticides, etc.

ii. *Maintenance of Water Balance*

Kidneys maintain the water balance in the body by conserving water when it is decreased and excreting water when it is excess in the body. This is an important process for homeostasis (Refer Chapter 4 for details).

iii. *Maintenance of Electrolyte Balance*

Maintenance of electrolyte balance, especially sodium is in relation to water balance. Kidneys retain sodium if the **osmolarity** of body water decreases and eliminate sodium when osmolarity increases.

iv. *Maintenance of Acid–Base Balance*

The pH of the blood and body fluids should be maintained within narrow range for healthy living. It is achieved by the function of kidneys (Chapter 54). Body is under constant threat to develop **acidosis,** because of production of lot of acids during metabolic activities. However, it is prevented by kidneys, lungs and blood buffers, which eliminate these acids. Among these organs, kidneys play major role in preventing acidosis. In fact, kidneys are the only organs, which are capable of eliminating certain metabolic acids like sulfuric and phosphoric acids.

■ 2. HEMOPOIETIC FUNCTION

Kidneys stimulate the production of erythrocytes by secreting **erythropoietin.** Erythropoietin is the important stimulating factor for erythropoiesis (Chapter 10). Kidney also secretes another factor called **thrombopoietin,** which stimulates the production of thrombocytes (Chapter 18).

■ 3. ENDOCRINE FUNCTION

Kidneys secrete many hormonal substances in addition to erythropoietin and thrombopoietin (Chapter 72).

Hormones secreted by kidneys

i. Erythropoietin
ii. Thrombopoietin
iii. Renin
iv. 1,25-dihydroxycholecalciferol (calcitriol)
v. Prostaglandins.

■ 4. REGULATION OF BLOOD PRESSURE

Kidneys play an important role in the long-term regulation of arterial blood pressure (Chapter 103) by two ways:

i. By regulating the volume of extracellular fluid
ii. Through **renin-angiotensin** mechanism.

■ 5. REGULATION OF BLOOD CALCIUM LEVEL

Kidneys play a role in the regulation of blood calcium level by activating 1,25-dihydroxycholecalciferol into **vitamin D.** Vitamin D is necessary for the absorption of calcium from intestine (Chapter 68).

■ FUNCTIONAL ANATOMY OF KIDNEY

Kidney is a compound tubular gland covered by a connective tissue capsule. There is a depression on the medial border of kidney called hilum, through which renal artery, renal veins, nerves and ureter pass.

■ DIFFERENT LAYERS OF KIDNEY

Components of kidney are arranged in three layers (Fig. 48.2):

1. Outer cortex
2. Inner medulla
3. Renal sinus.

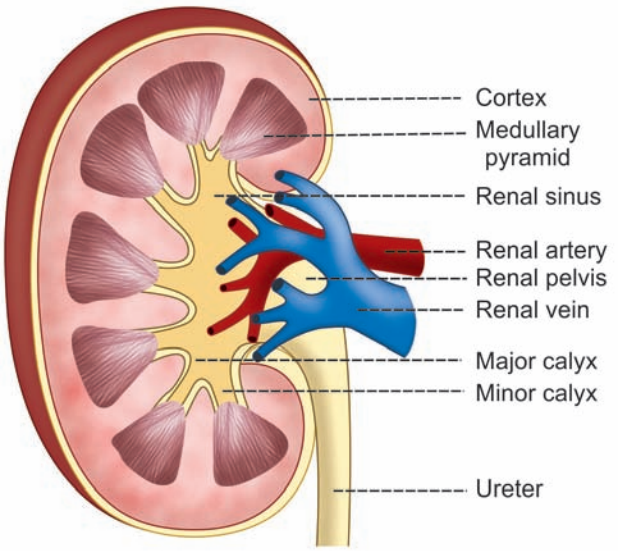


FIGURE 48.2: Longitudinal section of kidney

1. *Outer Cortex*

Cortex is dark and granular in appearance. It contains renal corpuscles and convoluted tubules. At intervals, cortical tissue penetrates medulla in the form of columns, which are called renal columns or **columns of Bertini.**

2. *Inner Medulla*

Medulla contains tubular and vascular structures arranged in parallel radial lines. Medullary mass is divided into 8 to 18 **medullary** or **Malpighian pyramids.** Broad base of each pyramid is in contact with cortex and the apex projects into **minor calyx.**

3. *Renal Sinus*

Renal sinus consists of the following structures:

i. Upper expanded part of ureter called **renal pelvis**
ii. Subdivisions of pelvis: 2 or 3 **major calyces** and about 8 minor calyces
iii. Branches of nerves, arteries and tributaries of veins
iv. Loose connective tissues and fat.

■ TUBULAR STRUCTURES OF KIDNEY

Kidney is made up of closely arranged tubular structures called **uriniferous tubules.** Blood vessels and interstitial connective tissues are interposed between these tubules.

Uriniferous tubules include:

1. Terminal or secretary tubules called **nephrons,** which are concerned with formation of urine
2. **Collecting ducts** or tubules, which are concerned with transport of urine from nephrons to pelvis of ureter.

Collecting ducts unite to form **ducts of Bellini,** which open into minor calyces through **papilla.** Other details are given in Chapter 49.

Chapter 49

Nephron

INTRODUCTION

Nephron is defined as the structural and functional unit of kidney. Each kidney consists of 1 to 1.3 millions of nephrons. The number of nephrons starts decreasing after about 45 to 50 years of age at the rate of 0.8% to 1% every year.

Each nephron is formed by two parts (Fig. 49.1):

1. A blind end called renal corpuscle or **Malpighian corpuscle**
2. A tubular portion called **renal tubule.**

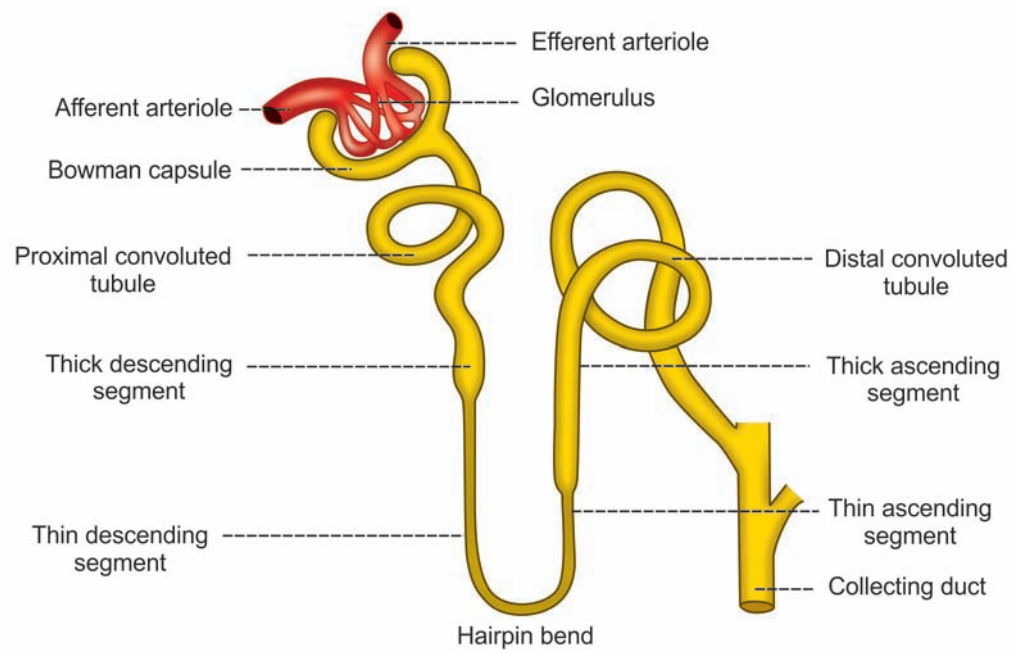


FIGURE 49.1: Structure of nephron

■ RENAL CORPUSCLE

Renal corpuscle or Malpighian corpuscle is a spheroidal and slightly flattened structure with a diameter of about 200 µ.

Function of the renal corpuscle is the filtration of blood which forms the first phase of urine formation.

■ SITUATION OF RENAL CORPUSCLE AND TYPES OF NEPHRON

Renal corpuscle is situated in the cortex of the kidney either near the periphery or near the medulla.

Classification of Nephrons

Based on the situation of renal corpuscle, the nephrons are classified into two types:

1. **Cortical nephrons** or superficial nephrons: Nephrons having the corpuscles in outer cortex of the kidney near the periphery (Fig. 49.2). In human kidneys, 85% nephrons are cortical nephrons.
2. **Juxtamedullary nephrons:** Nephrons having the corpuscles in inner cortex near medulla or corticomedullary junction.

Features of the two types of nephrons are given in Table 49.1.

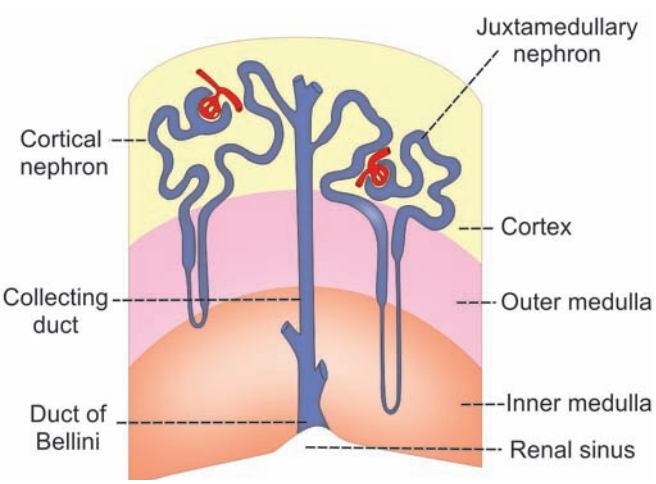


FIGURE 49.2: Types of nephron

■ STRUCTURE OF RENAL CORPUSCLE

Renal corpuscle is formed by two portions:

1. Glomerulus
2. Bowman capsule.

Glomerulus

Glomerulus is a tuft of capillaries enclosed by Bowman capsule. It consists of glomerular capillaries interposed between afferent arteriole on one end and efferent arteriole on the other end. Thus, the vascular system in the glomerulus is purely arterial (Fig. 49.3).

Glomerular capillaries arise from the afferent arteriole. After entering the Bowman capsule, the afferent

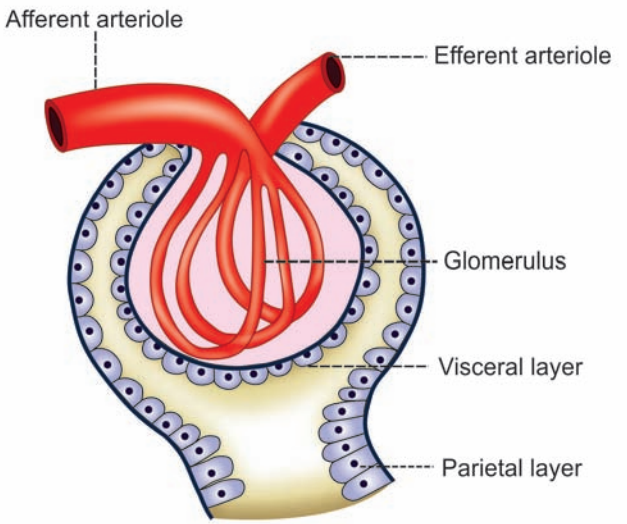


FIGURE 49.3: Renal corpuscle

TABLE 49.1: Features of two types of nephron

Features	Cortical nephron	Juxtamedullary nephron
Percentage	85%	15%
Situation of renal corpuscle	Outer cortex near the periphery	Inner cortex near medulla
Loop of Henle	Short	Long
	Hairpin bend penetrates only up to outer zone of medulla	Hairpin bend penetrates up to the tip of papilla
Blood supply to tubule	Peritubular capillaries	Vasa recta
Function	Formation of urine	Mainly the concentration of urine and also formation of urine

arteriole divides into 4 or 5 large capillaries. Each large capillary subdivides into many small capillaries. These small capillaries are arranged in irregular loops and form anastomosis. All the smaller capillaries finally reunite to form the efferent arteriole, which leaves the Bowman capsule.

Diameter of the efferent arteriole is less than that of afferent arteriole. This difference in diameter has got functional significance.

Functional histology

Glomerular capillaries are made up of single layer of endothelial cells, which are attached to a basement membrane. Endothelium has many pores called **fenestrae** or **filtration pores.** Diameter of each pore is 0.1 µ. Presence of the fenestra is the evidence of the filtration function of the glomerulus.

Bowman Capsule

Bowman capsule is a capsular structure, which encloses the glomerulus.

It is formed by two layers:

i. Inner visceral layer
ii. Outer parietal layer.

Visceral layer covers the glomerular capillaries. It is continued as the parietal layer at the visceral pole. Parietal layer is continued with the wall of the tubular portion of nephron. The cleft-like space between the visceral and parietal layers is continued as the lumen of the tubular portion.

Functional anatomy of Bowman capsule resembles a funnel with filter paper. Diameter of Bowman capsule is 200 µ.

Functional histology

Both the layers of Bowman capsule are composed of a single layer of flattened epithelial cells resting on a basement membrane. Basement membrane of the visceral layer fuses with the basement membrane of glomerular capillaries on which the capillary endothelial cells are arranged. Thus, the basement membranes, which are fused together, form the separation between the glomerular capillary endothelium and the epithelium of visceral layer of Bowman capsule.

Epithelial cells of the visceral layer fuse with the basement membrane but the fusion is not complete. Each cell is connected with basement membrane by cytoplasmic extensions of epithelial cells called **pedicles** or feet. These pedicles are arranged in an interdigitating manner leaving small cleft-like spaces in between. The cleft-like space is called **slit pore.** Epithelial cells with pedicles are called **podocytes** (Fig. 49.4).

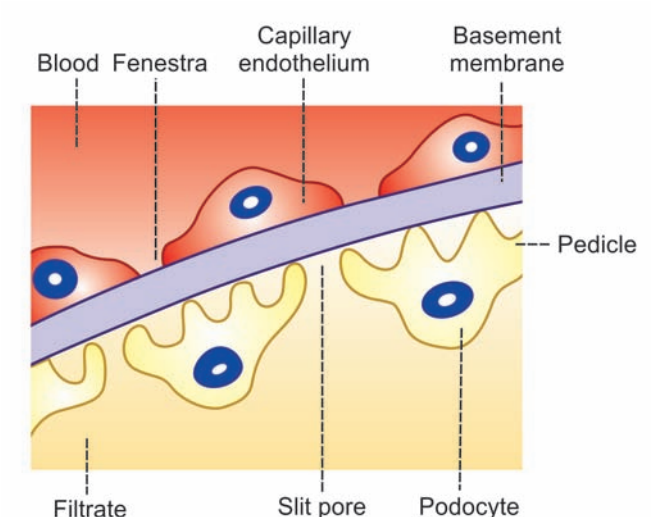


FIGURE 49.4: Filtering membrane in renal corpuscle. It is formed by capillary endothelium on one side (red) and visceral layer of Bowman capsule (yellow) on the other side.

■ TUBULAR PORTION OF NEPHRON

Tubular portion of nephron is the continuation of Bowman capsule.

It is made up of three parts:

1. Proximal convoluted tubule
2. Loop of Henle
3. Distal convoluted tubule.

■ PROXIMAL CONVOLUTED TUBULE

Proximal convoluted tubule is the coiled portion arising from Bowman capsule. It is situated in the cortex. It is continued as descending limb of loop of Henle. Length of proximal convoluted tubule is 14 mm and the diameter is 55 µ. Proximal convoluted tubule is continued as loop of Henle.

Functional histology

Proximal convoluted tubule is formed by single layer of cuboidal epithelial cells. Characteristic feature of these cells is the presence of hair-like projections directed towards the lumen of the tubule. Because of the presence of these projections, the epithelial cells are called **brush-bordered cells.**

■ LOOP OF HENLE

Loop of Henle consists of:

i. Descending limb
ii. Hairpin bend
iii. Ascending limb.

i. *Descending Limb*

Descending limb of loop of Henle is made up of two segments:

a. Thick descending segment
b. Thin descending segment.

Thick descending segment

Thick descending segment is the direct continuation of the proximal convoluted tubule. It descends down into medulla. It has a length of 6 mm and a diameter of 55 µ. It is formed by brush-bordered cuboidal epithelial cells.

Thin descending segment

Thick descending segment is continued as thin descending segment (Fig. 49.5). It is formed by flattened epithelial cells without brush border and it is continued as hairpin bend of the loop.

ii. *Hairpin Bend*

Hairpin bend formed by flattened epithelial cells without brush border and it is continued as the ascending limb of loop of Henle.

iii. *Ascending Limb*

Ascending limb or segment of Henle loop has two parts:

a. Thin ascending segment
b. Thick ascending segment.

Thin ascending segment

Thin ascending segment is the continuation of hairpin bend. It is also lined by flattened epithelial cells without brush border.

Total length of thin descending segment, hairpin bend and thin ascending segment of Henle loop is 10 mm to 15 mm and the diameter is 15 µ.

Thin ascending segment is continued as thick ascending segment.

Thick ascending segment

Thick ascending segment is about 9 mm long with a diameter of 30 µ. Thick ascending segment is lined by cuboidal epithelial cells without brush border.

The terminal portion of thick ascending segment, which runs between the afferent and efferent arterioles of the same nephrons forms the **macula densa.** Macula densa is the part of juxtaglomerular apparatus (Chapter 50).

Thick ascending segment ascends to the cortex and continues as distal convoluted tubule.

Length and Extent of Loop of Henle

Length and the extent of the loop of Henle vary in different nephrons:

i. In cortical nephrons, it is short and the hairpin bend penetrates only up to outer medulla

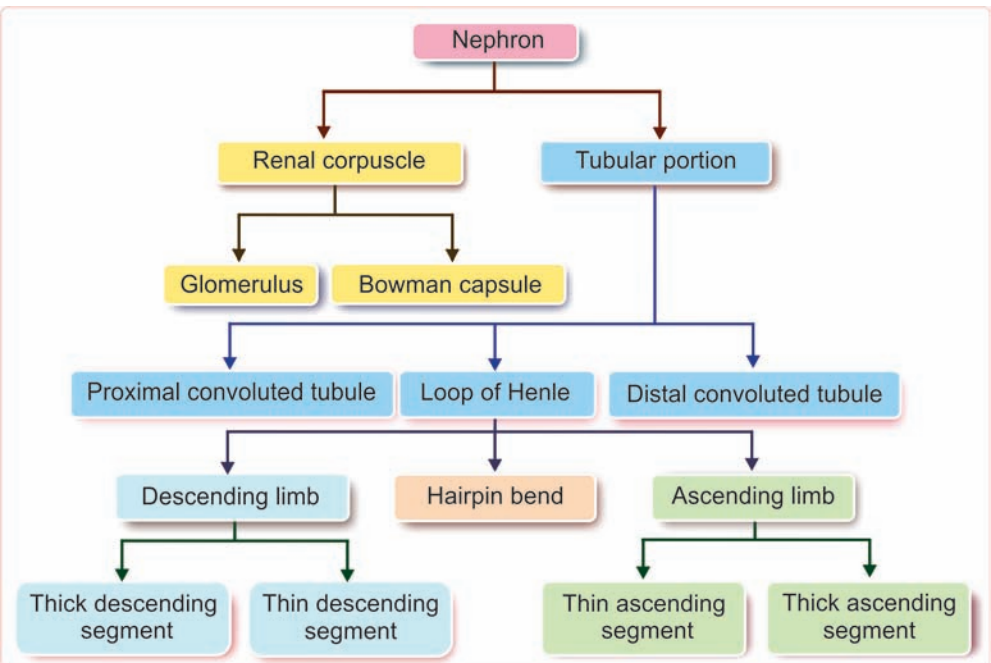


FIGURE 49.5: Parts of nephron

TABLE 49.2: Size and cells of different parts of nephron and collecting duct

Segment	Epithelium	Length (mm)	Diameter (μ)
Bowman Capsule	Flattened epithelium	-	200
Proximal convoluted tubule	Cuboidal cells with brush border	14	55
Thick descending segment	Cuboidal cells with brush border	6	55
Thin descending segment, hairpin bend and thin ascending segment	Flattened epithelium	10 to 15	15
Thick ascending segment	Cuboidal epithelium without brush border	9	30
Distal convoluted tubule	Cuboidal epithelium without brush border	14.5 to 15	22 to 50
Collecting duct	Cuboidal epithelium without brush border	20 to 22	40 to 200

ii. In juxtamedullary nephrons, this is long and the hairpin bend extends deep into the inner medulla. In some nephrons it even runs up to the papilla.

■ DISTAL CONVOLUTED TUBULE

Distal convoluted tubule is the continuation of thick ascending segment and occupies the cortex of kidney. It is continued as collecting duct. The length of the distal convoluted tubule is 14.5 to 15 mm. It has a diameter of 22 to 50 μ (Table 49.2).

Functional histology

Distal convoluted tubule is lined by single layer of cuboidal epithelial cells without brush border. Epithelial cells in distal convoluted tubule are called intercalated cells (I cells).

■ COLLECTING DUCT

Distal convoluted tubule continues as the initial or arched collecting duct, which is in cortex. The lower part of the collecting duct lies in medulla. Seven to ten initial collecting ducts unite to form the straight collecting duct, which passes through medulla.

Length of the collecting duct is 20 to 22 mm and its diameter varies between 40 and 200 μ. Collecting duct is formed by cuboidal or columnar epithelial cells.

Functional histology

Collecting duct is formed by two types of epithelial cells:

1. Principal or **P cells**
2. Intercalated or **I cells.**

These two types of cells have some functional significance (Chapters 53 and 54).

■ PASSAGE OF URINE

At the inner zone of medulla, the straight collecting ducts from each medullary pyramid unite to form **papillary ducts** or **ducts of Bellini,** which open into a 'V' shaped area called **papilla.** Urine from each medullary pyramid is collected in the papilla. From here it is drained into a **minor calyx.** Three or four minor calyces unite to form one **major calyx.** Each kidney has got about 8 minor calyces and 2 to 3 major calyces.

From minor calyces urine passes through major calyces, which open into the **pelvis** of the **ureter.** Pelvis is the expanded portion of ureter present in the renal sinus.

From renal pelvis, urine passes through remaining portion of ureter and reaches urinary bladder.

Chapter 50

Juxtaglomerular Apparatus

DEFINITION

Juxtaglomerular apparatus is a specialized organ situated near the glomerulus of each nephron (juxta = near).

STRUCTURE OF JUXTAGLOMERULAR APPARATUS

Juxtaglomerular apparatus is formed by three different structures (Fig. 50.1):

1. Macula densa
2. Extraglomerular mesangial cells
3. Juxtaglomerular cells.

MACULA DENSA

Macula densa is the end portion of thick ascending segment before it opens into distal convoluted tubule. It is situated between afferent and efferent arterioles of the same nephron. It is very close to afferent arteriole.

Macula densa is formed by tightly packed cuboidal epithelial cells.

EXTRAGLOMERULAR MESANGIAL CELLS

Extraglomerular mesangial cells are situated in the triangular region bound by afferent arteriole, efferent arteriole and macula densa. These cells are also called **agranular cells, lacis cells** or **Goormaghtigh cells.**

Glomerular Mesangial Cells

Besides extraglomerular mesangial cells there is another type of mesangial cells situated in between glomerular capillaries called **glomerular mesangial** or **intraglomerular mesangial cells.**

Glomerular mesangial cells support the glomerular capillary loops by surrounding the capillaries in the form of a cellular network.

These cells play an important role in regulating the glomerular filtration by their contractile property.

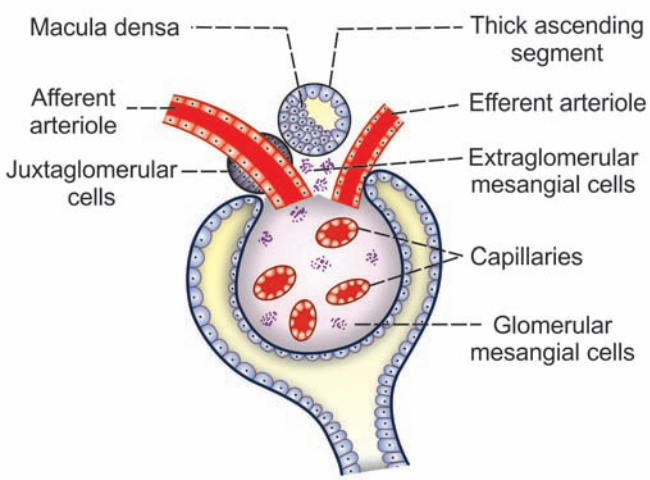


FIGURE 50.1: Juxtaglomerular apparatus

Glomerular mesangial cells are phagocytic in nature. These cells also secrete glomerular **interstitial matrix,** prostaglandins and cytokines.

■ JUXTAGLOMERULAR CELLS

Juxtaglomerular cells are specialized smooth muscle cells situated in the wall of afferent arteriole just before it enters the Bowman capsule. These smooth muscle cells are mostly present in tunica media and tunica adventitia of the wall of the afferent arteriole.

Juxtaglomerular cells are also called **granular cells** because of the presence of secretary granules in their cytoplasm.

Polar Cushion or Polkissen

Juxtaglomerular cells form a thick cuff called **polar cushion** or **polkissen** around the afferent arteriole before it enters the Bowman capsule.

■ FUNCTIONS OF JUXTAGLOMERULAR APPARATUS

Primary function of juxtaglomerular apparatus is the secretion of hormones. It also regulates the glomerular blood flow and glomerular filtration rate.

■ SECRETION OF HORMONES

Juxtaglomerular apparatus secretes two hormones:

1. Renin
2. Prostaglandin.

1. *Renin*

Juxtaglomerular cells secrete renin. Renin is a peptide with 340 amino acids. Along with angiotensins, renin forms the renin-angiotensin system, which is a hormone system that plays an important role in the maintenance of blood pressure (Chapter 103).

Stimulants for renin secretion

Secretion of renin is stimulated by four factors:

i. Fall in arterial blood pressure
ii. Reduction in the ECF volume
iii. Increased sympathetic activity
iv. Decreased load of sodium and chloride in macula densa.

Renin-angiotensin system

When renin is released into the blood, it acts on a specific plasma protein called **angiotensinogen** or **renin substrate.** It is the α_2-globulin. By the activity of renin, the angiotensinogen is converted into a **decapeptide** called angiotensin I. Angiotensin I is converted into angiotensin II, which is an **octapeptide** by the activity of **angiotensin-converting enzyme** (ACE) secreted from lungs. Most of the conversion of angiotensin I into angiotensin II takes place in lungs.

Angiotensin II has a short half-life of about 1 to 2 minutes. Then it is rapidly degraded into a **heptapeptide** called angiotensin III by **angiotensinases,** which are present in RBCs and vascular beds in many tissues. Angiotensin III is converted into angiotensin IV, which is a **hexapeptide** (Fig. 50.2).

Actions of Angiotensins

Angiotensin I

Angiotensin I is physiologically inactive and serves only as the precursor of angiotensin II.

Angiotensin II

Angiotensin II is the most active form. Its actions are:

On blood vessels:

i. Angiotensin II increases arterial blood pressure by directly acting on the blood vessels and causing vasoconstriction. It is a potent constrictor of arterioles. Earlier, when its other actions were not found it was called **hypertensin.**
ii. It increases blood pressure indirectly by increasing the release of noradrenaline from postganglionic sympathetic fibers. Noradrenaline is a general vasoconstrictor (Chapter 71).

On adrenal cortex:

It stimulates zona glomerulosa of adrenal cortex to secrete aldosterone. Aldosterone acts on renal tubules and increases retention of sodium, which is also responsible for elevation of blood pressure.

On kidney:

i. Angiotensin II regulates glomerular filtration rate by two ways:
   a. It constricts the efferent arteriole, which causes decrease in filtration after an initial increase (Chapter 52)
   b. It contracts the glomerular mesangial cells leading to decrease in surface area of glomerular capillaries and filtration (see above)
ii. It increases sodium reabsorption from renal tubules. This action is more predominant on proximal tubules.

On brain:

i. Angiotensin II inhibits the **baroreceptor reflex** and thereby indirectly increases the blood pressure. Baroreceptor reflex is responsible for decreasing the blood pressure (Chapter 103)

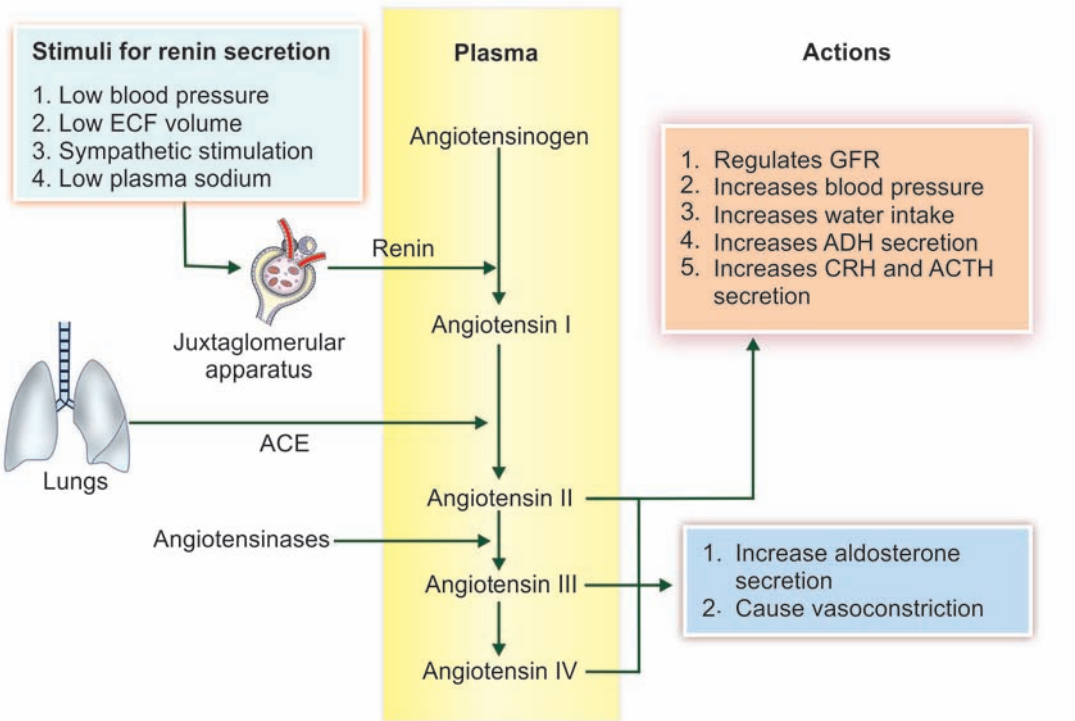


FIGURE 50.2: Renin-angiotensin system. ECF = Extracellular fluid, ACE = Angiotensin-converting enzyme, GFR = Glomerular filtration rate, ADH = Antidiuretic hormone, CRH = Corticotropin-releasing hormone, ACTH = Adrenocorticotropic hormone.

ii. It increases water intake by stimulating the thirst center
iii. It increases the secretion of orticotropin-releasing hormone (CRH) from hypothalamus. CRH in turn increases secretion of adrenocorticotropic hormone (ACTH) from pituitary
iv. It increases secretion of antidiuretic hormone (ADH) from hypothalamus.

Other actions:

Angiotensin II acts as a growth factor in heart and it is thought to cause muscular hypertrophy and cardiac enlargement.

Angiotensin III

Angiotensin III increases the blood pressure and stimulates aldosterone secretion from adrenal cortex. It has 100% adrenocortical stimulating activity and 40% vasopressor activity of angiotensin II.

Angiotensin IV

It also has adrenocortical stimulating and vasopressor activities.

2. Prostaglandin

Extraglomerular mesangial cells of juxtaglomerular apparatus secrete prostaglandin. Prostaglandin is also secreted by interstitial cells of medulla called type I medullary interstitial cells. Refer Chapter 72 for details.

■ SECRETION OF OTHER SUBSTANCES

1. Extraglomerular mesangial cells of juxtaglomerular apparatus secrete cytokines like interleukin-2 and tumor necrosis factor (Chapter 17)
2. Macula densa secretes thromboxane A_2.

■ REGULATION OF GLOMERULAR BLOOD FLOW AND GLOMERULAR FILTRATION RATE

Macula densa of juxtaglomerular apparatus plays an important role in the feedback mechanism called **tubuloglomerular feedback** mechanism, which regulates the renal blood flow and glomerular filtration rate (Refer Chapter 52 for details).

Chapter 51

Renal Circulation

INTRODUCTION

Blood vessels of kidneys are highly specialized to facilitate the functions of nephrons in the formation of urine. In the adults, during resting conditions both the kidneys receive 1,300 mL of blood per minute or about 26% of the cardiac output.

Maximum blood supply to kidneys has got the functional significance. Renal arteries supply blood to the kidneys.

RENAL BLOOD VESSELS

Renal Artery

Renal artery arises directly from abdominal aorta and enters the kidney through the hilus. While passing through renal sinus, the renal artery divides into many segmental arteries.

Segmental Artery

Segmental artery subdivides into interlobar arteries (Fig. 51.1).

Interlobar Artery

Interlobar artery passes in between the medullary pyramids. At the base of the pyramid, it turns and runs parallel to the base of pyramid forming arcuate artery.

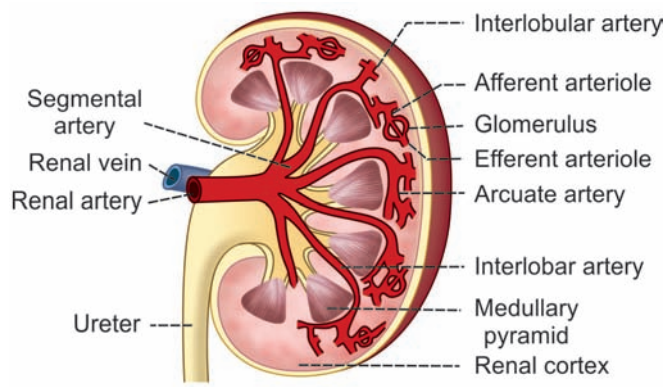


FIGURE 51.1: Renal blood vessels

Arcuate Artery

Each arcuate artery gives rise to interlobular arteries.

Interlobular Artery

Interlobular arteries run through the renal cortex perpendicular to arcuate artery. From each interlobular artery, numerous afferent arterioles arise.

Afferent Arteriole

Afferent arteriole enters the Bowman capsule and forms glomerular capillary tuft. After entering the Bowman capsule, the afferent arteriole divides into 4 or 5 large capillaries.

Glomerular Capillaries

Each large capillary divides into small glomerular capillaries, which form the loops. And, the **capillary loops** unite to form the efferent arteriole, which leaves the Bowman capsule.

Efferent Arteriole

Efferent arterioles form a second capillary network called peritubular capillaries, which surround the tubular portions of the nephrons. Thus, the renal circulation forms a portal system by the presence of two sets of capillaries namely glomerular capillaries and peritubular capillaries.

Peritubular Capillaries and Vasa Recta

Peritubular capillaries are found around the tubular portion of cortical nephrons only. The tubular portion of juxtamedullary nephrons is supplied by some specialized capillaries called vasa recta. These capillaries are straight blood vessels hence the name vasa recta. Vasa recta arise directly from the efferent arteriole of the juxtamedullary nephrons and run parallel to the renal tubule into the medulla and ascend up towards the cortex (Fig. 51.2).

Venous System

Peritubular capillaries and vasa recta drain into the venous system. Venous system starts with peritubular venules and continues as interlobular veins, arcuate veins, interlobar veins, segmental veins and finally the renal vein (Fig. 51.3).

Renal vein leaves the kidney through the hilus and joins inferior vena cava.

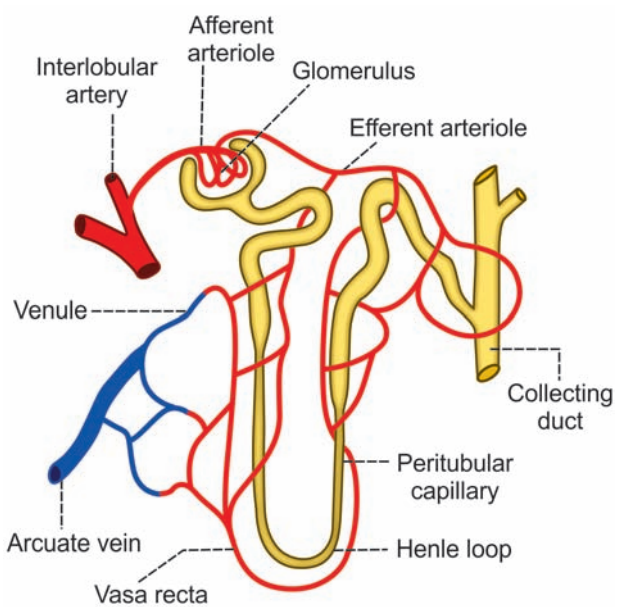


FIGURE 51.2: Renal capillaries

■ MEASUREMENT OF RENAL BLOOD FLOW

Blood flow to kidneys is measured by using plasma clearance of para-aminohippuric acid (Refer Chapter 55).

■ REGULATION OF RENAL BLOOD FLOW

Renal blood flow is regulated mainly by autoregulation. The nerves innervating renal blood vessels do not have any significant role in this.

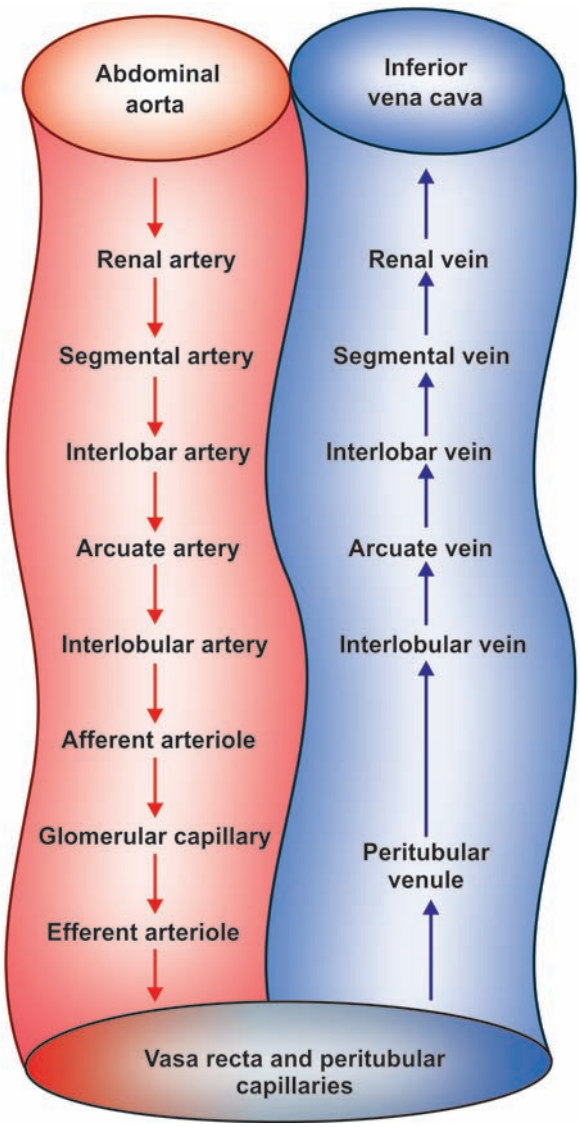


FIGURE 51.3: Schematic diagram showing renal blood flow

AUTOREGULATION

Autoregulation is the intrinsic ability of an organ to regulate its own blood flow (Chapter 102). Autoregulation is present in some vital organs in the body such as brain, heart and kidneys. It is highly significant and more efficient in kidneys.

Renal Autoregulation

Renal autoregulation is important to maintain the glomerular filtration rate (GFR). Blood flow to kidneys remains normal even when the mean arterial blood pressure vary widely between 60 mm Hg and 180 mm Hg. This helps to maintain normal GFR.

Two mechanisms are involved in renal autoregulation:

1. Myogenic response
2. Tubuloglomerular feedback.

1. *Myogenic Response*

Whenever the blood flow to kidneys increases, it stretches the elastic wall of the afferent arteriole.

Stretching of the vessel wall increases the flow of calcium ions from extracellular fluid into the cells. The influx of calcium ions leads to the contraction of smooth muscles in afferent arteriole, which causes constriction of afferent arteriole. So, the blood flow is decreased.

2. *Tubuloglomerular Feedback*

Macula densa plays an important role in tubuloglomerular feedback, which controls the renal blood flow and GFR. Refer Chapter 52 for details.

SPECIAL FEATURES OF RENAL CIRCULATION

Renal circulation has some special features to cope up with the functions of the kidneys. Such special features are:

1. Renal arteries arise directly from the aorta. So, the high pressure in aorta facilitates the high blood flow to the kidneys.
2. Both the kidneys receive about 1,300 mL of blood per minute, i.e. about 26% of cardiac output. Kidneys are the second organs to receive maximum blood flow, the first organ being the liver, which receives 1,500 mL per minute, i.e. about 30% of cardiac output.
3. Whole amount of blood, which flows to kidney has to pass through the glomerular capillaries before entering the venous system. Because of this, the blood is completely filtered at the renal glomeruli.
4. Renal circulation has a **portal system,** i.e. a double network of capillaries, the glomerular capillaries and peritubular capillaries.
5. Renal glomerular capillaries form **high pressure bed** with a pressure of 60 mm Hg to 70 mm Hg. It is much greater than the capillary pressure elsewhere in the body, which is only about 25 mm Hg to 30 mm Hg. High pressure is maintained in the glomerular capillaries because the diameter of afferent arteriole is more than that of efferent arteriole. The high capillary pressure augments glomerular filtration.
6. Peritubular capillaries form a **low pressure bed** with a pressure of 8 mm Hg to 10 mm Hg. This low pressure helps tubular reabsorption.
7. Autoregulation of renal blood flow is well established.

Chapter 52

Urine Formation

INTRODUCTION

Urine formation is a blood cleansing function. Normally, about 1,300 mL of blood (26% of cardiac output) enters the kidneys. Kidneys excrete the unwanted substances along with water from the blood as urine. Normal **urinary output** is 1 L/day to 1.5 L/day.

Processes of Urine Formation

When blood passes through glomerular capillaries, the plasma is filtered into the Bowman capsule. This process is called glomerular filtration.

Filtrate from Bowman capsule passes through the tubular portion of the nephron. While passing through the tubule, the filtrate undergoes various changes both in quality and in quantity. Many wanted substances like glucose, amino acids, water and electrolytes are reabsorbed from the tubules. This process is called tubular reabsorption.

And, some unwanted substances are secreted into the tubule from peritubular blood vessels. This process is called tubular secretion or excretion (Fig. 52.1).

Thus, the urine formation includes three processes:

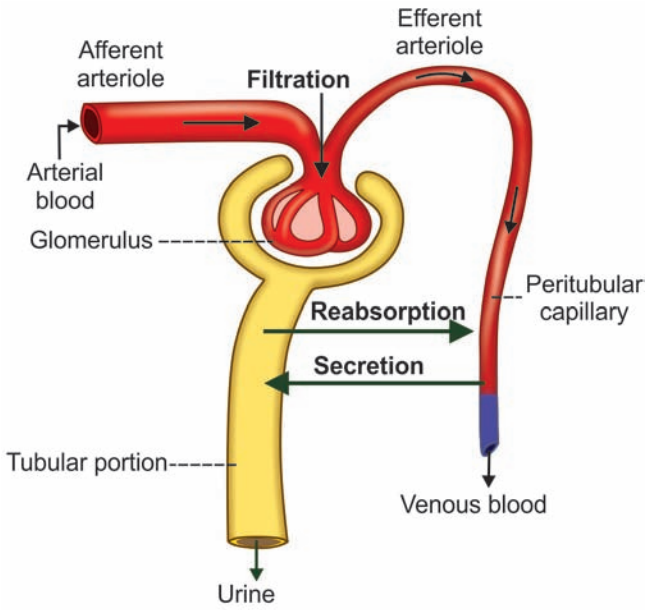


FIGURE 52.1: Events of urine formation

A. Glomerular filtration
B. Tubular reabsorption
C. Tubular secretion.

Among these three processes filtration is the function of the glomerulus. Reabsorption and secretion are the functions of tubular portion of the nephron.

GLOMERULAR FILTRATION

INTRODUCTION

Glomerular filtration is the process by which the blood is filtered while passing through the glomerular capillaries by filtration membrane. It is the first process of urine formation. The structure of filtration membrane is well suited for filtration.

Filtration Membrane

Filtration membrane is formed by three layers:

1. Glomerular capillary membrane
2. Basement membrane
3. Visceral layer of Bowman capsule.

1. *Glomerular capillary membrane*

Glomerular capillary membrane is formed by single layer of endothelial cells, which are attached to the basement membrane. The capillary membrane has many pores called **fenestrae** or **filtration pores** with a diameter of 0.1 µ.

2. *Basement membrane*

Basement membrane of glomerular capillaries and the basement membrane of visceral layer of Bowman capsule fuse together. The fused basement membrane separates the endothelium of glomerular capillary and the epithelium of visceral layer of Bowman capsule.

3. *Visceral layer of Bowman capsule*

This layer is formed by a single layer of flattened epithelial cells resting on a basement membrane. Each cell is connected with the basement membrane by cytoplasmic extensions called **pedicles** or **feet.** Epithelial cells with pedicles are called **podocytes** (Refer to Fig. 49.4). Pedicles interdigitate leaving small cleft-like spaces in between. The cleft-like space is called **slit pore** or **filtration slit.** Filtration takes place through these slit pores.

Process of Glomerular Filtration

When blood passes through glomerular capillaries, the plasma is filtered into the Bowman capsule. All the substances of plasma are filtered except the plasma proteins. The filtered fluid is called **glomerular filtrate.**

Ultrafiltration

Glomerular filtration is called ultrafiltration because even the minute particles are filtered. But, the plasma proteins are not filtered due to their large molecular size. The protein molecules are larger than the slit pores present in the endothelium of capillaries. Thus, the glomerular filtrate contains all the substances present in plasma except the plasma proteins.

METHOD OF COLLECTION OF GLOMERULAR FILTRATE

Glomerular filtrate is collected in experimental animals by micropuncture technique. This technique involves insertion of a **micropipette** into the Bowman capsule and aspiration of filtrate.

GLOMERULAR FILTRATION RATE

Glomerular filtration rate (GFR) is defined as the total quantity of filtrate formed in all the nephrons of both the kidneys in the given unit of time.

Normal GFR is 125 mL/minute or about 180 L/day.

FILTRATION FRACTION

Filtration fraction is the fraction (portion) of the renal plasma, which becomes the filtrate. It is the ratio

between renal plasma flow and glomerular filtration rate. It is expressed in percentage.

$$\text{Filtration fraction} = \frac{\text{GFR}}{\text{Renal plasma flow}} \times 100$$

$$= \frac{125 \text{ mL/min}}{650 \text{ mL/min}} \times 100$$

$$= 19.2\%.$$

Normal filtration fraction varies from 15% to 20%.

■ PRESSURES DETERMINING FILTRATION

Pressures, which determine the GFR are:

1. Glomerular capillary pressure
2. Colloidal osmotic pressure in the glomeruli
3. Hydrostatic pressure in the Bowman capsule.

These pressures determine the GFR by either favoring or opposing the filtration.

1. *Glomerular Capillary Pressure*

Glomerular capillary pressure is the pressure exerted by the blood in glomerular capillaries. It is about 60 mm Hg and, varies between 45 and 70 mm Hg. Glomerular capillary pressure is the highest capillary pressure in the body. This pressure favors glomerular filtration.

2. *Colloidal Osmotic Pressure*

It is the pressure exerted by plasma proteins in the glomeruli. The plasma proteins are not filtered through the glomerular capillaries and remain in the glomerular capillaries. These proteins develop the colloidal osmotic pressure, which is about 25 mm Hg. It opposes glomerular filtration.

3. *Hydrostatic Pressure in Bowman Capsule*

It is the pressure exerted by the filtrate in Bowman capsule. It is also called **capsular pressure.** It is about 15 mm Hg. It also opposes glomerular filtration.

Net Filtration Pressure

Net filtration pressure is the balance between pressure favoring filtration and pressures opposing filtration. It is otherwise known as **effective filtration pressure** or **essential filtration pressure.**

$$\text{Net filtration pressure} = \left\{ \begin{array}{c} \text{Glomerular} \\ \text{capillary} \\ \text{pressure} \end{array} - \begin{array}{c} \text{Colloidal} \\ \text{osmotic} \\ \text{pressure} \end{array} + \begin{array}{c} \text{Hydrostatic} \\ \text{pressure in} \\ \text{Bowman capsule} \end{array} \right\}$$

$$= 60 - (25 + 15) = 20 \text{ mm Hg.}$$

Net filtration pressure is about 20 mm Hg and, it varies between 15 and 20 mm Hg.

Starling Hypothesis and Starling Forces

Determination of net filtration pressure is based on Starling hypothesis. Starling hypothesis states that the net filtration through capillary membrane is proportional to hydrostatic pressure difference across the membrane minus oncotic pressure difference. Hydrostatic pressure within the glomerular capillaries is the glomerular capillary pressure.

All the pressures involved in determination of filtration are called **Starling forces.**

■ FILTRATION COEFFICIENT

Filtration coefficient is the GFR in terms of net filtration pressure. It is the GFR per mm Hg of net filtration pressure. For example, when GFR is 125 mL/min and net filtration pressure is 20 mm Hg.

$$\text{Filtration coefficient} = \frac{125 \text{ mL}}{20 \text{ mm Hg}}$$

$$= 6.25 \text{ mL/mm Hg}$$

■ FACTORS REGULATING (AFFECTING) GFR

1. *Renal Blood Flow*

It is the most important factor that is necessary for glomerular filtration. GFR is directly proportional to renal blood flow. Normal blood flow to both the kidneys is 1,300 mL/minute. The renal blood flow itself is controlled by **autoregulation.** Refer previous chapter for details.

2. *Tubuloglomerular Feedback*

Tubuloglomerular feedback is the mechanism that regulates GFR through renal tubule and macula densa (Fig. 52.2). **Macula densa** of juxtaglomerular apparatus in the terminal portion of thick ascending limb is sensitive to the sodium chloride in the tubular fluid.

When the glomerular filtrate passes through the terminal portion of thick ascending segment, macula densa acts like a sensor. It detects the concentration of sodium chloride in the tubular fluid and accordingly alters the glomerular blood flow and GFR. Macula densa detects the sodium chloride concentration via Na^+-K^+-$2Cl^-$ cotransporter (NKCC2).

When the concentration of sodium chloride increases in the filtrate

When GFR increases, concentration of sodium chloride increases in the filtrate. Macula densa releases **adenosine**

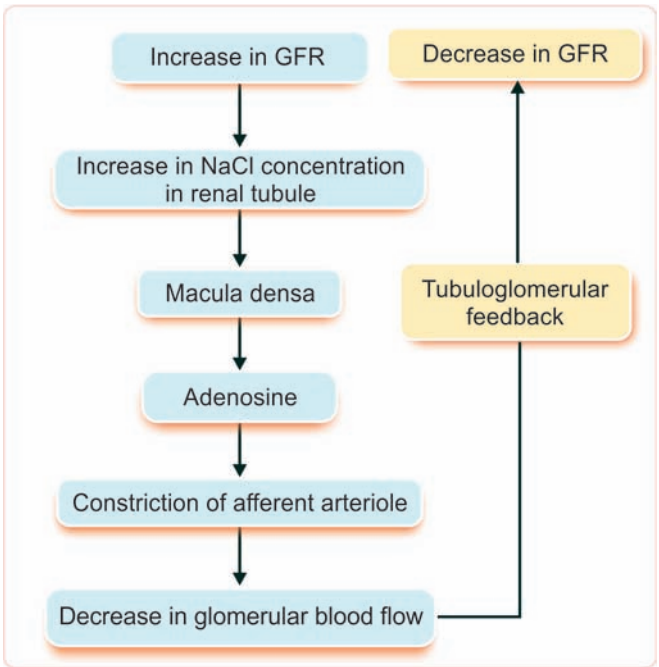


FIGURE 52.2: Tubuloglomerular feedback.
NaCl = Sodium chloride, GFR = Glomerular filtration rate.

from ATP. Adenosine causes constriction of afferent arteriole. So the blood flow through glomerulus decreases leading to decrease in GFR. Adenosine acts on afferent arteriole via adenosine A_1 receptors.

There are several other factors, which increase or decrease the sensitivity of tubuloglomerular feedback.

Factors increasing the sensitivity of tubuloglomerular feedback:

i. Adenosine
ii. Thromboxane
iii. Prostaglandin E_2
iv. Hydroxyeicosatetranoic acid.

Factors decreasing the sensitivity of tubuloglomerular feedback:

i. Atrial natriuretic peptide
ii. Prostaglandin I_2
iii. Cyclic AMP (cAMP)
iv. Nitrous oxide.

When the concentration of sodium chloride decreases in the filtrate

When GFR decreases, concentration of sodium chloride decreases in the filtrate. Macula densa secretes prostaglandin (PGE_2), bradykinin and renin.

PGE_2 and bradykinin cause dilatation of afferent arteriole. Renin induces the formation of angiotensin II, which causes constriction of efferent arteriole. The dilatation of afferent arteriole and constriction of efferent arteriole leads to increase in glomerular blood flow and GFR.

3. *Glomerular Capillary Pressure*

Glomerular filtration rate is directly proportional to glomerular capillary pressure. Normal glomerular capillary pressure is 60 mm Hg. When glomerular capillary pressure increases, the GFR also increases. Capillary pressure, in turn depends upon the renal blood flow and arterial blood pressure.

4. *Colloidal Osmotic Pressure*

Glomerular filtration rate is inversely proportional to colloidal osmotic pressure, which is exerted by plasma proteins in the glomerular capillary blood. Normal colloidal osmotic pressure is 25 mm Hg. When colloidal osmotic pressure increases as in the case of **dehydration** or increased plasma protein level GFR decreases. When colloidal osmotic pressure is low as in **hypoproteinemia,** GFR increases.

5. *Hydrostatic Pressure in Bowman Capsule*

GFR is inversely proportional to this. Normally, it is 15 mm Hg. When the hydrostatic pressure increases in the Bowman capsule, it decreases GFR. Hydrostatic pressure in Bowman capsule increases in conditions like obstruction of urethra and edema of kidney beneath renal capsule.

6. *Constriction of Afferent Arteriole*

Constriction of afferent arteriole reduces the blood flow to the glomerular capillaries, which in turn reduces GFR.

7. *Constriction of Efferent Arteriole*

If efferent arteriole is constricted, initially the GFR increases because of stagnation of blood in the capillaries. Later when all the substances are filtered from this blood, further filtration does not occur. It is because, the efferent arteriolar constriction prevents outflow of blood from glomerulus and no fresh blood enters the glomerulus for filtration.

8. *Systemic Arterial Pressure*

Renal blood flow and GFR are not affected as long as the mean arterial blood pressure is in between 60 and 180 mm Hg due to the autoregulatory mechanism (Chapter 51). Variation in pressure above 180 mm Hg or below 60 mm Hg affects the renal blood flow and GFR

accordingly, because the autoregulatory mechanism fails beyond this range.

9. *Sympathetic Stimulation*

Afferent and efferent arterioles are supplied by sympathetic nerves. The mild or moderate stimulation of sympathetic nerves does not cause any significant change either in renal blood flow or GFR.

Strong sympathetic stimulation causes severe constriction of the blood vessels by releasing the neurotransmitter substance, noradrenaline. The effect is more severe on the efferent arterioles than on the afferent arterioles. So, initially there is increase in filtration but later it decreases. However, if the stimulation is continued for more than 30 minutes, there is recovery of both renal blood flow and GFR. It is because of reduction in sympathetic neurotransmitter.

10. *Surface Area of Capillary Membrane*

GFR is directly proportional to the surface area of the capillary membrane.

If the glomerular capillary membrane is affected as in the cases of some renal diseases, the surface area for filtration decreases. So there is reduction in GFR.

11. *Permeability of Capillary Membrane*

GFR is directly proportional to the permeability of glomerular capillary membrane. In many abnormal conditions like hypoxia, lack of blood supply, presence of toxic agents, etc. the permeability of the capillary membrane increases. In such conditions, even plasma proteins are filtered and excreted in urine.

12. *Contraction of Glomerular Mesangial Cells*

Glomerular mesangial cells are situated in between the glomerular capillaries. Contraction of these cells decreases surface area of capillaries resulting in reduction in GFR (refer Chapter 51 for details).

13. *Hormonal and Other Factors*

Many hormones and other secretory factors alter GFR by affecting the blood flow through glomerulus.

Factors increasing GFR by vasodilatation

i. Atrial natriuretic peptide
ii. Brain natriuretic peptide
iii. cAMP
iv. Dopamine
v. Endothelial-derived nitric oxide
vi. Prostaglandin (PGE_2).

Factors decreasing GFR by vasoconstriction

i. Angiotensin II
ii. Endothelins
iii. Noradrenaline
iv. Platelet-activating factor
v. Platelet-derived growth factor
vi. Prostaglandin (PGF_2).

TUBULAR REABSORPTION

INTRODUCTION

Tubular reabsorption is the process by which water and other substances are transported from renal tubules back to the blood. When the glomerular filtrate flows through the tubular portion of nephron, both quantitative and qualitative changes occur. Large quantity of water (more than 99%), electrolytes and other substances are reabsorbed by the tubular epithelial cells. The reabsorbed substances move into the interstitial fluid of renal medulla. And, from here, the substances move into the blood in peritubular capillaries.

Since the substances are taken back into the blood from the glomerular filtrate, the entire process is called tubular reabsorption.

METHOD OF COLLECTION OF TUBULAR FLUID

There are two methods to collect the tubular fluid for analysis.

1. *Micropuncture Technique*

A micropipette is inserted into the Bowman capsule and different parts of tubular portion in the nephrons of experimental animals, to collect the fluid. The fluid samples are analyzed and compared with each other to assess the changes in different parts of nephron.

2. *Stop-flow Method*

Ureter is obstructed so that the back pressure rises and stops the glomerular filtration. The obstruction is continued for 8 minutes. It causes some changes in the fluid present in different parts of the tubular portion.

Later, the obstruction is released and about 30 samples of 0.5 mL of urine are collected separately at regular intervals of 30 seconds. The first sample contains the fluid from collecting duct. Successive samples contain the fluid from distal convoluted tubule, loops of Henle and proximal convoluted tubule respectively. All the samples are analyzed.

■ SELECTIVE REABSORPTION

Tubular reabsorption is known as selective reabsorption because the tubular cells reabsorb only the substances necessary for the body. Essential substances such as glucose, amino acids and vitamins are completely reabsorbed from renal tubule. Whereas the unwanted substances like metabolic waste products are not reabsorbed and excreted through urine.

■ MECHANISM OF REABSORPTION

Basic transport mechanisms involved in tubular reabsorption are of two types:

1. Active reabsorption
2. Passive reabsorption.

1. *Active Reabsorption*

Active reabsorption is the movement of molecules against the **electrochemical (uphill) gradient.** It needs liberation of energy, which is derived from ATP.

Substances reabsorbed actively

Substances reabsorbed actively from the renal tubule are sodium, calcium, potassium, phosphates, sulfates, bicarbonates, glucose, amino acids, ascorbic acid, uric acid and ketone bodies.

2. *Passive Reabsorption*

Passive reabsorption is the movement of molecules along the **electrochemical (downhill) gradient.** This process does not need energy.

Substances reabsorbed passively

Substances reabsorbed passively are chloride, urea and water.

■ ROUTES OF REABSORPTION

Reabsorption of substances from tubular lumen into the peritubular capillary occurs by two routes:

1. Trancelluar route
2. Paracellular route.

1. *Transcellular Route*

In this route the substances move through the cell.

It includes transport of substances from:

a. Tubular lumen into tubular cell through apical (luminal) surface of the cell membrane
b. Tubular cell into interstitial fluid
c. Interstitial fluid into capillary.

2. *Paracelluar Route*

In this route, the substances move through the intercellular space.

It includes transport of substances from:

i. Tubular lumen into interstitial fluid present in lateral intercellular space through the tight junction between the cells
ii. Interstitial fluid into capillary (Fig. 52.3).

■ SITE OF REABSORPTION

Reabsorption of the substances occurs in almost all the segments of tubular portion of nephron.

1. *Substances Reabsorbed from Proximal Convoluted Tubule*

About 7/8 of the filtrate (about 88%) is reabsorbed in proximal convoluted tubule. The brush border of epithelial cells in proximal convoluted tubule increases the surface area and facilitates the reabsorption.

Substances reabsorbed from proximal convoluted tubule are glucose, amino acids, sodium, potassium, calcium, bicarbonates, chlorides, phosphates, urea, uric acid and water.

2. *Substances Reabsorbed from Loop of Henle*

Substances reabsorbed from loop of Henle are sodium and chloride.

3. *Substances Reabsorbed from Distal Convoluted Tubule*

Sodium, calcium, bicarbonate and water are reabsorbed from distal convoluted tubule.

■ REGULATION OF TUBULAR REABSORPTION

Tubular reabsorption is regulated by three factors:

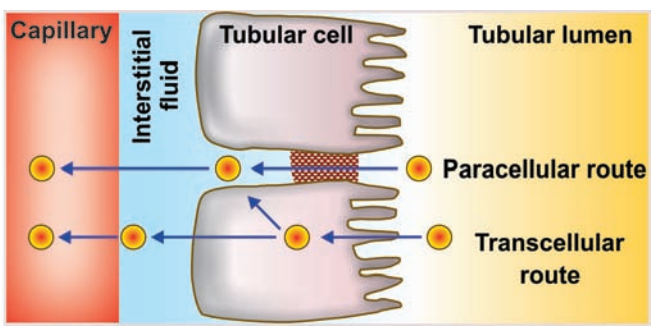


FIGURE 52.3: Routes of reabsorption

1. Glomerulotubular balance
2. Hormonal factors
3. Nervous factors.

1. *Glomerulotubular Balance*

Glomerulotubular balance is the balance between the filtration and reabsorption of solutes and water in kidney. When GFR increases, the tubular load of solutes and water in the proximal convoluted tubule is increased. It is followed by increase in the reabsorption of solutes and water. This process helps in the constant reabsorption of solute particularly sodium and water from renal tubule.

Mechanism of glomerulotubular balance

Glomerulotubular balance occurs because of osmotic pressure in the peritubular capillaries. When GFR increases, more amount of plasma proteins accumulate in the glomerulus. Consequently, the osmotic pressure increases in the blood by the time it reaches efferent arteriole and peritubular capillaries. The elevated osmotic pressure in the peritubular capillaries increases reabsorption of sodium and water from the tubule into the capillary blood.

2. *Hormonal Factors*

Hormones, which regulate GFR are listed in Table 52.1.

3. *Nervous Factor*

Activation of sympathetic nervous system increases the tubular reabsorption (particularly of sodium) from renal tubules. It also increases the tubular reabsorption indirectly by stimulating secretion of renin from juxtaglomerular cells. Renin causes formation of angiotensin II, which increases the sodium reabsorption (Chapter 50).

■ THRESHOLD SUBSTANCES

Depending upon the degree of reabsorption, various substances are classified into three categories:

1. High-threshold substances
2. Low-threshold substances
3. Non-threshold substances.

1. *High-threshold Substances*

High-threshold substances are those substances, which do not appear in urine under normal conditions. The food substances like glucose, amino acids, acetoacetate ions and vitamins are completely reabsorbed from renal tubules and do not appear in urine under normal conditions. These substances can appear in urine, only if their concentration in plasma is abnormally high or in renal diseases when reabsorption is affected. So, these substances are called high-threshold substances.

2. *Low-threshold Substances*

Low-threshold substances are the substances, which appear in urine even under normal conditions. The substances such as urea, uric acid and phosphate are reabsorbed to a little extend. So, these substances appear in urine even under normal conditions.

3. *Non-threshold Substances*

Non-threshold substances are those substances, which are not at all reabsorbed and are excreted in urine irrespective of their plasma level. The metabolic end products such as creatinine are the non-threshold substances.

■ TRANSPORT MAXIMUM – Tm VALUE

Tubular transport maximum or Tm is the rate at which the maximum amount of a substance is reabsorbed from the renal tubule.

So, for every actively reabsorbed substance, there is a maximum rate at which it could be reabsorbed. For example, the transport maximum for glucose (TmG) is 375 mg/minute in adult males and about 300 mg/minute in adult females.

TABLE 52.1: Hormones regulating tubular reabsorption

Hormone	Action
Aldosterone	Increases sodium reabsorption in ascending limb, distal convoluted tubule and collecting duct
Angiotensin II	Increases sodium reabsorption in proximal tubule, thick ascending limb, distal tubule and collecting duct (mainly in proximal convoluted tubule)
Antidiuretic hormone	Increases water reabsorption in distal convoluted tubule and collecting duct
Atrial natriuretic factor	Decreases sodium reabsorption
Brain natriuretic factor	Decreases sodium reabsorption
Parathormone	Increases reabsorption of calcium, magnesium and hydrogen Decreases phosphate reabsorption
Calcitonin	Decreases calcium reabsorption

Threshold Level in Plasma for Substances having Tm Value

Renal threshold is the plasma concentration at which a substance appears in urine. Every substance having Tm value has also a threshold level in plasma or blood. Below that threshold level, the substance is completely reabsorbed and does not appear in urine. When the concentration of that substance reaches the threshold, the excess amount is not reabsorbed and, so it appears in urine. This level is called the renal threshold of that substance.

For example, the renal threshold for glucose is 180 mg/dL. That is, glucose is completely reabsorbed from tubular fluid if its concentration in blood is below 180 mg/dL. So, the glucose does not appear in urine. When the blood level of glucose reaches 180 mg/dL it is not reabsorbed completely; hence it appears in urine.

■ REABSORPTION OF IMPORTANT SUBSTANCES

Reabsorption of Sodium

From the glomerular filtrate, 99% of sodium is reabsorbed. Two thirds of sodium is reabsorbed in proximal convoluted tubule and remaining one third in other segments (except descending limb) and collecting duct.

Sodium reabsorption occurs in three steps:

1. Transport from lumen of renal tubules into the tubular epithelial cells
2. Transport from tubular cells into the interstitial fluid
3. Transport from interstitial fluid to the blood.

1. *Transport from Lumen of Renal Tubules into the Tubular Epithelial Cells*

Active reabsorption of sodium ions from lumen into the tubular cells occurs by two ways:

i. In exchange for hydrogen ion by **antiport** (sodium counterport protein) – in proximal convoluted tubules

ii. Along with other substances like glucose and amino acids by **symport** (sodium co-transport protein) – in other segments and collecting duct.

It is believed that some amount of sodium diffuses along the electrochemical gradient from lumen into tubular cell across the luminar membrane. The electrochemical gradient is developed by sodium-potassium pump (see below).

2. *Transport from Tubular Cells into the Interstitial Fluid*

Sodium is pumped outside the cells by sodium-potassium pump. This pump moves three sodium ions from the cell into interstitium and two potassium ions from interstitium into the cell.

Tubular epithelial cells are connected with their neighboring cells by tight junctions at their apical luminal edges. But, beyond the tight junction, a small space is left between the adjoining cells along their lateral borders. This space is called **lateral intercellular space.** The interstitium extends into this space.

Most of the sodium ions are pumped into the lateral intercellular space by sodium-potassium pump. The rest of the sodium ions are pumped into the interstitium by the sodium-potassium pump situated at the basal part of the cell membrane.

(Transport of sodium out of the tubular cell by sodium-potassium pump, decreases the sodium concentration within the cell. This develops an electrochemical gradient between the lumen and tubular cell resulting in diffusion of sodium into the cell).

3. *Transport from Interstitial Fluid to the Blood*

From the interstitial fluid, sodium ions enter the peritubular capillaries by concentration gradient.

In the distal convoluted tubule, the sodium reabsorption is stimulated by the hormone aldosterone secreted by adrenal cortex.

Reabsorption of Water

Reabsorption of water occurs from proximal and distal convoluted tubules and in collecting duct.

Reabsorption of water from proximal convoluted tubule – obligatory water reabsorption

Obligatory reabsorption is the type of water reabsorption in proximal convoluted tubule, which is secondary (obligatory) to sodium reabsorption. When sodium is reabsorbed from the tubule, the osmotic pressure decreases. It causes osmosis of water from renal tubule.

Reabsorption of water from distal convoluted tubule and collecting duct – facultative water reabsorption

Facultative reabsorption is the type of water reabsorption in distal convoluted tubule and collecting duct that occurs by the activity of antidiuretic hormone (ADH). Normally, the distal convoluted tubule and the collecting duct are not permeable to water. But in the presence of ADH, these segments become permeable to water, so it is reabsorbed.

Mechanism of action of ADH – Aquaporins

Antidiuretic hormone increases water reabsorption in distal convoluted tubules and collecting ducts by

stimulating the water channels called aquaporins. ADH combines with vasopressin (V2) receptors in the tubular epithelial membrane and activates adenyl cyclase, to form cyclic AMP. This cyclic AMP activates the aquaporins, which increase the water reabsorption.

Aquaporins (AQP) are the membrane proteins, which function as water channels. Though about 10 aquaporins are identified in mammals only 5 are found in humans. Aquaporin-1, 2 and 3 are present in renal tubules. Aquaporin-4 is present in brain and aquaporin-5 is found in salivary glands. Aquaporin-2 forms the water channels in renal tubules.

Reabsorption of Glucose

Glucose is completely reabsorbed in the proximal convoluted tubule. It is transported by secondary active transport (sodium cotransport) mechanism. Glucose and sodium bind to a common carrier protein in the luminal membrane of tubular epithelium and enter the cell. The carrier protein is called **sodium-dependant glucose cotransporter 2** (SGLT2). From tubular cell glucose is transported into medullary interstitium by another carrier protein called **glucose transporter 2** (GLUT2).

Tubular maximum for glucose (TmG)

In adult male, TmG is 375 mg/minute and in adult females it about 300 mg/minute.

Renal threshold for glucose

Renal threshold for glucose is 180 mg/dL in venous blood. When the blood level reaches 180 mg/dL glucose is not reabsorbed completely and appears in urine.

Splay

Splay means deviation. With normal GFR of 125 mL/minute and TmG of 375 mg/minute in an adult male the predicted (expected) renal threshold for glucose should be 300 mg/dL. But actually it is only 180 mg/dL.

When the renal threshold curves are drawn by using these values, the actual curve deviates from the 'should be' or predicted or ideal curve (Fig. 52.4). This type of deviation is called splay. Splay is because of the fact that all the nephrons do not have the same filtering and reabsorbing capacities.

Reabsorption of Amino Acids

Amino acids are also reabsorbed completely in proximal convoluted tubule. Amino acids are reabsorbed actively by the secondary active transport mechanism along with sodium.

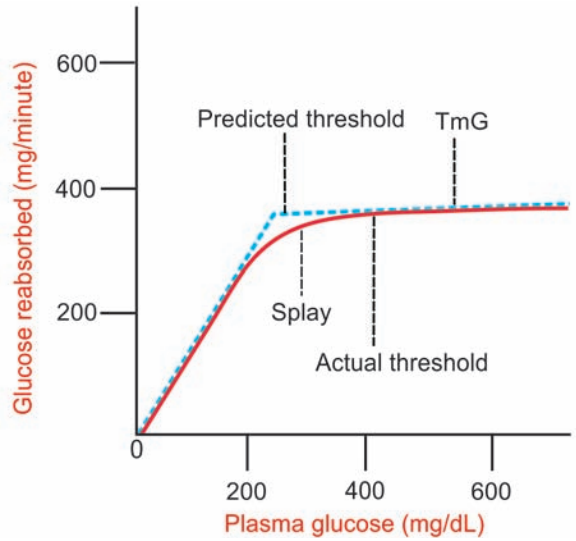


FIGURE 52.4: Splay in renal threshold curve for glucose

Reabsorption of Bicarbonates

Bicarbonate is reabsorbed actively, mostly in proximal tubule (Chapter 54). It is reabsorbed in the form of carbon dioxide.

Bicarbonate is mostly present as sodium bicarbonate in the filtrate. Sodium bicarbonate dissociates into sodium and bicarbonate ions in the tubular lumen. Sodium diffuses into tubular cell in exchange of hydrogen. Bicarbonate combines with hydrogen to form carbonic acid. Carbonic acid dissociates into carbon dioxide and water in the presence of carbonic anhydrase. Carbon dioxide and water enter the tubular cell.

In the tubular cells, carbon dioxide combines with water to form carbonic acid. It immediately dissociates into hydrogen and bicarbonate. Bicarbonate from the tubular cell enters the interstitium. There it combines with sodium to form sodium bicarbonate (Fig. 54.1).

■ TUBULAR SECRETION

■ INTRODUCTION

Tubular secretion is the process by which the substances are transported from blood into renal tubules. It is also called tubular excretion. In addition to reabsorption from renal tubules, some substances are also secreted into the lumen from the peritubular capillaries through the tubular epithelial cells.

Dye phenol red was the first substance found to be secreted in renal tubules in experimental conditions. Later many other substances were found to be secreted.

Such substances are:

1. Para-aminohippuric acid (PAH)
2. Diodrast
3. 5-hydroxyindoleacetic acid (5-HIAA)
4. Amino derivatives
5. Penicillin.

■ SUBSTANCES SECRETED IN DIFFERENT SEGMENTS OF RENAL TUBULES

1. Potassium is secreted actively by sodium-potassium pump in proximal and distal convoluted tubules and collecting ducts
2. Ammonia is secreted in the proximal convoluted tubule
3. Hydrogen ions are secreted in the proximal and distal convoluted tubules. Maximum hydrogen ion secretion occurs in proximal tubule
4. Urea is secreted in loop of Henle.

Thus, urine is formed in nephron by the processes of glomerular filtration, selective reabsorption and tubular secretion.

■ SUMMARY OF URINE FORMATION

Urine formation takes place in three processes (Refer to Fig. 52.1):

1. *Glomerular filtration*

Plasma is filtered in glomeruli and the substances reach the renal tubules along with water as filtrate.

2. *Tubular Reabsorption*

The 99% of filtrate is reabsorbed in different segments of renal tubules.

3. *Tubular Secretion*

Some substances are transported from blood into the renal tubule.

With all these changes, the filtrate becomes urine.

Concentration of Urine

Chapter 53

- INTRODUCTION
- MEDULLARY GRADIENT
- COUNTERCURRENT MECHANISM
- ROLE OF ADH
- SUMMARY OF URINE CONCENTRATION
- APPLIED PHYSIOLOGY

INTRODUCTION

Every day 180 L of glomerular filtrate is formed with large quantity of water. If this much of water is excreted in urine, body will face serious threats. So the concentration of urine is very essential.

Osmolarity of glomerular filtrate is same as that of plasma and it is 300 mOsm/L. But, normally urine is concentrated and its osmolarity is four times more than that of plasma, i.e. 1,200 mOsm/L.

Osmolarity of urine depends upon two factors:

1. Water content in the body
2. Antidiuretic hormone (ADH).

Mechanism of urine formation is the same for dilute urine and concentrated urine till the fluid reaches the distal convoluted tubule. However, dilution or concentration of urine depends upon water content of the body.

FORMATION OF DILUTE URINE

When, water content in the body increases, kidney excretes dilute urine. This is achieved by inhibition of ADH secretion from posterior pituitary (Chapter 66). So water reabsorption from renal tubules does not take place (see Fig. 53.4) leading to excretion of large amount of water. This makes the urine dilute.

FORMATION OF CONCENTRATED URINE

When the water content in body decreases, kidney retains water and excretes concentrated urine. Formation of concentrated urine is not as simple as that of dilute urine.

It involves two processes:

1. Development and maintenance of medullary gradient by countercurrent system
2. Secretion of ADH.

MEDULLARY GRADIENT

MEDULLARY HYPEROSMOLARITY

Cortical interstitial fluid is isotonic to plasma with the osmolarity of 300 mOsm/L. Osmolarity of medullary interstitial fluid near the cortex is also 300 mOsm/L.

However, while proceeding from outer part towards the inner part of medulla, the osmolarity increases gradually and reaches the maximum at the inner most part of medulla near renal sinus. Here, the interstitial fluid is hypertonic with osmolarity of 1,200 mOsm/L (Fig. 53.1).

This type of gradual increase in the osmolarity of the medullary interstitial fluid is called the medullary gradient. It plays an important role in the concentration of urine.

DEVELOPMENT AND MAINTENANCE OF MEDULLARY GRADIENT

Kidney has some unique mechanism called countercurrent mechanism, which is responsible for the development and maintenance of medullary gradient and hyperosmolarity of interstitial fluid in the inner medulla.

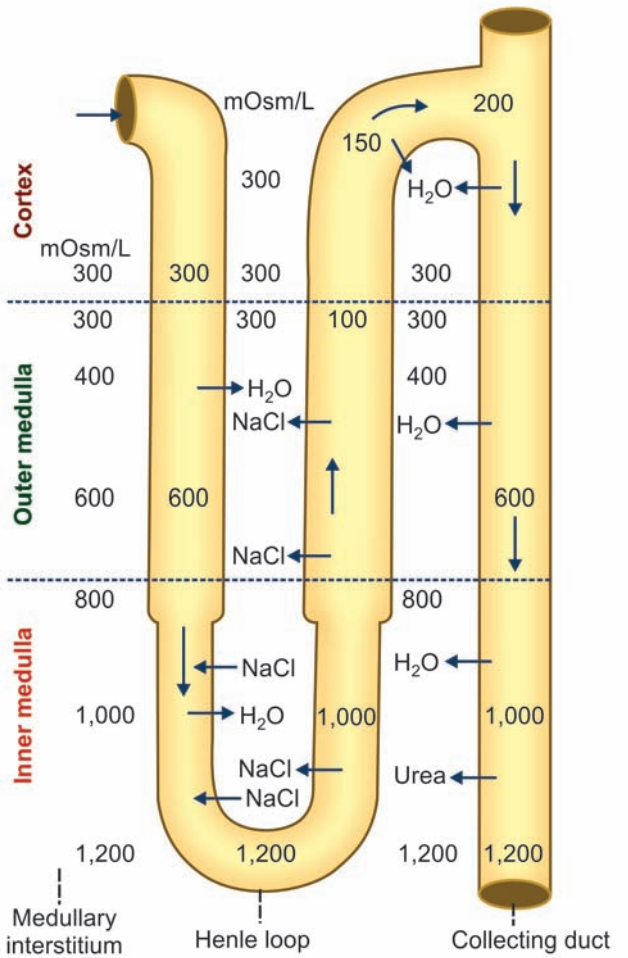


FIGURE 53.1: Countercurrent multiplier. Numerical indicate osmolarity (mOsm/L)

■ COUNTERCURRENT MECHANISM

■ COUNTERCURRENT FLOW

A countercurrent system is a system of 'U'-shaped tubules (tubes) in which, the flow of fluid is in opposite direction in two limbs of the 'U'-shaped tubules.

Divisions of Countercurrent System

Countercurrent system has two divisions:

1. Countercurrent multiplier formed by loop of Henle
2. Countercurrent exchanger formed by vasa recta.

■ COUNTERCURRENT MULTIPLIER

Loop of Henle

Loop of Henle functions as countercurrent multiplier. It is responsible for development of hyperosmolarity of medullary interstitial fluid and medullary gradient.

Role of Loop of Henle in Development of Medullary Gradient

Loop of Henle of juxtamedullary nephrons plays a major role as countercurrent multiplier because loop of these nephrons is long and extends upto the deeper parts of medulla.

Main reason for the hyperosmolarity of medullary interstitial fluid is the active reabsorption of sodium chloride and other solutes from ascending limb of Henle loop into the medullary interstitium. These solutes accumulate in the medullary interstitium and increase the osmolarity.

Now, due to the concentration gradient, the sodium and chlorine ions diffuse from medullary interstitium into the descending limb of Henle loop and reach the ascending limb again via hairpin bend.

Thus, the sodium and chlorine ions are repeatedly re-circulated between the descending limb and ascending limb of Henle loop through medullary interstitial fluid leaving a small portion to be excreted in the urine.

Apart from this there is regular addition of more and more new sodium and chlorine ions into descending limb by constant filtration. Thus, the reabsorption of sodium chloride from ascending limb and addition of new sodium chlorine ions into the filtrate increase or multiply the osmolarity of medullary interstitial fluid and medullary gradient. Hence, it is called countercurrent multiplier.

Other Factors Responsible for Hyperosmolarity of Medullary Interstitial Fluid

In addition to countercurrent multiplier action provided by the loop of Henle, two more factors are involved in hyperosmolarity of medullary interstitial fluid.

i. *Reabsorption of sodium from collecting duct*

Reabsorption of sodium from medullary part of collecting duct into the medullary interstitium, adds to the osmolarity of inner medulla.

ii. *Recirculation of urea*

Fifty percent of urea filtered in glomeruli is reabsorbed in proximal convoluted tubule. Almost an equal amount of urea is secreted in the loop of Henle. So the fluid in distal convoluted tubule has as much urea as amount filtered.

Collecting duct is impermeable to urea. However, due to the water reabsorption from distal convoluted tubule and collecting duct in the presence of ADH, urea concentration increases in collecting duct. Now due to concentration gradient, urea diffuses from inner medullary part of collecting duct into medullary interstitium.

Due to continuous diffusion, the concentration of urea increases in the inner medulla resulting in hyperosmolarity of interstitium in inner medulla.

Again, by concentration gradient, urea enters the ascending limb. From here, it passes through distal convoluted tubule and reaches the collecting duct. Urea enters the medullary interstitium from collecting duct. By this way urea **recirculates** repeatedly and helps to maintain the hyperosmolarity of inner medullary interstitium. Only a small amount of urea is excreted in urine.

Urea recirculation accounts for 50% of hyperosmolarity in inner medulla. Diffusion of urea from collecting duct into medullary interstitium is carried out by **urea transporters,** UT-A1 and UT-A3, which are activated by ADH.

■ COUNTERCURRENT EXCHANGER

Vasa Recta

Vasa recta functions as countercurrent exchanger. It is responsible for the maintenance of medullary gradient, which is developed by countercurrent multiplier (Fig. 53.2).

Role of Vasa Recta in the Maintenance of Medullary Gradient

Vasa recta acts like countercurrent exchanger because of its position. It is also 'U'-shaped tubule with a descending limb, hairpin bend and an ascending limb. Vasa recta runs parallel to loop of Henle. Its descending limb runs along the ascending limb of Henle loop and its ascending limb runs along with descending limb of Henle loop.

The sodium chloride reabsorbed from ascending limb of Henle loop enters the medullary interstitium. From here it enters the descending limb of vasa recta. Simultaneously water diffuses from descending limb of vasa recta into medullary interstitium.

The blood flows very slowly through vasa recta. So, a large quantity of sodium chloride accumulates in descending limb of vasa recta and flows slowly towards ascending limb. By the time the blood reaches the ascending limb of vasa recta, the concentration of sodium chloride increases very much. This causes diffusion of sodium chloride into the medullary interstitium. Simultaneously, water from medullary interstitium enters the ascending limb of vasa recta. And the cycle is repeated.

If the vasa recta would be a straight vessel without hairpin arrangement, blood would leave the kidney quickly at renal papillary level. In that case, the blood would remove all the sodium chloride from medullary

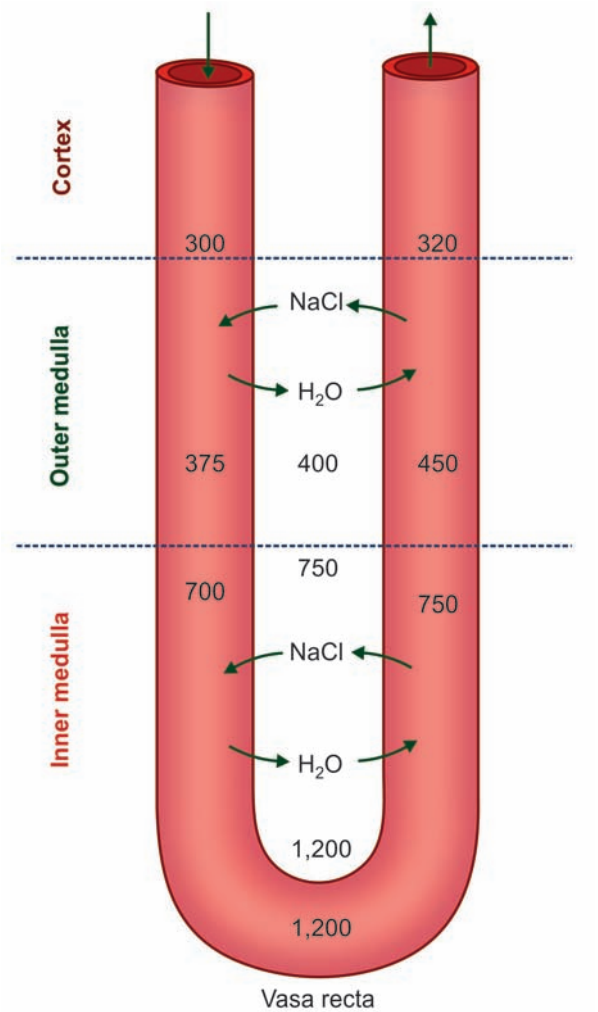


FIGURE 53.2: Countercurrent exchanger. Numerical indicate osmolarity (mOsm/L)

interstitium and thereby the hyperosmolarity will be decreased. However, this does not happen, since the vasa recta has a hairpin bend.

Therefore, when blood passes through the ascending limb of vasa recta, sodium chloride diffuses out of blood and enters the interstitial fluid of medulla and, water diffuses into the blood.

Thus, vasa recta retains sodium chloride in the medullary interstitium and removes water from it. So, the hyperosmolarity of medullary interstitium is maintained. The blood passing through the ascending limb of vasa recta may carry very little amount of sodium chloride from the medulla.

Recycling of urea also occurs through vasa recta. From medullary interstitium, along with sodium chloride, urea also enters the descending limb of vasa recta. When blood passes through ascending limb of vasa

recta, urea diffuses back into the medullary interstitium along with sodium chloride.

Thus, sodium chloride and urea are exchanged for water between the ascending and descending limbs of vasa recta, hence this system is called countercurrent exchanger.

■ ROLE OF ADH

Final concentration of urine is achieved by the action of ADH. Normally, the distal convoluted tubule and collecting duct are not permeable to water. But the presence of ADH makes them permeable, resulting in water reabsorption. Water reabsorption induced by ADH is called **facultative reabsorption of water** (Refer Chapter 52 for details).

A large quantity of water is removed from the fluid while passing through distal convoluted tubule and collecting duct. So, the urine becomes hypertonic with an osmolarity of 1,200 mOsm/L (Fig. 53.3).

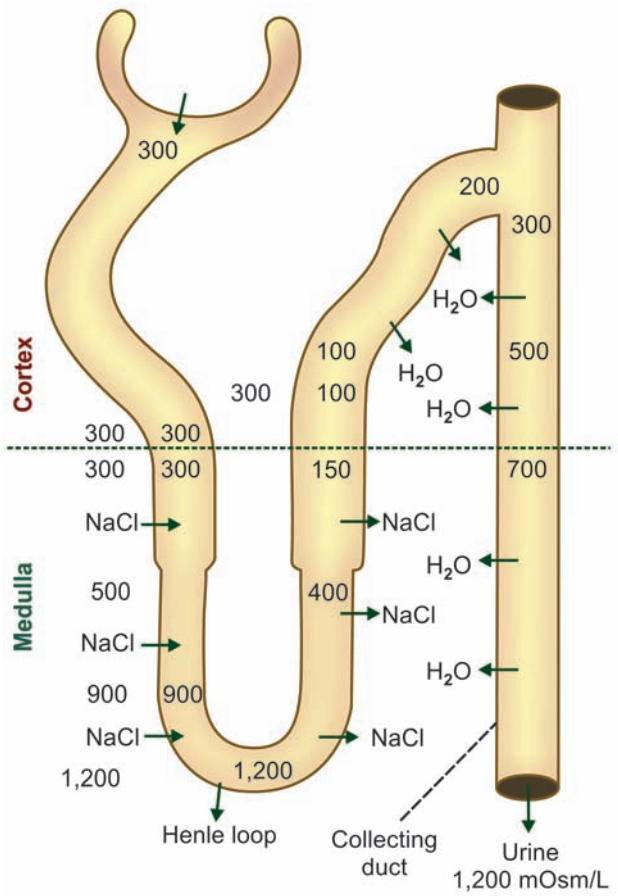


FIGURE 53.3: Role of ADH in the formation of concentrated urine. ADH increases the permeability for water in distal convoluted tubule and collecting duct. Numerical indicate osmolarity (mOsm/L)

■ SUMMARY OF URINE CONCENTRATION

When the glomerular filtrate passes through renal tubule, its osmolarity is altered in different segments as described below (Fig. 53.4).

■ 1. BOWMAN CAPSULE

Glomerular filtrate collected at the Bowman capsule is **isotonic to plasma**. This is because it contains all the substances of plasma except proteins. Osmolarity of the filtrate at Bowman capsule is 300 mOsm/L.

■ 2. PROXIMAL CONVOLUTED TUBULE

When the filtrate flows through proximal convoluted tubule, there is active reabsorption of sodium and chloride followed by **obligatory reabsorption of water.**

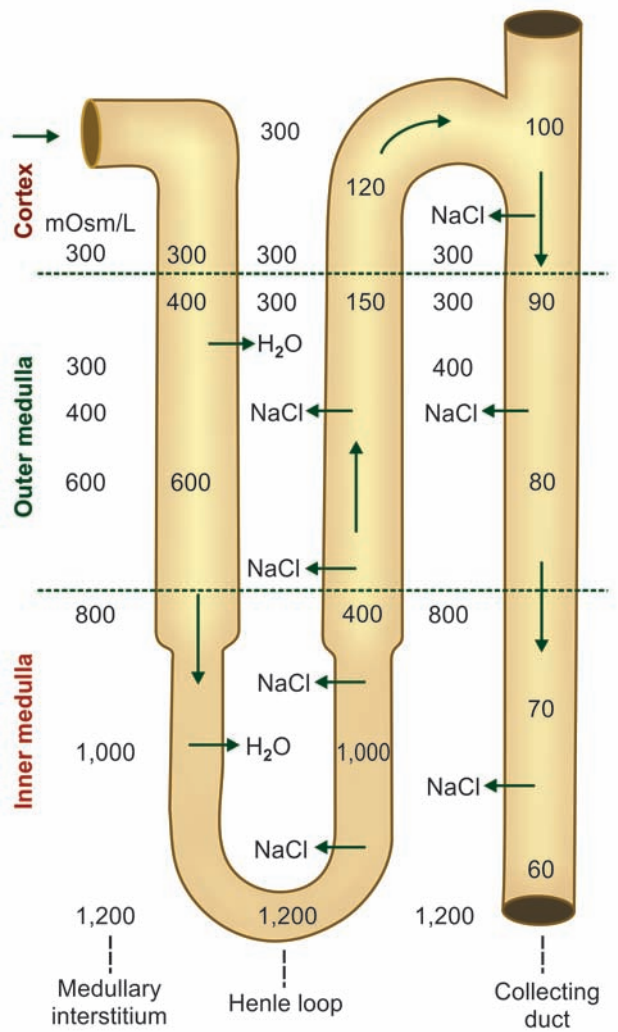


FIGURE 53.4: Mechanism for the formation of dilute urine. Numerical indicate osmolarity (mOsm/L)

So, the osmolarity of fluid remains the same as in the case of Bowman capsule, i.e. 300 mOsm/L. Thus, in proximal convoluted tubules, the fluid is **isotonic to plasma.**

■ 3. THICK DESCENDING SEGMENT

When the fluid passes from proximal convoluted tubule into the thick descending segment, water is reabsorbed from tubule into outer medullary interstitium by means of osmosis. It is due to the increased osmolarity in the medullary interstitium, i.e. outside the thick descending tubule. The osmolarity of the fluid inside this segment is between 450 and 600 mOsm/L. That means the fluid is slightly **hypertonic to plasma.**

■ 4. THIN DESCENDING SEGMENT OF HENLE LOOP

As the thin descending segment of Henle loop passes through the inner medullary interstitium (which is increasingly hypertonic) more water is reabsorbed. This segment is highly permeable to water and so the osmolarity of tubular fluid becomes equal to that of the surrounding medullary interstitium.

In the short loops of cortical nephrons, the osmolarity of fluid at the hairpin bend of loop becomes 600 mOsm/L. And, in the long loops of juxtamedullary nephrons, at the hairpin bend, the osmolarity is 1,200 mOsm/L. Thus in this segment the fluid is **hypertonic to plasma.**

■ 5. THIN ASCENDING SEGMENT OF HENLE LOOP

When the thin ascending segment of the loop ascends upwards through the medullary region, osmolarity decreases gradually.

Due to concentration gradient, sodium chloride diffuses out of tubular fluid and osmolarity decreases to 400 mOsm/L. The fluid in this segment is slightly **hypertonic to plasma.**

■ 6. THICK ASCENDING SEGMENT

This segment is impermeable to water. But there is active reabsorption of sodium and chloride from this. Reabsorption of sodium decreases the osmolarity of tubular fluid to a greater extent. The osmolarity is between 150 and 200 mOsm/L. The fluid inside becomes **hypotonic to plasma.**

■ 7. DISTAL CONVOLUTED TUBULE AND COLLECTING DUCT

In the presence of ADH, distal convoluted tubule and collecting duct become permeable to water resulting in water reabsorption and final concentration of urine. It is found that in the collecting duct, Principal (P) cells are responsible for ADH induced water reabsorption.

Reabsorption of large quantity of water increases the osmolarity to 1,200 mOsm/L (Fig. 53.3). The urine becomes **hypertonic to plasma.**

■ APPLIED PHYSIOLOGY

1. *Osmotic Diuresis*

Diuresis is the excretion of large quantity of water through urine. Osmotic diuresis is the diuresis induced by the osmotic effects of solutes like glucose. It is common in **diabetes mellitus** (Chapter 69).

2. *Polyuria*

Polyuria is the increased urinary output with frequent voiding. It is common in **diabetes insipidus.** In this disorder, the renal tubules fail to reabsorb water because of ADH deficiency (Chapter 66).

3. *Syndrome of Inappropriate Hypersecretion of ADH (SIADH)*

It is a pituitary disorder characterized by hypersecretion of ADH is the SIADH. Excess ADH causes water retention, which decreases osmolarity of ECF (Chapter 66).

4. *Nephrogenic Diabetes Insipidus*

Sometimes, ADH secretion is normal but the renal tubules fail to give response to ADH resulting in polyuria. This condition is called nephrogenic diabetes insipidus.

5. *Bartter Syndrome*

Bartter syndrome is a genetic disorder characterized by defect in the thick ascending segment. This causes decreased sodium and water reabsorption resulting in loss of sodium and water through urine.

Acidification of Urine and Role of Kidney in Acid-base Balance

Chapter 54

INTRODUCTION

Kidney plays an important role in maintenance of acid-base balance by excreting hydrogen ions and retaining bicarbonate ions.

Normally, urine is acidic in nature with a pH of 4.5 to 6. Metabolic activities in the body produce large quantity of acids (with lot of hydrogen ions), which threaten to push the body towards acidosis.

However, kidneys prevent this by two ways:

1. Reabsorption of bicarbonate ions (HCO_3^-)
2. Secretion of hydrogen ions (H^+).

REABSORPTION OF BICARBONATE IONS

About 4,320 mEq of HCO_3^- is filtered by the glomeruli everyday. It is called **filtered load** of HCO_3^-. Excretion of this much HCO_3^- in urine will affect the acid-base balance of body fluids. So, HCO_3^- must be taken back from the renal tubule by reabsorption.

SECRETION OF HYDROGEN IONS

Reabsorption of filtered HCO_3^- occurs by the secretion of H^+ in the renal tubules. About 4,380 mEq of H^+ appear every day in the renal tubule by means of filtration and secretion. Not all the H^+ are excreted in urine. Out of 4,380 mEq, about 4,280 to 4,330 mEq of H^+ is utilized for the reabsorption of filtered HCO_3^-. Only the remaining 50 to 100 mEq is excreted. It results in the acidification of urine.

Secretion of H^+ into the renal tubules occurs by the formation of carbonic acid. Carbon dioxide formed in the tubular cells or derived from tubular fluid combines with water to form carbonic acid in the presence of **carbonic anhydrase.** This enzyme is available in large quantities in the epithelial cells of the renal tubules. The carbonic acid immediately dissociates into H^+ and HCO_3^- (Fig. 54.1).

H^+ is secreted into the lumen of proximal convoluted tubule, distal convoluted tubule and collecting duct. Distal convoluted tubule and collecting duct have a special type of cells called **intercalated cells (I cells)** that are involved in handling hydrogen and bicarbonate ions.

Secretion of H^+ occurs by two pumps:

i. Sodium-hydrogen antiport pump
ii. ATP-driven proton pump.

SODIUM-HYDROGEN ANTIPORT PUMP

When sodium ion (Na^+) is reabsorbed from the tubular fluid into the tubular cell, H^+ is secreted from the cell into the tubular fluid in exchange for Na^+. The sodium-hydrogen antiport pump present in the tubular cells

is responsible for the exchange of Na^+ and H^+. This type of sodium-hydrogen counter transport occurs predominantly in distal convoluted tubule (Table 54.1).

■ ATP-DRIVEN PROTON PUMP

This is an additional pump for H^+ secretion in distal convoluted tubule and collecting duct. This pump operates by energy from ATP.

■ REMOVAL OF HYDROGEN IONS AND ACIDIFICATION OF URINE

Role of Kidney in Preventing Metabolic Acidosis

Kidney plays an important role in preventing metabolic acidosis (Chapter 5) by excreting H^+.

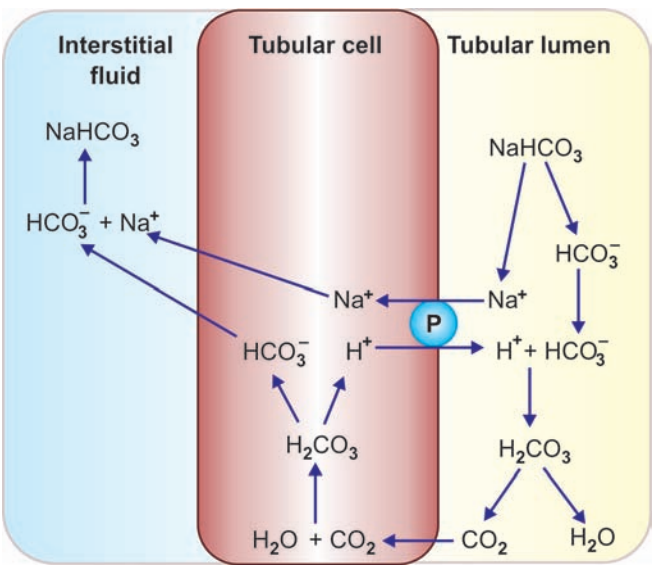


FIGURE 54.1: Reabsorption of bicarbonate ions by secretion of hydrogen ions in renal tubule. P = sodium-hydrogen antiport pump

TABLE 54.1: Mechanisms involved in secretion of hydrogen ions in renal tubule

Mechanism	Segment of renal tubule
Sodium-hydrogen pump	Distal convoluted tubule
ATP-driven proton pump	Distal convoluted tubule Collecting duct
Bicarbonate mechanism	Proximal convoluted tubule Henle loop Distal convoluted tubule
Phosphate mechanism	Distal convoluted tubule Collecting duct
Ammonia mechanism	Proximal convoluted tubule.

Excretion of H^+ occurs by three mechanisms:

1. Bicarbonate mechanism
2. Phosphate mechanism
3. Ammonia mechanism.

■ BICARBONATE MECHANISM

All the filtered HCO_3^- in the renal tubules is reabsorbed. About 80% of it is reabsorbed in proximal convoluted tubule, 15% in Henle loop and 5% in distal convoluted tubule and collecting duct. The reabsorption of HCO_3^- utilizes the H^+ secreted into the renal tubules.

H^+ secreted into the renal tubule, combines with filtered HCO_3^- forming carbonic acid (H_2CO_3). Carbonic acid dissociates into carbon dioxide and water in the presence of carbonic anhydrase. Carbon dioxide and water enter the tubular cell.

In the tubular cells, carbon dioxide combines with water to form carbonic acid. It immediately dissociates into H^+ and HCO_3^-. HCO_3^- from the tubular cell enters the interstitium. Simultaneously Na^+ is reabsorbed from the renal tubule under the influence of aldosterone. HCO_3^- combines with Na^+ to form sodium bicarbonate ($NaHCO_3$). Now, the H^+ is secreted into the tubular lumen from the cell in exchange for Na^+ (Fig. 54.1).

Thus, for every hydrogen ion secreted into lumen of tubule, one bicarbonate ion is reabsorbed from the tubule. In this way, kidneys conserve the HCO_3^-. The reabsorption of filtered HCO_3^- is an important factor in maintaining pH of the body fluids.

■ PHOSPHATE MECHANISM

In the tubular cells, carbon dioxide combines with water to form carbonic acid. It immediately dissociates into H^+ and HCO_3^-. HCO_3^- from the tubular cell enters the interstitium. Simultaneously, Na^+ is reabsorbed from renal tubule under the influence of aldosterone. Na^+ enters the interstitium and combines with HCO_3^-. H^+ is secreted into the tubular lumen from the cell in exchange for Na^+ (Fig. 54.2).

H^+, which is secreted into renal tubules, reacts with phosphate buffer system. It combines with sodium hydrogen phosphate to form sodium dihydrogen phosphate. Sodium dihydrogen phosphate is excreted in urine. The H^+, which is added to urine in the form of sodium dihydrogen, makes the urine acidic. It happens mainly in distal tubule and collecting duct because of the presence of large quantity of sodium hydrogen phosphate in these segments.

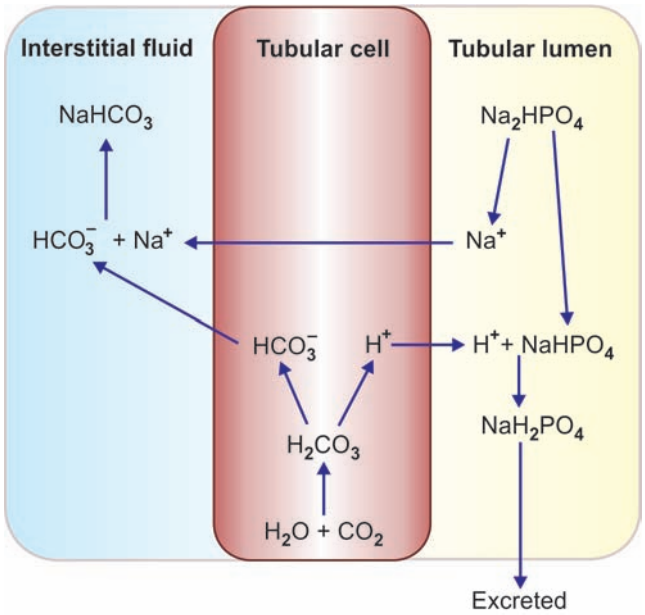


FIGURE 54.2: Excretion of hydrogen ions in combination with phosphate ions

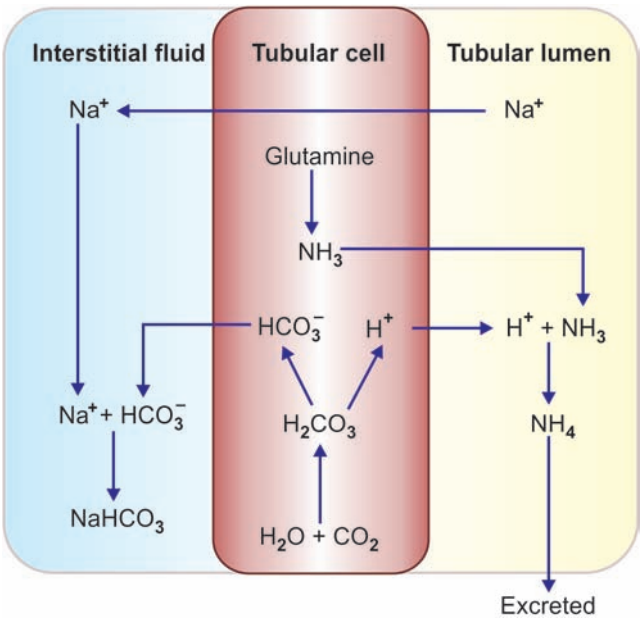


FIGURE 54.3: Excretion of hydrogen ions in combination with ammonia

■ AMMONIA MECHANISM

This is the most important mechanism by which kidneys excrete H^+ and make the urine acidic. In the tubular epithelial cells, ammonia is formed when the amino acid **glutamine** is converted into **glutamic acid** in the presence of the enzyme **glutaminase.** Ammonia is also formed by the deamination of some of the amino acids such as **glycine** and **alanine** (Fig. 54.3).

Ammonia (NH_3) formed in tubular cells is secreted into tubular lumen in exchange for sodium ion. Here, it combines with H^+ to form **ammonium** (NH_4). The tubular cell membrane is not permeable to ammonium. Therefore, it remains in the lumen and then excreted into urine. Thus, H^+ is added to urine in the form of ammonium compounds resulting in acidification of urine. For each NH_4 excreted one HCO_3^- is added to interstitial fluid.

This process takes place mostly in the proximal convoluted tubule because glutamine is converted into ammonia in the cells of this segment.

Thus, by excreting H^+ and conserving HCO_3^-, kidneys produce acidic urine and help to maintain the acid-base balance of body fluids.

■ APPLIED PHYSIOLOGY

Metabolic acidosis occurs when kidneys fail to excrete metabolic acids. **Metabolic alkalosis** occurs when kidneys excrete large quantity of hydrogen. Refer Chapter 5 for details.

Chapter 55

Renal Function Tests

PROPERTIES AND COMPOSITION OF NORMAL URINE

PROPERTIES OF URINE

Volume	:	1,000 to 1,500 mL/day
Reaction	:	Slightly acidic with pH of 4.5 to 6
Specific gravity	:	1.010 to 1.025
Osmolarity	:	1,200 mOsm/L
Color	:	Normally, straw colored
Odor	:	Fresh urine has light aromatic odor. If stored for some time, the odor becomes stronger due to bacterial decomposition.

COMPOSITION OF URINE

Urine consists of water and solids. Solids include organic and inorganic substances (Fig. 55.1).

RENAL FUNCTION TESTS

Renal function tests are the group of tests that are performed to assess the functions of kidney.

Renal function tests are of three types:

A. Examination of urine alone

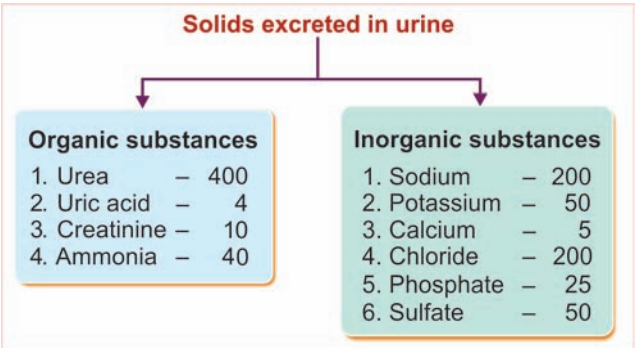


FIGURE 55.1: Quantity of solids excreted in urine (mMols/day)

B. Examination of blood alone

C. Examination of blood and urine.

EXAMINATION OF URINE – URINALYSIS

Routine examination of urine or urinalysis is a group of diagnostic tests performed on the sample of urine.

Urinalysis is done by:

i. Physical examination
ii. Microscopic examination
iii. Chemical analysis.

■ PHYSICAL EXAMINATION

1. *Volume*

Increase in urine volume indicates increase in protein catabolism and renal disorders such as **chronic renal failure, diabetes insipidus** and **glycosuria.**

2. *Color*

Normally urine is straw colored. Abnormal coloration of urine is due to several causes such as **jaundice, hematuria, hemoglobinuria,** medications, excess urobilinogen, ingestion of beetroot or color added to food.

3. *Appearance*

Normally urine is clear. It becomes turbid in both physiological and pathological conditions. Physiological conditions causing turbidity of urine are precipitation of crystals, presence of mucus or vaginal discharge. Pathological conditions causing turbidity are presence of blood cells, bacteria or yeast.

4. *Specific Gravity*

Specific gravity of urine is the measure of dissolved solutes (particles) in urine. It is low in diabetes insipidus and high in **diabetes mellitus, acute renal failure** and excess medications.

5. *Osmolarity*

Osmolarity of urine decreases in diabetes insipidus.

6. *pH and Reaction*

Measurement of pH is useful in determining the metabolic or respiratory acidosis or alkalosis. The pH decreases in renal diseases. In normal conditions, pH of urine depends upon diet. It is slightly alkaline in vegetarians and acidic in non-vegetarians.

■ MICROSCOPIC EXAMINATION

Microscopic examination of centrifuged sediment of urine is useful in determining the renal diseases.

1. *Red Blood Cells*

Presence of red blood cells in urine indicates glomerular disease such as **glomerulonephritis.**

2. *White Blood Cells*

Normally few white blood cells appear in high power field. The number increases in acute **glomerulonephritis,** infection of urinary tract, vagina or cervix.

3. *Epithelial Cells*

Normally few tubular epithelial cells slough into urine. Presence of many epithelial cells suggests **nephrotic syndrome** and **tubular necrosis.**

4. *Casts*

Casts are the cylindrical bodies that are casted (molded) in the shape of renal tubule. Casts may be hyaline, granular or cellular in nature. Hyaline and granular casts, which are formed by precipitation of proteins may appear in urine in small numbers. The number increases in proteinuria due to **glomerulonephritis.**

Cellular casts are formed by sticking together of some cells. Red blood cell casts appear in urine during glomerulonephritis and tubular necrosis. White blood cell casts appear in pyelonephritis. Epithelial casts are formed during acute **tubular necrosis.**

5. *Crystals*

Several types of crystals are present in normal urine. Common crystals are the crystals of calcium oxalate, calcium phosphate, uric acid and triple phosphate (calcium, ammonium and magnesium).

Abnormal crystals such as crystals of cystine and tyrosine appear in liver diseases.

6. *Bacteria*

Bacteria are common in urine specimens because of normal microbial flora of urinary tract, urethra and vagina and because of their ability to multiply rapidly in urine. Culture studies are necessary to determine the presence of bacteria in urine.

■ CHEMICAL ANALYSIS

Chemical analysis of urine helps to determine the presence of abnormal constituents of urine or presence of normal constituents in abnormal quantity. Both the findings reveal the presence of renal abnormality. Following are the common chemical tests of urine:

1. *Glucose*

Glucose appears in urine when the blood glucose level increases above 180 mg/dL. **Glycosuria** (presence of glucose in urine) may be the first indicator of diabetes mellitus.

2. *Protein*

Presence of excess protein **(proteinuria)** particularly albumin **(albuminuria)** in urine indicates renal diseases. Urinary excretion of albumin in a normal healthy adult

is about 30 mg/day. It exceeds this level in glomerulonephritis. It also increases in fever and severe exercise.

3. *Ketone Bodies*

Ketonuria (presence of ketone bodies in urine) occurs in pregnancy, fever, diabetes mellitus, prolonged starvation and glycogen storage diseases.

4. *Bilirubin*

Bilirubin appears in urine **(bilirubinuria)** during hepatic and posthepatic jaundice.

5. *Urobilinogen*

Normally, about 1 to 3.5 mg of urobilinogen is excreted in urine daily. Excess of urobilinogen in urine indicates **hemolytic jaundice.**

6. *Bile Salts*

Presence of bile salts in urine reveals jaundice.

7. *Blood*

Presence of blood in urine **(hematuria)** indicates glomerulonephritis, renal stones, infection or malignancy of urinary tract. Hematuria must be confirmed by microscopic examination since chemical test fails to distinguish the presence of red blood cells or hemoglobin in urine.

8. *Hemoglobin*

Hemoglobin appears in urine **(hemoglobinuria)** during excess hemolysis.

9. *Nitrite*

Presence of nitrite in urine indicates presence of bacteria in urine since some bacteria convert nitrate into nitrite in urine.

■ EXAMINATION OF BLOOD

1. *Estimation of Plasma Proteins*

Normal values of plasma proteins:

Total proteins	:	7.3 g/dL (6.4 to 8.3 g/dL)
Serum albumin	:	4.7 g/dL
Serum globulin	:	2.3 g/dL
Fibrinogen	:	0.3 g/dL

Level of plasma proteins is altered during renal failure.

2. *Estimation of Urea, Uric Acid and Creatinine*

Normal values :

Urea	:	25 to 40 mg/dL
Uric acid	:	2.5 mg/dL
Creatinine	:	0.5 to 1.5 mg/dL

The blood level of these substances increases in renal failure.

■ EXAMINATION OF BLOOD AND URINE

Plasma Clearance

Plasma clearance is defined as the amount of plasma that is cleared off a substance in a given unit of time. It is also known as renal clearance. It is based on Fick principle.

Determination of clearance value for certain substances helps in assessing the following renal functions:

1. Glomerular filtration rate
2. Renal plasma flow
3. Renal blood flow.

Value of following factors is required to determine the plasma clearance of a particular substance:

1. Volume of urine excreted
2. Concentration of the substance in urine
3. Concentration of the substance in blood.

Formula to calculate clearance value

$$C = \frac{U\,V}{P}$$

Where, C = Clearance
U = Concentration of the substance in urine
V = Volume of urine flow
P = Concentration of the substance in plasma.

1. *Measurement of Glomerular Filtration Rate*

A substance that is completely filtered but neither reabsorbed nor secreted should be used to measure glomerular filtration rate (GFR). Inulin is the ideal substance used to measure GFR. It is completely filtered and neither reabsorbed nor secreted. So, inulin clearance indicates GFR.

Inulin clearance

A known amount of inulin is injected into the body. After sometime, the concentration of inulin in plasma and urine and the volume of urine excreted are estimated.

For example,

Concentration of inulin in urine	=	125 mg/dL
Concentration of inulin in plasma	=	1 mg/dL
Volume of urine output	=	1 mL/min

Thus,

$$\text{Glomerular filtration rate} = \frac{U\,V}{P} = \frac{125 \times 1}{1}$$

$$= 125 \text{ mL/min}$$

Creatinine clearance is also used to measure GFR accurately. It is easier than inulin clearance, because, creatinine is already present in body fluids and its plasma concentration is steady throughout the day. It is completely filtered and being a metabolite it is neither reabsorbed nor secreted. The normal value of GFR by this method is approximately the same as determined by inulin clearance.

2. *Measurement of Renal Plasma Flow*

To measure renal plasma flow, a substance, which is filtered and secreted but not reabsorbed, should be used. Such a substance is **para-aminohippuric acid** (PAH). PAH clearance indicates the amount of plasma passed through kidneys.

A known amount of PAH is injected into the body. After sometime, the concentration of PAH in plasma and urine and the volume of urine excreted are estimated.

For example,

Concentration of PAH in urine = 66 mg/dL
Concentration of PAH in plasma = 0.1 mg/dL
Volume of urine output = 1 mL/min

Thus,

$$\text{Renal plasma flow} = \frac{U\,V}{P}$$

$$= \frac{66 \times 1}{0.1}$$

$$= 660 \text{ mL/min}$$

Diodrast clearance also can be used to measure this.

3. *Measurement of Renal Blood Flow*

Values of factors necessary to determine renal blood flow are:

i. Renal plasma flow
ii. Percentage of plasma volume in blood.

i. *Renal plasma flow*

Renal plasma flow is measured by using PAH clearance.

ii. *Percentage of plasma volume in blood*

Percentage of plasma volume is indirectly determined by using packed cell volume (PCV).

For example,

If PCV = 45%

Plasma volume in the blood = 100 – 45 = 55%

That is 55 mL of plasma is present in every 100 mL of blood.

Calculation of renal blood blow

Renal blood flow is calculated with the values of renal plasma volume and percentage of plasma in blood by using a formula given below.

$$\text{Renal blood flow} = \frac{\text{Renal plasma flow}}{\%\text{ of plasma in blood}}$$

For example,

Renal plasma flow = 660 mL/min
Amount of plasma in blood = 55%

$$\text{Renal blood flow} = \frac{660}{55/100}$$

$$= 1{,}200 \text{ mL/min}$$

Urea Clearance Test

Urea clearance test is a clinical test to assess renal function by using clearance of urea from plasma by kidney every minute. This test requires a blood sample to determine urea level in blood and two urine sample collected at 1 hour interval to determine the urea cleared by kidneys into urine. Normal value of urea clearance is 70 mL/min.

Urea is a waste product formed during protein metabolism and excreted in urine. So, determination of urea clearance forms a specific test to assess renal function.

Renal Failure

Chapter 56

INTRODUCTION

Renal failure refers to failure of excretory functions of kidney. It is usually, characterized by decrease in glomerular filtration rate (GFR). So GFR is considered as the best index of renal failure. However, decrease in GFR is not affected much during the initial stages of renal failure. If 50% of the nephrons are affected, GFR decreases only by 20% to 30%. It is because of the compensatory mechanism by the unaffected nephrons. The renal failure may be either acute or chronic.

Renal failure is always accompanied by other complications such as:

1. Deficiency of calcitriol (activated vitamin D) resulting in reduction of calcium absorption from intestine and hypocalcemia (Chapter 72). Deficiency of calcitriol and hypocalcemia may cause secondary hyperparathyroidism in some patients
2. Deficiency of erythropoietin resulting in anemia
3. Disturbances in acid-base balance.

ACUTE RENAL FAILURE

Acute renal failure is the abrupt or sudden stoppage of renal functions. It is often reversible within few days to few weeks. Acute renal failure may result in sudden **life-threatening reactions** in the body with the need for emergency treatment.

CAUSES

1. Acute **nephritis** (inflammation of kidneys), which usually develops by immune reaction
2. Damage of renal tissues by poisons like lead, mercury and carbon tetrachloride
3. **Renal ischemia,** which develops during circulatory shock
4. Acute **tubular necrosis** (necrosis of tubular cells in kidney) caused by burns, hemorrhage, snake bite, toxins (like insecticides, heavy metals and carbon tetrachloride) and drugs (like diuretics, aminoglycosides and platinum derivatives)
5. Severe **transfusion reactions**
6. Sudden fall in blood pressure during hemorrhage, diarrhea, severe burns and cholera
7. Blockage of ureter due to the formation of calculi (renal stone) or tumor.

FEATURES

1. **Oliguria** (decreased urinary output)
2. **Anuria** (cessation of urine formation) in severe cases
3. **Proteinuria** (appearance of proteins in urine) including albuminuria (excretion of albumin in urine)
4. **Hematuria** (presence of blood in urine)

5. **Edema** due to increased volume of extracellular fluid (ECF) caused by retention of sodium and water
6. **Hypertension** within few days because of increased ECF volume
7. **Acidosis** due to the retention of metabolic end products
8. **Coma** due to severe acidosis (if the patient is not treated in time) resulting in death within 10 to 14 days.

CHRONIC RENAL FAILURE

Chronic renal failure is the progressive, long standing and irreversible impairment of renal functions.

When some of the nephrons loose the function, the unaffected nephrons can compensate it. However, when more and more nephrons start losing the function over the months or years, the compensatory mechanism fails and chronic renal failure develops.

CAUSES

1. Chronic nephritis
2. Polycystic kidney disease
3. Renal calculi (kidney stones)
4. Urethral constriction
5. Hypertension
6. Atherosclerosis
7. Tuberculosis
8. Slow poisoning by drugs or metals.

FEATURES

1. *Uremia*

Uremia is the condition characterized by excess accumulation of end products of protein metabolism such as urea, nitrogen and creatinine in blood. There is also accumulation of some toxic substances like organic acids and phenols. Uremia occurs because of the failure of kidney to excrete the metabolic end products and toxic substances.

Common features of uremia

i. Anorexia (loss of appetite)
ii. Lethargy
iii. Drowsiness
iv. Nausea and vomiting
v. Pigmentation of skin
vi. Muscular twitching, tetany and convulsion
vii. Confusion and mental deterioration
viii. Coma.

2. *Acidosis*

Uremia results in acidosis, which leads to coma and death.

3. *Edema*

Failure of kidney to excrete sodium and electrolytes causes increase in extracellular fluid volume resulting in development of edema.

4. *Blood Loss*

Gastrointestinal bleeding accompanied by platelet dysfunction leads to heavy loss of blood.

5. *Anemia*

Since, erythropoietin is not secreted in the kidney during renal failure, the production of RBC decreases resulting in normocytic normochromic anemia.

6. *Hyperparathyroidism*

Secondary hyperparathyroidism is developed due to the deficiency of calcitriol (1,25-dihydroxycholecalciferol). It increases the removal of calcium from bones resulting in **osteomalacia.**

Micturition

Chapter 57

INTRODUCTION

Micturition is a process by which urine is voided from the urinary bladder. It is a reflex process. However, in grown up children and adults, it can be controlled voluntarily to some extent. The functional anatomy and nerve supply of urinary bladder are essential for the process of micturition.

FUNCTIONAL ANATOMY OF URINARY BLADDER AND URETHRA

URINARY BLADDER

Urinary bladder is a triangular hollow organ located in lower abdomen. It consists of a body and neck. Wall of the bladder is formed by smooth muscle. It consists of three ill-defined layers of muscle fibers called **detrusor muscle**, viz. the inner longitudinal layer, middle circular layer and outer longitudinal layer. Inner surface of urinary bladder is lined by mucus membrane. In empty bladder, the **mucosa** falls into many folds called **rugae.**

At the posterior surface of the bladder wall, there is a triangular area called **trigone.** At the upper angles of this trigone, two ureters enter the bladder. Lower part of the bladder is narrow and forms the neck. It opens into urethra via **internal urethral sphincter.**

URETHRA

Male urethra has both urinary function and reproductive function. It carries urine and semen. Female urethra has only urinary function and it carries only urine. So, male urethra is structurally different from female urethra.

Male Urethra

Male urethra is about 20 cm long. After origin from bladder it traverses the prostate gland, which lies below the bladder and then runs through the penis (Fig. 57.1).

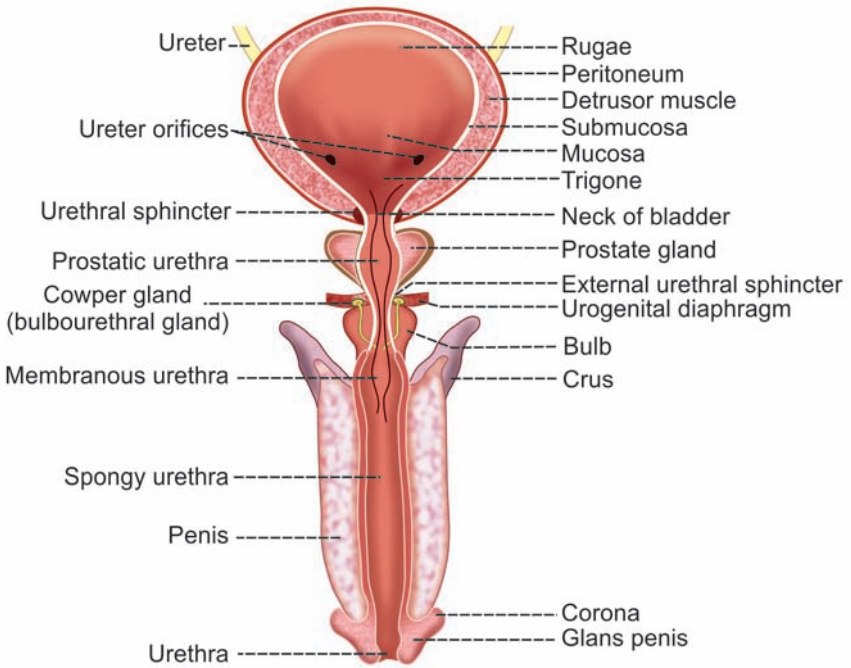


FIGURE 57.1: Male urinary bladder and urethra

Throughout its length, the urethra has mucus glands called glands of Littre.

Male urethra is divided into three parts:

1. Prostatic urethra
2. Membranous urethra
3. Spongy urethra.

1. *Prostatic urethra*

Prostatic urethra is 3 cm long and it runs through prostate gland. The prostatic fluid is emptied into this part of urethra through **prostatic sinuses.** Sperms from vas deferens and the fluid from seminal vesicles are also emptied into prostatic urethra via **ejaculatory ducts** (Chapter 74).

Part of the urethra after taking origin from neck of bladder before entering the prostate gland is known as preprostatic urethra. Its length is about 0.5 to 1.5 cm. This part of urethra is considered as part of prostatic urethra.

2. *Membranous urethra*

Membranous urethra is about 1 to 2 cm long. It runs from base of the prostate gland through **urogenital diaphragm** up to the bulb of urethra.

3. *Spongy urethra*

Spongy urethra is also known as cavernous urethra and its length is about 15 cm. Spongy urethra is surrounded by **corpus spongiosum** of penis. It is divided into a proximal bulbar urethra and a distal penil urethra. Penile urethra is narrow with a length of about 6 cm. It ends with external urethral meatus or orifice, which is located at the end of penis.

The bilateral bulbourethral glands open into spongy urethra. **Bulbourethral glands** are also called **Cowper glands.**

Female Urethra

Female urethra is narrower and shorter than male urethra. It is about 3.5 to 4 cm long. After origin from bladder it traverses through **urogenital diaphragm** and runs along anterior wall of vagina. Then it terminates at external orifice of urethra, which is located between clitoris and vaginal opening (Fig. 57.2).

■ URETHRAL SPHINCTERS

There are two urethral sphincters in urinary tract:

1. Internal urethral sphincter
2. External urethral sphincter.

1. *Internal Urethral sphincter*

This sphincter is situated between neck of the bladder and upper end of urethra. It is made up of smooth muscle fibers and formed by thickening of detrusor muscle. It is innervated by autonomic nerve fibers. This sphincter closes the urethra when bladder is emptied.

2. *External Urethral sphincter*

External sphincter is located in the urogenital diaphragm. This sphincter is made up of circular skeletal muscle fibers, which are innervated by somatic nerve fibers.

■ NERVE SUPPLY TO URINARY BLADDER AND SPHINCTERS

Urinary bladder and the internal sphincter are supplied by sympathetic and parasympathetic divisions of autonomic nervous system where as, the external sphincter is supplied by the somatic nerve fibers (Fig. 57.3).

■ SYMPATHETIC NERVE SUPPLY

Preganglionic fibers of sympathetic nerve arise from first two lumbar segments (L1 and L2) of spinal cord. After leaving spinal cord, the fibers pass through lateral sympathetic chain without any synapse in the sympathetic ganglia and finally terminate in **hypogastric ganglion.** The postganglionic fibers arising from this ganglion form the **hypogastric nerve,** which supplies the detrusor muscle and internal sphincter.

Function of Sympathetic Nerve

The stimulation of sympathetic (hypogastric) nerve causes relaxation of detrusor muscle and constriction of the internal sphincter. It results in filling of urinary bladder and so, the sympathetic nerve is called **nerve of filling.**

■ PARASYMPATHETIC NERVE SUPPLY

Preganglionic fibers of parasympathetic nerve form the **pelvic nerve** or **nervus erigens.** Pelvic nerve fibers arise from second, third and fourth sacral segments (S1, S2 and S3) of spinal cord. These fibers run through hypogastric ganglion and synapse with postganglionic neurons situated in close relation to urinary bladder and internal sphincter (Table 57.1).

Function of Parasympathetic Nerve

Stimulation of parasympathetic (pelvic) nerve causes contraction of detrusor muscle and relaxation of the internal sphincter leading to emptying of urinary bladder. So, parasympathetic nerve is called the **nerve of emptying** or nerve of micturition.

Pelvic nerve has also the sensory fibers, which carry impulses from stretch receptors present on the wall of the urinary bladder and urethra to the central nervous system.

■ SOMATIC NERVE SUPPLY

External sphincter is innervated by the somatic nerve called **pudendal nerve.** It arises from second, third and fourth sacral segments of the spinal cord.

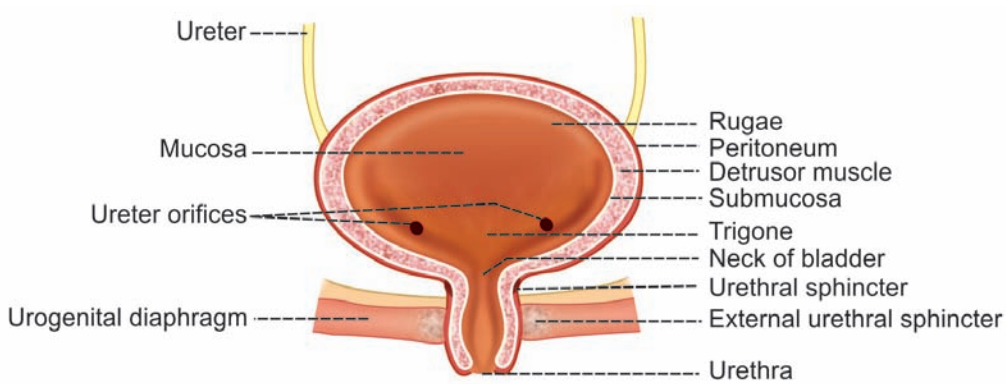


FIGURE 57.2: Female urinary bladder and urethra

TABLE 57.1: Functions of nerves supplying urinary bladder and sphincters

Nerve	On detrusor muscle	On internal sphincter	On external sphincter	Function
Sympathetic nerve	Relaxation	Constriction	Not supplied	Filling of urinary bladder
Parasympathetic nerve	Contraction	Relaxation	Not supplied	Emptying of urinary bladder
Somatic nerve	Not supplied	Not supplied	Constriction	Voluntary control of micturition

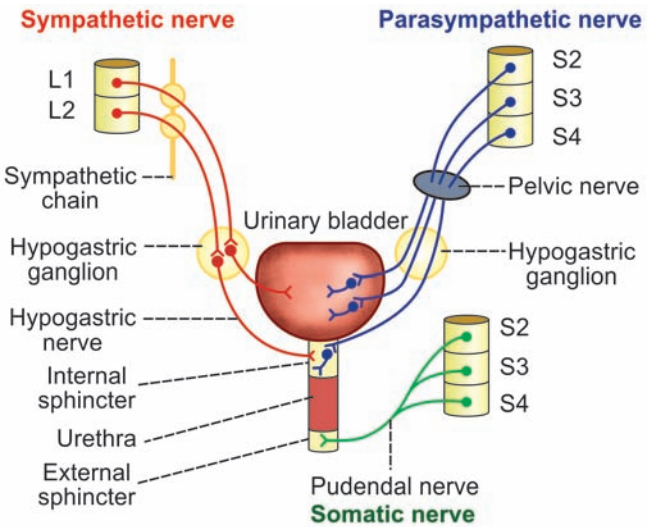


FIGURE 57.3: Nerve supply to urinary bladder and urethra

Function of Pudendal Nerve

Pudendal nerve maintains the **tonic contraction** of the skeletal muscle fibers of the external sphincter and keeps the external sphincter constricted always.

During micturition, this nerve is inhibited. It causes relaxation of external sphincter leading to voiding of urine. Thus, the pudendal nerve is responsible for **voluntary control** of micturition.

■ FILLING OF URINARY BLADDER

■ PROCESS OF FILLING

Urine is continuously formed by nephrons and it flows into urinary bladder drop by drop through ureters. When urine collects in the pelvis of ureter, the contraction sets up in pelvis. This contraction is transmitted through rest of the ureter in the form of peristaltic wave up to trigone of the urinary bladder. **Peristaltic wave** usually travels at a velocity of 3 cm/second. It develops at a frequency of 1 to 5 per minute. The peristaltic wave moves the urine into the bladder.

After leaving the kidney, the direction of the ureter is initially downward and outward. Then, it turns horizontally before entering the bladder. At the entrance of ureters into urinary bladder, a valvular arrangement is present. When peristaltic wave pushes the urine towards bladder, this valve opens towards the bladder. The position of ureter and the valvular arrangement at the end of ureter prevent the back flow of urine from bladder into the ureter when the detrusor muscle contracts. Thus, urine is collected in bladder drop by drop.

A reasonable volume of urine can be stored in urinary bladder without any discomfort and without much increase in pressure inside the bladder **(intravesical pressure).** It is due to the adaptation of detrusor muscle. This can be explained by cystometrogram.

■ CYSTOMETROGRAM

Definition

Cystometry is the technique used to study the relationship between intravesical pressure and volume of urine in the bladder. Cystometrogram is the graphical registration (recording) of pressure changes in urinary bladder in relation to volume of urine collected in it.

Method of Recording Cystometrogram

A double-lumen catheter is introduced into the urinary bladder. One of the lumen is used to infuse fluid into the bladder and the other one is used to record the pressure changes by connecting it to a suitable recording instrument.

First, the bladder is emptied completely. Then, a known quantity of fluid is introduced into the bladder at regular intervals. The intravesical pressure developed by the fluid is recorded continuously. A graph is obtained by plotting all the values of volume and the pressure. This graph is the cystometrogram (Fig. 57.4).

Description of Cystometrogram

Cystometrogram shows three segments.

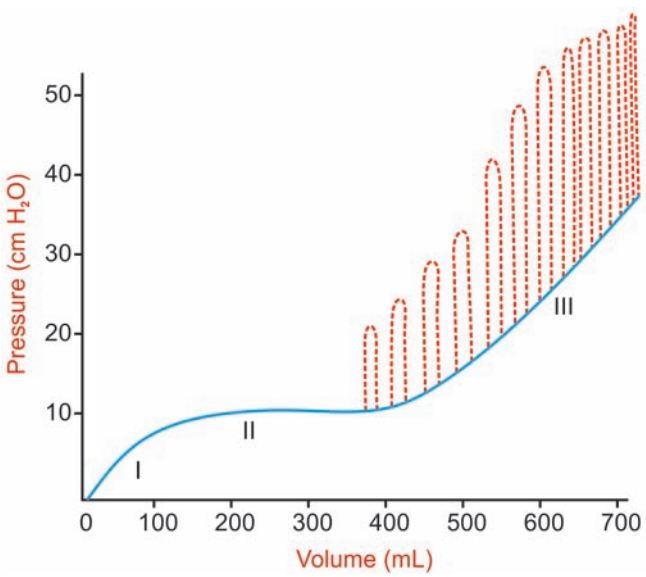


FIGURE 57.4: Cystometrogram. Dotted lines indicate the contraction of detrusor muscle.

Segment I

Initially, when the urinary bladder is empty, the intravesical pressure is 0. When about 100 mL of fluid is collected, the pressure rises sharply to about 10 cm H_2O.

Segment II

Segment II shows the plateau, i.e. no change in intravesical pressure. It remains at 10 cm H_2O even after introducing 300 to 400 mL of fluid. It is because of adaptation of urinary bladder by relaxation. It is in accordance with law of Laplace.

Law of Laplace

According to this law, the pressure in a spherical organ is inversely proportional to its radius, the tone remaining constant. That is, if radius is more, the pressure is less and if radius is less the pressure is more, provided the tone remains constant.

$$P = \frac{T}{R}$$

Where, P = Pressure
T = Tension
R = Radius

Accordingly in the bladder, the tension increases as the urine is filled. At the same time, the radius also increases due to relaxation of detrusor muscle. Because of this, the pressure does not change and plateau appears in the graph.

With 100 mL of urine and 10 cm H_2O of intravesical pressure, the desire for micturition occurs. Desire for micturition is associated with a vague feeling in the perineum. But it can be controlled voluntarily.

An additional volume of about 200 to 300 mL of urine can be collected in bladder without much increase in pressure. However, when total volume rises beyond 400 mL, the pressure starts rising sharply.

Segment III

As the pressure increases with collection of 300 to 400 mL of fluid, the contraction of detrusor muscle becomes intense, increasing the consciousness and the urge for micturition. Still, voluntary control is possible up to volume of 600 to 700 mL at which the pressure rises to about 35 to 40 cm H_2O.

When the intravesical pressure rises above 40 cm water, the contraction of detrusor muscle becomes still more intense. And, voluntary control of micturition is not possible. Now, pain sensation develops and micturition is a must at this stage.

■ MICTURITION REFLEX

Micturition reflex is the reflex by which micturition occurs. This reflex is elicited by the stimulation of stretch receptors situated on the wall of urinary bladder and urethra. When about 300 to 400 mL of urine is collected in the bladder, intravesical pressure increases. This stretches the wall of bladder resulting in stimulation of stretch receptors and generation of sensory impulses.

Pathway for Micturition Reflex

Sensory (afferent) impulses from the receptors reach the sacral segments of spinal cord via the sensory fibers of pelvic (parasympathetic) nerve. Motor (efferent) impulses produced in spinal cord, travel through motor fibers of pelvic nerve towards bladder and internal sphincter. Motor impulses cause contraction of detrusor muscle and relaxation of internal sphincter so that, urine enters the urethra from the bladder (Fig. 57.5).

Once urine enters urethra, the **stretch receptors** in the urethra are stimulated and send afferent impulses to spinal cord via pelvic nerve fibers. Now the impulses generated from spinal centers inhibit pudendal nerve. So, the external sphincter relaxes and micturition occurs.

Once a micturition reflex begins, it is **self-regenerative,** i.e. the initial contraction of bladder further activates the receptors to cause still further increase in sensory impulses from the bladder and urethra. These impulses, in turn cause further increase in reflex contraction of bladder. The cycle continues repeatedly until the force of contraction of bladder reaches the maximum and the urine is voided out completely.

During micturition, the flow of urine is facilitated by the increase in the abdominal pressure due to the voluntary contraction of abdominal muscles.

Higher Centers for Micturition

Spinal centers for micturition are present in sacral and lumbar segments. But, these spinal centers are regulated by higher centers. The higher centers, which control micturition are of two types, inhibitory centers and facilitatory centers.

Inhibitory centers for micturition

Centers in midbrain and cerebral cortex inhibit the micturition by suppressing spinal micturition centers.

Facilitatory centers for micturition

Centers in pons facilitate micturition via spinal centers. Some centers in cerebral cortex also facilitate micturition.

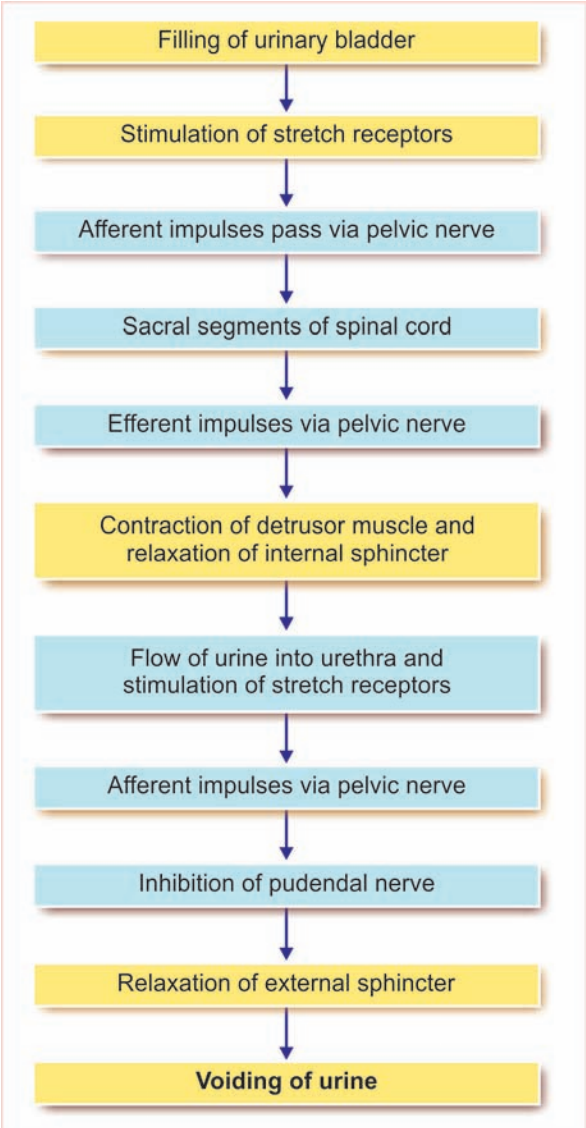


FIGURE 57.5: Micturition reflex

■ APPLIED PHYSIOLOGY – ABNORMALITIES OF MICTURITION

■ ATONIC BLADDER – EFFECT OF DESTRUCTION OF SENSORY NERVE FIBERS

Atonic bladder is the urinary bladder with loss of tone in detrusor muscle. It is also called **flaccid neurogenic bladder** or **hypoactive neurogenic bladder.** It is caused by destruction of sensory (pelvic) nerve fibers of urinary bladder.

Due to the destruction of sensory nerve fibers, the bladder is filled without any stretch signals to spinal cord. Due to the absence of stretch signals, detrusor muscle loses the tone and becomes **flaccid.** So the bladder is completely filled with urine without any micturition.

Now, urine overflows in drops as and when it enters the bladder. It is called **overflow incontinence** or **overflow dribbling.**

Conditions of Destruction of Sensory Nerve Fibers

1. *Spinal injury:* During the first stage (stage of spinal shock) after injury to sacral segments of spinal cord (Chapter 143) the bladder becomes atonic
2. *Syphilis:* Syphilis results in the degenerative nervous disorder called **tabes dorsalis,** which is characterized by the degeneration of dorsal (sensory) nerve roots (Chapter 143). Degeneration of sensory nerve roots of sacral region develops **atonic bladder.** The atonic bladder in tabes dorsalis is called **tabetic bladder.**

■ AUTOMATIC BLADDER

Automatic bladder is the urinary bladder characterized by hyperactive micturition reflex with loss of voluntary control. So, even a small amount of urine collected in the bladder elicits the micturition reflex resulting in emptying of bladder.

This occurs during the second stage (stage of recovery) after complete transection of spinal cord above the sacral segments.

During the first stage (stage of spinal shock) after complete transection of spinal cord above sacral segments, the urinary bladder loses the tone and becomes atonic resulting in **overflow incontinence.**

During the second stage after shock period, the micturition reflex returns. However, the voluntary control is lacking because of absence of inhibition or facilitation of micturition by higher centers. There is hypertrophy of detrusor muscles so that the capacity of bladder reduces. Some patients develop hyperactive micturition reflex.

■ UNINHIBITED NEUROGENIC BLADDER

Uninhibited neurogenic bladder is the urinary bladder with frequent and uncontrollable micturition caused by lesion in midbrain. It is also called **spastic neurogenic bladder** or **hyperactive neurogenic bladder.**

The lesion in midbrain causes continuous excitation of spinal micturition centers resulting in frequent and uncontrollable micturition. Even a small quantity of urine collected in bladder will elicit the micturition reflex.

■ NOCTURNAL MICTURITION

Nocturnal micturition is the involuntary voiding of urine during night. It is otherwise known as **enuresis** or

bedwetting. It occurs due to the absence of voluntary control of micturition. It is a common and normal process in infants and children below 3 years. It is because of incomplete myelination of motor nerve fibers of the bladder. When myelination is complete, voluntary control of micturition develops and bedwetting stops.

If nocturnal micturition occurs after 3 years of age it is considered abnormal. It occurs due to neurological disorders like **lumbosacral vertebral defects.** It can also occur due to psychological factors. Loss of voluntary control of micturition occurs even during the impairment of motor area of cerebral cortex.

Dialysis and **Artificial Kidney**

Chapter 58

DIALYSIS

Dialysis is the procedure to remove waste materials and toxic substances and to restore normal volume and composition of body fluid in severe renal failure. It is also called **hemodialysis.**

ARTIFICIAL KIDNEY

Artificial kidney is the machine that is used to carry out dialysis during renal failure. It is used to treat the patients suffering from:

1. Acute renal failure
2. Chronic or permanent renal failure.

MECHANISM OF FUNCTION OF ARTIFICIAL KIDNEY

The term **dialysis** refers to diffusion of solutes from an area of higher concentration to the area of lower concentration, through a semipermeable membrane. This forms the principle of artificial kidney.

Patient's arterial blood is passed continuously or intermittently through the artificial kidney and then back to the body through the vein. Heparin is used as an anticoagulant while passing the blood through the machine.

Inside the artificial kidney, the blood passes through a dialyzer called **hemofilter,** which contains minute channels interposed between two **cellophane membranes** (Fig. 58.1). The cellophane membranes are porous in nature. The outer surface of these membranes is bathed in the dialyzing fluid called **dialysate.** The used dialysate in the artificial kidney is constantly replaced by fresh dialysate.

Urea, creatinine, phosphate and other unwanted substances from the blood pass into the dialysate by concentration gradient. The essential substances required by the body diffuse from dialysate into blood. Almost all the substances, except plasma proteins are exchanged between the blood and dialysate through the cellophane membranes.

In addition to the dialyzer, the dialysis machine has several blood pumps with pressure monitors, which enable easy flow of blood from the patient to the machine and back to the patient. It also has pumps for flow of fresh dialysate and for drainage of used dialysate.

Total amount of blood in the dialysis machine at a time is about 500 mL. The rate of blood flow through the dialysis machine is about 200 to 300 mL/minute. The rate of dialysate flow is about 500 mL/minute.

FREQUENCY AND DURATION OF DIALYSIS

The frequency and duration of dialysis depends upon the severity of renal dysfunction. Dialysis is done usually thrice a week in severe uremia. Each time, the artificial kidney is used for about 6 hours.

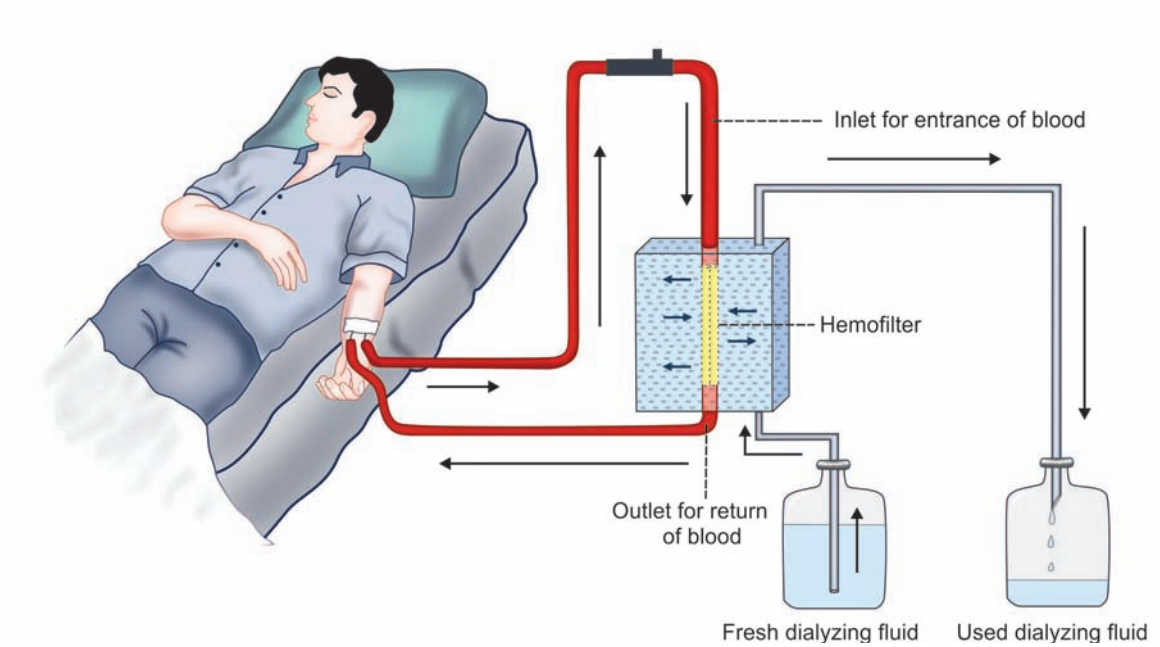


FIGURE 58.1: Principle of dialysis

■ DIALYSATE

The concentration of various substances in the dialysate is adjusted in accordance with the needs of the patient's body. The fluid does not contain urea, urate, sulfate, phosphate or creatinine, so that, these substances move from the blood to the dialysate.

The fluid has low concentration of sodium, potassium and chloride ions than in the uremic blood. But the concentration of glucose, bicarbonate and calcium ions is more in the dialysate than in the uremic blood.

■ PERITONEAL DIALYSIS

Peritoneal dialysis is the technique in which peritoneal membrane is used as a semipermeable membrane. It is also used to treat the patients suffering from renal failure.

A catheter is inserted into the peritoneal cavity through anterior abdominal wall and sutured. The dialysate is passed through this catheter under gravity. The required electrolytes from dialysate pass through vascular peritoneum into blood vessels of abdominal cavity. Urea, creatinine, phosphate and other unwanted substances diffuse from blood vessels into dialysate. Later, dialysate is drained from peritoneal cavity by gravity.

Peritoneal dialysis is a simple, convenient and less-expensive technique, compared to hemodialysis. Patients themselves can change the fluid on an outpatient basis. However, it has few drawbacks. It is less efficient in removing some of the toxic substances and it may lead to complications by infections.

■ UREMIA

Uremia is explained in Chapter 56. Blood level of urea, nitrogen and creatinine increases during uremia. Toxic substances such as organic acids and phenols also accumulate in blood.

Artificial kidney can excrete more than double the amount of urea that could be excreted by both the normal kidneys. About 200 to 250 mL of plasma could be cleared off urea per minute by the artificial kidney. But, the **urea clearance** by normal kidney is only about 70 mL/minute. Refer Chapter 55 for urea clearance test.

■ COMPLICATIONS OF DIALYSIS

Complications of dialysis depend upon the patient's condition, age, existence of diseases other than renal failure and many other factors.

Common complications of dialysis in individuals having only renal dysfunction are:

1. Sleep disorders
2. Anxiety
3. Depression.

Chapter 59

Diuretics

INTRODUCTION

Diuretics or **diuretic agents** are the substances which enhance the urine formation and output. These substances increase the excretion of water, sodium and chloride through urine. Diuretic agents increase the urine formation, by influencing any of the processes involved in urine formation. Diuretics are commonly called **'water pills'.**

GENERAL USES OF DIURETICS

Diuretics are generally used for the treatment of disorders involving increase in extracellular fluid volume like:

1. Hypertension
2. Congestive cardiac failure
3. Edema.

Diuretic agents prevent hypertension, congestive cardiac failure and edema, by increasing the urinary output and reducing extracellular fluid (ECF) volume.

ABUSES AND COMPLICATIONS OF DIURETICS

Nowadays, diuretics are misused in order to reduce the body weight and keep the body slim. Even persons suffering from eating disorders attempt to reduce body weight by misusing the diuretics.

However, prolonged use of these substances leads to complications like **syndrome of diuretic-dependent sodium retention,** characterized by edema. The adverse effects depend upon the type of diuretic agents used.

Adverse Effects of Diuretics

1. Dehydration
2. Electrolyte imbalance
3. Potassium deficiency
4. Headache
5. Dizziness
6. Renal damage
7. Cardiac arrhythmia
8. Heart palpitations.

TYPES OF DIURETICS

Diuretics are classified into seven types:

1. Osmotic diuretics
2. Diuretics which inhibit active reabsorption of electrolytes
3. Diuretics which inhibit action of aldosterone

4. Diuretics which inhibit activity of carbonic anhydrase
5. Diuretics which increase glomerular filtration rate
6. Diuretics which inhibit secretion of ADH
7. Diuretics which inhibit ADH receptors.

■ OSMOTIC DIURETICS

Osmotic diuretics are the substances that induce osmotic diuresis. Osmotic diuresis is the type of diuresis that occurs because of increased osmotic pressure. Some of the osmotically active substances are not reabsorbed from renal tubules. When injected in large quantities into the body, these substances increase the osmotic pressure in the tubular fluid. Increased osmotic pressure in the tubular fluid, in turn reduces water reabsorption. It leads to excretion of excess of water through urine.

Elevated blood sugar level in diabetes can also cause osmotic diuresis in the same manner.

Examples

i. Urea
ii. Mannitol
iii. Sucrose
iv. Glucose.

■ DIURETICS WHICH INHIBIT ACTIVE REABSORPTION OF ELECTROLYTES

Diuretics of this type inhibits the active reabsorption of electrolytes like sodium and potassium from the renal tubular fluid. Inhibition of electrolyte reabsorption causes osmotic diuresis. These diuretic agents are of three types:

1. *Loop Diuretics – Diuretics which Inhibit the Electrolyte Reabsorption in Thick Ascending Limb of Henle Loop*

Loop diuretics are the substances that inhibit electrolyte reabsorption in Henle loop. These diuretics inhibit the sodium and chloride reabsorption from thick ascending limb of Henle loop. So, the osmotic pressure in tubular fluid increases, leading to diuresis. The osmolarity of medullary interstitial fluid also decreases due to inhibition of sodium reabsorption into medullary interstitium. So, the medullary interstitium fails to concentrate the urine, resulting in loss of excess fluid through urine.

Examples

i. Furosemide
ii. Torasemide
iii. Bumetanide.

2. *Diuretics which Inhibit Active Transport of Electrolytes In Proximal Part of Distal Convoluted Tubule*

Diuretics of this type inhibit sodium reabsorption in proximal part of the distal convoluted tubules. These diuretics are usually called **thiazide and related diuretics.**

Examples

i. Chlorothiazide
ii. Metolazone
iii. Chlortalidone.

3. *Diuretics which Inhibit Active Transport of Electrolytes in Distal Part of Distal Convoluted Tubule and Collecting Duct*

Some of the diuretics inhibit reabsorption of sodium and excretion of potassium in distal portion of the distal convoluted tubule and collecting duct. Such substances are called **potassium-retaining diuretics** or **potassium-sparing diuretics.**

Examples

i. Triamterene
ii. Amiloride.

■ DIURETICS WHICH INHIBIT ACTION OF ALDOSTERONE

Some diuretics inhibit sodium reabsorption and potassium excretion in the distal convoluted tubule and collecting duct, by inhibiting the action of aldosterone. These substances are also called the potassium-retaining diuretics or **aldosterone antagonists.**

Examples

i. Spironolactone
ii. Eperenone.

■ DIURETICS WHICH INHIBIT ACTIVITY OF CARBONIC ANHYDRASE

Some diuretics inhibit the activity of carbonic anhydrase in proximal convoluted tubules and prevent reabsorption of bicarbonates from renal tubules, resulting in osmotic diuresis. Such diuretic agents are called **carbonic anhydrase inhibitors.** Acetazolamide is a carbonic anhydrase inhibitor.

■ DIURETICS WHICH INCREASE GLOMERULAR FILTRATION RATE

Some xanthines (alkaloids, used as mild stimulants) cause diuresis by increasing the glomerular filtration rate and to some extent by decreasing the sodium reabsorption.

Examples

i. Caffeine
ii. Theophylline.

■ DIURETICS WHICH INHIBIT SECRETION OF ANTIDIURETIC HORMONE

Some diuretics produce diuresis by inhibiting the secretion of ADH.

Examples

i. Water
ii. Ethanol.

■ DIURETICS WHICH INHIBIT ANTIDIURETIC HORMONE RECEPTORS

The antagonists of V2 receptors cause diuresis by inhibiting the receptors of antidiuretic hormone, thereby preventing the activity of this hormone.

Chapter 60

Structure of Skin

INTRODUCTION

Skin is the **largest organ** of the body. It is not uniformly thick. At some places it is thick and at some places it is thin. The average thickness of the skin is about 1 to 2 mm. In the sole of the foot, palm of the hand and in the interscapular region, it is considerably thick, measuring about 5 mm. In other areas of the body, the skin is thin. It is thinnest over eyelids and penis, measuring about 0.5 mm only.

LAYERS OF SKIN

Skin is made up of two layers:

I. Outer epidermis
II. Inner dermis.

EPIDERMIS

Epidermis is the outer layer of skin. It is formed by stratified epithelium. Important feature of epidermis is that, it does not have blood vessels (Fig. 60.1). Nutrition is provided to the epidermis by the capillaries of dermis.

Layers of Epidermis

Epidermis is formed by five layers:

1. Stratum corneum
2. Stratum lucidum
3. Stratum granulosum
4. Stratum spinosum
5. Stratum germinativum.

1. STRATUM CORNEUM

Stratum corneum is also known as **horny layer.** It is the outermost layer and consists of **dead cells,** which are called **corneocytes.** These cells lose their nucleus due to pressure and become dead cells. The cytoplasm is flattened with fibrous protein known as **keratin.** Apart from this, these cells also contain phospholipids and glycogen.

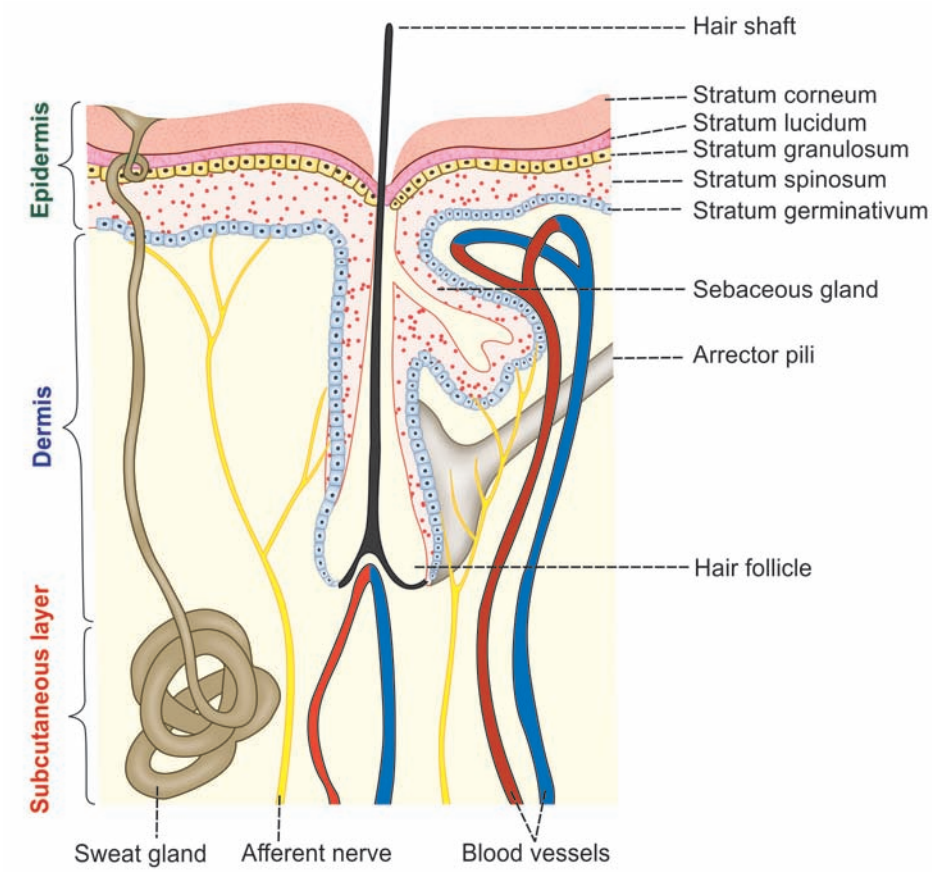


FIGURE 60.1: Structure of skin

■ 2. STRATUM LUCIDUM

Stratum lucidum is made up of flattened epithelial cells. Many cells have degenerated nucleus and in some cells, the nucleus is absent. As these cells exhibit shiny character, the layer looks like a **homogeneous translucent zone.** So, this layer is called stratum lucidum (lucid = clear).

■ 3. STRATUM GRANULOSUM

Stratum granulosum is a thin layer with two to five rows of flattened **rhomboid cells.** Cytoplasm contains granules of a protein called **keratohyalin.** Keratohyalin is the precursor of **keratin.**

■ 4. STRATUM SPINOSUM

Stratum spinosum is also known as **prickle cell layer** because, the cells of this layer possess some spine-like protoplasmic projections. By these projections, the cells are connected to one another.

■ 5. STRATUM GERMINATIVUM

Stratum germinativum is a thick layer made up of polygonal cells, superficially and columnar or cuboidal epithelial cells in the deeper parts. Here, new cells are constantly formed by mitotic division. The newly formed cells move continuously towards the stratum corneum. The stem cells, which give rise to new cells, are known as **keratinocytes.**

Another type of cells called **melanocytes** are scattered between the keratinocytes. Melanocytes produce the pigment called **melanin.** The color of the skin depends upon melanin.

From this layer, some projections called **rete ridges** extend down up to dermis. These projections provide anchoring and nutritional function.

■ DERMIS

Dermis is the inner layer of the skin. It is a connective tissue layer, made up of dense and stout collagen fibers,

fibroblasts and histiocytes. Collagen fibers exhibit elastic property and are capable of storing or holding water. Collagen fibers contain the enzyme collagenase, which is responsible for wound healing.

Layers of Dermis

Dermis is made up of two layers:

1. Superficial papillary layer
2. Deeper reticular layer.

■ SUPERFICIAL PAPILLARY LAYER

Superficial papillary layer projects into the epidermis. It contains blood vessels, lymphatics and nerve fibers. This layer also has some pigment-containing cells known as **chromatophores.**

Dermal papillae are finger-like projections, arising from the superficial papillary dermis. Each papilla contains a plexus of capillaries and lymphatics, which are oriented perpendicular to the skin surface. The papillae are surrounded by rete ridges, extending from the epidermis.

■ RETICULAR LAYER

Reticular layer is made up of reticular and elastic fibers. These fibers are found around the hair bulbs, sweat glands and sebaceous glands. The reticular layer also contains mast cells, nerve endings, lymphatics, epidermal appendages and fibroblasts.

Immediately below the dermis, subcutaneous tissue is present. It is a loose connective tissue, which connects the skin with the internal structures of the body. It serves as an insulator to protect the body from excessive heat and cold of the environment. Lot of smooth muscles called **arrector pili** are also found in skin around the hair follicles.

■ APPENDAGES OF SKIN

Hair follicles with hair, nails, sweat glands, sebaceous glands and mammary glands are considered as appendages of the skin.

■ COLOR OF SKIN

Color of skin depends upon two important factors:

1. Pigmentation of skin
2. Hemoglobin in the blood.

■ PIGMENTATION OF SKIN

Cells of the skin contain a brown pigment called **melanin,** which is responsible for the color of the skin. It is synthesized by **melanocytes,** which are present mainly in the stratum germinativum and stratum spinosum of epidermis. After synthesis, this pigment spreads to the cells of the other layers.

Melanin

Melanin is the skin pigment and it forms the major color determinant of human skin. Skin becomes dark when melanin content increases. It is protein in nature and it is synthesized from the amino acid tyrosine via dihydroxyphenylalanine (DOPA).

Deficiency of melanin leads to **albinism** (hypopigmentary congenital disorder).

■ HEMOGLOBIN IN THE BLOOD

Amount and nature of hemoglobin that circulates in the cutaneous blood vessels play an important role in the coloration of the skin.

Skin becomes:

i. Pale, when hemoglobin content decreases
ii. Pink, when blood rushes to skin due to cutaneous vasodilatation (blushing)
iii. Bluish during cyanosis, which is caused by excess amount of reduced hemoglobin.

Chapter 61

Functions of Skin

- FUNCTIONS OF SKIN
  - PROTECTIVE FUNCTION
  - SENSORY FUNCTION
  - STORAGE FUNCTION
  - SYNTHETIC FUNCTION
  - REGULATION OF BODY TEMPERATURE
  - REGULATION OF WATER AND ELECTROLYTE BALANCE
  - EXCRETORY FUNCTION
  - ABSORPTIVE FUNCTION
  - SECRETORY FUNCTION

FUNCTIONS OF SKIN

Primary function of skin is protection of organs. However, it has many other important functions also.

1. PROTECTIVE FUNCTION

Skin forms the covering of all the organs of the body and protects these organs from the following factors:

i. Bacteria and toxic substances
ii. Mechanical blow
iii. Ultraviolet rays.

i. *Protection from Bacteria and Toxic Substances*

Skin covers the organs of the body and protects the organs from having direct contact with external environment. Thus, it prevents the bacterial infection.

Lysozyme secreted in skin destroys the bacteria. Keratinized stratum corneum of epidermis is responsible for the protective function of skin. This layer also offers resistance against toxic chemicals like acids and alkalis. If the skin is injured, infection occurs due to invasion of bacteria from external environment.

During injury or skin infection, the keratinocytes secrete:

a. **Cytokines** like interleukins, α-tumor necrosis factor and γ-interferon, which play important role in inflammation, immunological reactions, tissue repair and wound healing
b. Antimicrobial peptides like β-defensins, which prevent invasion of microbes.

ii. *Protection from Mechanical Blow*

Skin is not tightly placed over the underlying organs or tissues. It is somewhat loose and moves over the underlying subcutaneous tissues. So, the mechanical impact of any blow to the skin is not transmitted to the underlying tissues.

iii. *Protection from Ultraviolet Rays*

Skin protects the body from **ultraviolet rays** of sunlight. Exposure to sunlight or to any other source of ultraviolet rays increases the production of **melanin** pigment in skin. Melanin absorbs ultraviolet rays. At the same time, the thickness of stratum corneum increases. This layer of epidermis also absorbs the ultraviolet rays.

2. SENSORY FUNCTION

Skin is considered as the **largest sense organ** in the body. It has many nerve endings, which form the specialized cutaneous receptors (Chapter 139).

These receptors are stimulated by sensations of touch, pain, pressure or temperature sensation and convey these sensations to the brain via afferent nerves. At the brain level, perception of different sensations occurs.

■ 3. STORAGE FUNCTION

Skin stores fat, water, chloride and sugar. It can also store blood by the dilatation of the cutaneous blood vessels.

■ 4. SYNTHETIC FUNCTION

Vitamin D3 is synthesized in skin by the action of ultraviolet rays from sunlight on cholesterol.

■ 5. REGULATION OF BODY TEMPERATURE

Skin plays an important role in the regulation of body temperature. Excess heat is lost from the body through skin by radiation, conduction, convection and evaporation. Sweat glands of the skin play an active part in heat loss, by secreting sweat. The lipid content of sebum prevents loss of heat from the body in cold environment. More details are given in Chapter 63.

■ 6. REGULATION OF WATER AND ELECTROLYTE BALANCE

Skin regulates water balance and electrolyte balance by excreting water and salts through sweat.

■ 7. EXCRETORY FUNCTION

Skin excretes small quantities of waste materials like urea, salts and fatty substance.

■ 8. ABSORPTIVE FUNCTION

Skin absorbs fat-soluble substances and some ointments.

■ 9. SECRETORY FUNCTION

Skin secretes **sweat** through **sweat glands** and **sebum** through **sebaceous glands.** By secreting sweat, skin regulates body temperature and water balance. Sebum keeps the skin smooth and moist.

Chapter 62

Glands of Skin

- GLANDS OF SKIN
- SEBACEOUS GLANDS
- SWEAT GLANDS
  - ECCRINE GLANDS
  - APOCRINE GLANDS

GLANDS OF SKIN

Skin contains two types of glands, namely sebaceous glands and sweat glands.

SEBACEOUS GLANDS

Sebaceous glands are simple or branched alveolar glands, situated in the dermis of skin.

Structure

Sebaceous glands are ovoid or spherical in shape and are situated at the side of the **hair follicle.** These glands develop from hair follicles. So, the sebaceous glands are absent over the thick skin, which is devoid of hair follicles. Each gland is covered by a connective tissue capsule. The alveoli of the gland are lined by stratified epithelial cells.

Sebaceous glands open into the neck of the hair follicle through a duct. In some areas like face, lips, nipple, glans penis and labia minora, the sebaceous glands open directly into the exterior.

Secretion of Sebaceous Gland – Sebum

Sebaceous glands secrete an oily substance called sebum. Sebum is formed by the liquefaction of the alveolar cells and poured out through the ducts either via the hair follicle or directly into the exterior.

Composition of Sebum

Sebum contains:

1. Free fatty acids
2. Triglycerides
3. Squalene
4. Sterols
5. Waxes
6. Paraffin.

Functions of Sebum

1. Free fatty acid content of the sebum has antibacterial and antifungal actions. Thus, it prevents the infection of skin by bacteria or fungi
2. Lipid nature of sebum keeps the skin smooth and oily. It protects the skin from unnecessary desquamation and injury caused by dryness
3. Lipids of the sebum prevent heat loss from the body. It is particularly useful in cold climate.

Activation of Sebaceous Glands at Puberty

Sebaceous glands are inactive till puberty. At the time of puberty, these glands are activated by sex hormones in both males and females.

At the time of puberty, particularly in males, due to the increased secretion of sex hormones, especially dehydroepiandrosterone, the sebaceous glands are stimulated suddenly. It leads to the development of acne on the face.

Acne

Acne is the localized inflammatory condition of the skin, characterized by pimples on face, chest and back. It occurs because of overactivity of sebaceous glands. Acne vulgaris is the common type of acne that is

developed during adolescence. Acne disappears within few years, when the sebaceous glands become adapted to the sex hormones.

■ SWEAT GLANDS

Sweat glands are of two types:
1. Eccrine glands
2. Apocrine glands.

■ ECCRINE GLANDS

Distribution

Eccrine glands are distributed throughout the body (Table 62.1). There are many eccrine glands over thick skin.

Structure

Eccrine sweat gland is a tubular coiled gland.

It consists of two parts:
1. A coiled portion lying deeper in dermis, which secretes the sweat
2. A duct portion, which passes through dermis and epidermis.

Eccrine sweat gland opens out through the sweat pore. The coiled portion is formed by single layer of columnar or cuboidal epithelial cells, which are secretory in nature. Epithelial cells are interposed by the **myoepithelial cells.** Myoepithelial cells support the secretory epithelial cells.

The duct of eccrine gland is formed by two layers of cuboidal epithelial cells.

Secretory Activity of Eccrine Glands

Eccrine glands function throughout the life since birth. These glands secrete a clear **watery sweat.** The secretion increases during increase in temperature and emotional conditions.

Eccrine glands play an important role in regulating the body temperature by secreting sweat. Sweat contains water, sodium chloride, urea and lactic acid.

Control of Eccrine Glands

Eccrine glands are under nervous control and are supplied by sympathetic postganglionic cholinergic nerve fibers, which secrete acetylcholine. Stimulation of these nerves causes secretion of sweat.

■ APOCRINE GLANDS

Distribution

Apocrine glands are situated only in certain areas of the body like axilla, pubis, areola and umbilicus.

Structure

Apocrine glands are also tubular coiled glands. The coiled portion lies in deep dermis. But, the duct opens into the hair follicle above the opening of sebaceous gland.

Secretory Activity of Apocrine Glands

Apocrine sweat glands are nonfunctional till puberty and start functioning only at the time of puberty. In old age, the function of these glands gradually declines.

The secretion of the apocrine glands is thick and milky. At the time of secretion, it is odorless. When microorganisms grow in this secretion, a characteristic odor develops in the regions where apocrine glands are present. Secretion increases only in emotional conditions.

TABLE 62.1: Differences between eccrine and apocrine sweat glands

Features	Eccrine glands	Apocrine glands
1. Distribution	Throughout the body	Only in limited areas like axilla, pubis, areola and umbilicus
2. Opening	Exterior through sweat pore	Into the hair follicle
3. Period of functioning	Function throughout life	Start functioning only at puberty
4. Secretion	Clear and watery	Thick and milky
5. Regulation of body temperature	Play important role in temperature regulation	Do not play any role in temperature regulation
6. Conditions when secretion increases	During increased temperature and emotional conditions	Only during emotional conditions
7. Control of secretory activity	Under nervous control	Under hormonal control
8. Nerve supply	Sympathetic cholinergic fibers	Sympathetic adrenergic fibers

Apocrine glands do not play any role in temperature regulation like eccrine glands.

Control of Apocrine Glands

Apocrine glands are innervated by sympathetic adrenergic nerve fibers. But, the secretory activity is not under nervous control. However, adrenaline from adrenal medulla causes secretion by apocrine glands.

Glands of eyelids, glands of external auditory meatus and mammary glands are the modified apocrine glands.

Pheromones

Pheromones are a group of chemical substances that are secreted by apocrine glands. Some scientists call this substance as **vomeropherins.** When secreted into environment by an organism, pheromones produce some behavioral or physiological changes in other members of the same species. Pheromones are mostly present in urine, vaginal fluid and other secretions of mammals and influence the behavior and reproductive cycle in these animals.

Details of pheromones in lower animals are well documented. However, human pheromones are not fully studied.

Recently, it is found that the pheromones excreted in axilla of a woman affects the menstrual cycle of her room-mate or other woman living with her. These substances stimulate receptors of vomeronasal receptors. **Vomeronasal receptors** are distinct from other olfactory receptors and detect specially the odor of pheromones. Impulses from these receptors are transmitted to hypothalamus, which influences the menstrual cycle via pituitary gonadal axis. This effect of pheromones on the menstrual cycle of other individuals is called **dormitory effect.** Refer Chapter 177 for details of vomeronasal organ and its receptors.

Chapter 63

Body Temperature

INTRODUCTION

Living organisms are classified into two groups, depending upon the maintenance (regulation) of body temperature:

1. Homeothermic animals
2. Poikilothermic animals.

HOMEOTHERMIC ANIMALS

Homeothermic animals are the animals in which the body temperature is maintained at a constant level, irrespective of the environmental temperature. Birds and mammals including man belong to this category. They are also called **warm-blooded animals.**

POIKILOTHERMIC ANIMALS

Poikilothermic animals are the animals in which the body temperature is not constant. It varies according to the environmental temperature. Amphibians and reptiles are the poikilothermic animals. These animals are also called **cold-blooded animals.**

BODY TEMPERATURE

Body temperature can be measured by placing the **clinical thermometer** in different parts of the body such as:

1. Mouth (oral temperature)
2. Axilla (axillary temperature)
3. Rectum (rectal temperature)
4. Over the skin (surface temperature).

NORMAL BODY TEMPERATURE

Normal body temperature in human is 37°C (98.6°F), when measured by placing the clinical thermometer in the mouth (oral temperature). It varies between 35.8°C and 37.3°C (96.4°F and 99.1°F).

TEMPERATURE AT DIFFERENT PARTS OF THE BODY

Axillary temperature is 0.3°C to 0.6°C (0.5°F to 1°F) lower than the **oral temperature.** The **rectal temperature** is 0.3°C to 0.6°C (0.5°F to 1°F) higher than oral temperature.

The superficial temperature (skin or surface temperature) varies between 29.5°C and 33.9°C (85.1°F and 93°F).

Core Temperature

Core temperature is the average temperature of structures present in deeper part of the body. The core temperature is always more than oral or rectal temperature. It is about 37.8°C (100°F).

■ VARIATIONS OF BODY TEMPERATURE

Physiological Variations

1. *Age*

In infants, the body temperature varies in accordance to environmental temperature for the first few days after birth. It is because the temperature regulating system does not function properly during infancy. In children, the temperature is slightly (0.5°C) more than in adults because of more physical activities. In old age, since the heat production is less, the body temperature decreases slightly.

2. *Sex*

In females, the body temperature is less because of low basal metabolic rate, when compared to that of males. During menstrual phase it decreases slightly.

3. *Diurnal variation*

In early morning, the temperature is 1°C less. In the afternoon, it reaches the maximum (about 1°C more than normal).

4. *After meals*

The body temperature rises slightly (0.5°C) after meals.

5. *Exercise*

During exercise, the temperature raises due to production of heat in muscles.

6. *Sleep*

During sleep, the body temperature decreases by 0.5°C.

7. *Emotion*

During emotional conditions, the body temperature increases.

8. *Menstrual cycle*

In females, immediately after ovulation, the temperature rises (0.5°C to 1°C) sharply. It decreases (0.5°C) during menstrual phase.

Pathological Variations

Abnormal increase in body temperature is called **hyperthermia** or **fever** and decreased body temperature is called **hypothermia** (Refer applied physiology in this Chapter).

■ HEAT BALANCE

Regulation of body temperature depends upon the balance between heat produced in the body and the heat lost from the body.

■ HEAT GAIN OR HEAT PRODUCTION IN THE BODY

Various mechanisms involved in heat production in the body are:

1. *Metabolic Activities*

Major portion of heat produced in the body is due to the metabolism of foodstuffs. It is called **heat of metabolism.**

Heat production is more during metabolism of fat. About 9 calories of heat is produced during metabolism of fats, when 1 L of oxygen is utilized. For the same amount of oxygen, carbohydrate metabolism produces 4.7 calories of heat. Protein metabolism produces 4.5 calories/L.

Liver is the organ where maximum heat is produced due to metabolic activities.

2. *Muscular Activity*

Heat is produced in the muscle both at rest and during activities. During rest, heat is produced by muscle tone. Heat produced during muscular activity is called **heat of activity.** About 80% of heat of activity is produced by skeletal muscles.

3. *Role of Hormones*

Thyroxine and adrenaline increase the heat production by accelerating the metabolic activities.

4. *Radiation of Heat from the Environment*

Body gains heat by radiation. It occurs when the environmental temperature is higher than the body temperature.

5. *Shivering*

Shivering refers to shaking of the body caused by rapid involuntary contraction or twitching of the muscles as during exposure to cold. Shivering is a compensatory physiological mechanism in the body, during which enormous heat is produced.

6. *Brown Fat Tissue*

Brown adipose tissue is one of the two types of adipose tissues, the other being white adipose tissue.

It produces enormous body heat, particularly in infants. Refer Chapter 47 for details.

HEAT LOSS FROM THE BODY

Maximum heat is lost from the body through skin and small amount of heat is lost through respiratory system, kidney and GI tract. When environmental temperature is less than body temperature, heat is lost from the body. Heat loss occurs by the following methods:

1. *Conduction*

Three percent of heat is lost from the surface of the body to other objects such as chair or bed, by means of conduction.

2. *Radiation*

Sixty percent of heat is lost by means of radiation, i.e. transfer of heat by infrared electromagnetic radiation from body to other objects through the surrounding air.

3. *Convection*

Fifteen percent of heat is lost from body to the air by convection. First the heat is conducted to the air surrounding the body and then carried away by air currents, i.e. convection.

4. *Evaporation – Insensible Perspiration*

When water evaporates, heat is lost. Twenty two percent of heat is lost through evaporation of water.

Normally, a small quantity of water is continuously evaporated from skin and lungs. We are not aware of it. So it is called the insensible perspiration or insensible water loss. It is about 50 mL/hour. When body temperature increases, sweat secretion is increased and water evaporation is more with more of heat loss.

5. *Panting*

Panting is the rapid shallow breathing, associated with dribbling of more saliva. In some animals like dogs which do not have sweat glands, heat is lost by evaporation of water from lungs and saliva by means of panting.

REGULATION OF BODY TEMPERATURE

Body temperature is regulated by hypothalamus, which sets the normal range of body temperature. The set point under normal physiological conditions is 37°C.

Hypothalamus has two centers which regulate the body temperature:

1. Heat loss center
2. Heat gain center.

HEAT LOSS CENTER

Heat loss center is situated in **preoptic nucleus** of anterior hypothalamus. Neurons in preoptic nucleus are heat-sensitive nerve cells, which are called **thermoreceptors** (Fig. 63.1).

Stimulation of preoptic nucleus results in cutaneous vasodilatation and sweating. Removal or lesion of this nucleus increases the body temperature.

HEAT GAIN CENTER

Heat gain is otherwise known as heat production center. It is situated in **posterior hypothalamic nucleus.** Stimulation of posterior hypothalamic nucleus causes shivering. The removal or lesion of this nucleus leads to fall in body temperature.

MECHANISM OF TEMPERATURE REGULATION

When Body Temperature Increases

When body temperature increases, blood temperature also increases. When blood with increased temperature passes through hypothalamus, it stimulates the thermoreceptors present in the heat loss center in preoptic nucleus. Now, the heat loss center brings the temperature back to normal by two mechanisms:

1. Promotion of heat loss
2. Prevention of heat production

1. *Promotion of heat loss*

When body temperature increases, heat loss center promotes heat loss from the body by two ways:

i. By increasing the secretion of sweat: When sweat secretion increases, more water is lost from skin along with heat

ii. By inhibiting sympathetic centers in posterior hypothalamus: This causes cutaneous vasodilatation. Now, the blood flow through skin increases causing excess sweating. It increases the heat loss through sweat, leading to decrease in body temperature.

2. *Prevention of heat production*

Heat loss center prevents heat production in the body by inhibiting mechanisms involved in heat production, such as shivering and chemical (metabolic) reactions.

When Body Temperature Decreases

When the body temperature decreases, it is brought back to normal by two mechanisms:

1. Prevention of heat loss
2. Promotion of heat production.

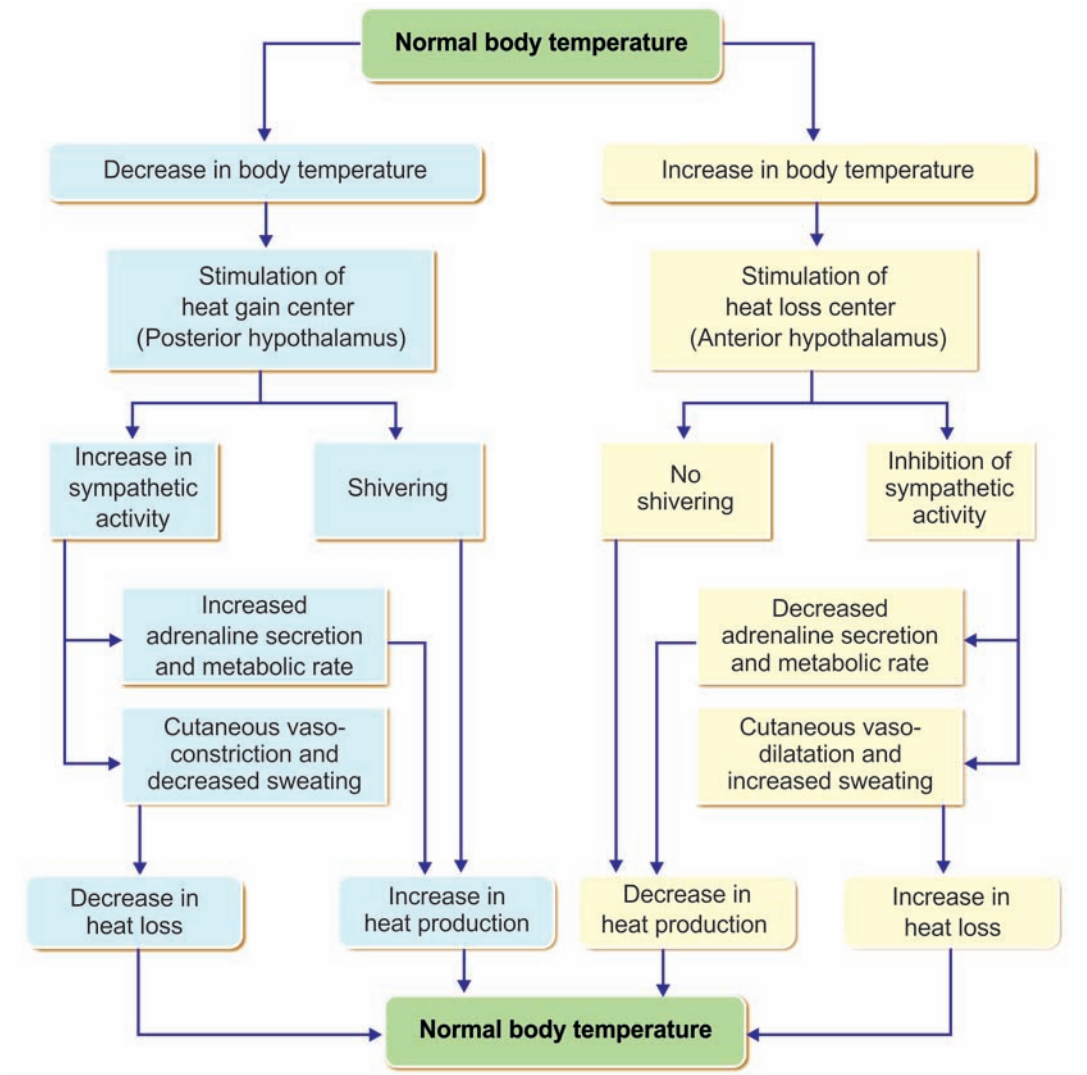


FIGURE 63.1: Regulation of body temperature

1. *Prevention of heat loss*

When body temperature decreases, sympathetic centers in posterior hypothalamus cause cutaneous vasoconstriction. This leads to decrease in blood flow to skin and so the heat loss is prevented.

2. *Promotion of heat production*

Heat production is promoted by two ways:

i. *Shivering:* When body temperature is low, the heat gain center stimulates the primary motor center for shivering, situated in posterior hypothalamus near the wall of the III ventricle and shivering occurs. During shivering, enormous heat is produced because of severe muscular activities.

ii. *Increased metabolic reactions:* Sympathetic centers, which are activated by heat gain center, stimulate secretion of adrenaline and noradrenaline. These hormones, particularly adrenaline increases the heat production by accelerating cellular metabolic activities.

Simultaneously, hypothalamus secretes thyrotropin-releasing hormone. It causes release of thyroid-stimulating hormone from pituitary. It in turn, increases release of thyroxine from thyroid. Thyroxine accelerates the metabolic activities in the body and this increases heat production.

Chemical thermogenesis: It is the process in which heat is produced in the body by metabolic activities induced by hormones.

APPLIED PHYSIOLOGY

HYPERTHERMIA – FEVER

Elevation of body temperature above the set point is called hyperthermia, fever or **pyrexia.** Fever itself is not

an illness. But it is an important sign of something going wrong in the body. It is the part of body's response to disease. Fever may be beneficial to body and on many occasions, it plays an important role in helping the body fight the diseases, particularly the infections.

Classification of Fever

Fever is classified into three categories:

1. *Low-grade fever:* When the body temperature rises to 38°C to 39°C, (100.4°F to 102.2°F)
2. *Moderate-grade fever:* When the temperature rises to 39°C to 40°C (102.2°F to 104°F)
3. *High-grade fever:* When the temperature rises above 40°C to 42°C (104°F to 107.6°F).

Hyperpyrexia

Hyperpyrexia is the rise in body temperature beyond 42°C (107.6°F). Hyperpyrexia results in damage of body tissues. Further increase in temperature becomes life threatening.

Causes of Fever

1. *Infection:* Certain substances (pyrogens) released from bacteria or parasites affect the heat-regulating system in hypothalamus, resulting in the production of excess heat and fever.
2. *Hyperthyroidism:* Increased basal metabolic rate during hyperthyroidism causes fever
3. *Brain lesions:* When lesion involves temperature-regulating centers, fever occurs.
4. *Diabetes insipidus:* In this condition, fever occurs without any apparent cause.

Signs and Symptoms

Signs and symptoms depend upon the cause of fever:

1. Headache
2. Sweating
3. Shivering
4. Muscle pain
5. Dehydration
6. Loss of appetite
7. General weakness.

Hyperpyrexia may result in:

1. Confusion
2. Hallucinations
3. Irritability
4. Convulsions.

■ HYPOTHERMIA

Decrease in body temperature below 35°C (95°F) is called hypothermia. It is considered as the clinical state of subnormal body temperature, when the body fails to produce enough heat to maintain the normal activities. The major setback of this condition is the impairment of metabolic activities of the body. When the temperature drops below 31°C (87.8°F), it becomes fatal. Elderly persons are more susceptible for hypothermia.

Classification of Hypothermia

Hypothermia is classified into three categories:

1. *Mild hypothermia:* When the body temperature falls to 35°C to 33°C (95°F to 91.4°F)
2. *Moderate hypothermia:* When the body temperature falls to 33°C to 31°C (91.4°F to 87.8°F)
3. *Severe hypothermia:* When the body temperature falls below 31° C (87.8°F).

Causes of Hypothermia

1. Exposure to cold temperatures
2. Immersion in cold water
3. Drug abuse
4. Hypothyroidism
5. Hypopituitarism
6. Lesion in hypothalamus
7. Hemorrhage in certain parts of the brainstem, particularly pons.

Signs and Symptoms

1. *Mild hypothermia*

Uncontrolled intense shivering occurs. The affected person can manage by self. But the movements become less coordinated. The chillness causes pain and discomfort.

2. *Moderate hypothermia*

Shivering slows down or stops but the muscles become stiff. Mental confusion and apathy (lack of feeling or emotions) occurs. Respiration becomes shallow, followed by drowsiness. Pulse becomes weak and blood pressure drops. Sometimes a strange behavior develops.

3. *Severe hypothermia*

The person feels very weak and exhausted with incoordination and physical disability. The skin becomes chill and its color changes to bluish gray. Eyes are dilated. The person looses consciousness gradually. Breathing slows down, followed by stiffness of arms and legs. Pulse becomes very weak and blood pressure decreases very much, resulting in unconsciousness.

Further drop in body temperature leads to death.

QUESTIONS IN RENAL PHYSIOLOGY AND SKIN

LONG QUESTIONS

1. Describe the process of urine formation.
2. What are the different stages of urine formation? Explain the role of glomerulus of nephron in the formation of urine.
3. Give an account of role of renal tubule in the process of urine formation.
4. What is countercurrent mechanism? Describe the anatomical and physiological basis of counter-current mechanism in kidney.
5. Describe the mechanism involved in the concentration of urine.
6. Describe the role of kidneys in maintaining acid-base balance.
7. Give an account of micturition.
8. What is normal body temperature? Explain heat balance and regulation of body temperature. Add a note on fever.

SHORT QUESTIONS

1. Functions of kidney.
2. Structure of nephron.
3. Renal corpuscle.
4. Juxtaglomerular apparatus.
5. Renin-angiotensin system.
6. Peculiarities of renal circulation.
7. Autoregulation of renal circulation.
8. Glomerular filtration rate.
9. Effective filtration pressure in kidney.
10. Tubuloglomerular feedback.
11. Glomerulotubular feedback.
12. Reabsorption of glucose in renal tubule.
13. Reabsorption of water in renal tubule.
14. Reabsorption of sodium in renal tubules.
15. Reabsorption of bicarbonate in renal tubules.
16. Secretion in renal tubule.
17. Renal failure.
18. Renal medullary gradient.
19. Countercurrent multiplier.
20. Countercurrent exchanger.
21. Actions of hormones on renal tubules.
22. Acidification of urine.
23. Role of kidney in maintaining acid-base balance.
24. Plasma clearance.
25. Measurement of glomerular filtration rate.
26. Measurement of renal blood (or plasma) flow.
27. Nerve supply to urinary bladder and sphincters.
28. Cystometrogram.
29. Micturition reflex.
30. Abnormalities of urinary bladder.
31. Dialysis/artificial kidney.
32. Diuretics/loop diuretics.
33. Renal failure.
34. Structure of skin.
35. Functions of skin.
36. Sebaceous glands.
37. Sweat glands.
38. Differences between eccrine glands and apocrine glands.
39. Pheromones.
40. Regulation of body temperature.
41. Role of hypothalamus in temperature regulation.
42. Heat balance.
43. Hyperthermia.
44. Hypothermia.