13
Urinary System

Physiological Anatomy of the Kidneys

General organization of the kidneys and urinary tract : The two kidneys lie on the posterior wall of the abdomen, outside the peritoneal cavity. Each kidney of the adult human weights about 150 grams and is about the size of a *clenched fist*. The medial side of each kidney contains an inverted region called the *hilum* through which pass the renal artery and vein, lymphatics, nerve supply, and ureter that carries the final urine from the kidney to the bladder, where it is stored until emptied. If the kidney is disected from top to bottom, the two major regions that can be visualized are the outer cortex and the inner region referred to as the medulla. The medulla of the kidney is divided into multiple cone shaped masses of tissue called renal pyramids. The base of each pyramid originates at the border between the cortex and medulla and terminates in the papilla, which projects into the space of the renal pelvis, a funnel-shaped continuation of the uper end of the ureter. The outer border of the pelvis is divided into open ended pouches called *major calices* that extend downward and divide into *minor calices*, which collect urine from the tubules of each papilla. The walls of the calices, pelvis, and ureter contain contractile elements that propel the urine toward the bladder, where urine is stored until it is emptied by micturition.

(Ref. Guyton & Hall 11th edition, page 308, 309)

In the kidneys, a fluid that resembles plasma is filtered through the glomerular capillaries into the renal tubules (*glomerular filtration*). As this glomerular filtrate passes down the tubules, its volume is reduced and its composition altered by the processes of *tubular reabsorption* (removal of water and solutes from the tubular fluid) and *tubular secretion* (secretion of solutes into the tubular fluid) to form the urine that enters the renal pelvis. A comparison of the composition of the plasma and an average urine specimen illustrates the magnitude of some of these changes and emphasizes the manner in which wastes are eliminated while water and important electrolites and metabolites are conserved. Furthermore, the composition of the urine can be varied, and many homeostatic regulatory mechanisms minimize or prevent changes in the composition of the ECF by changing the amount of water and various specific solutes in the urine. From the renal pelvis, the urine passes to the bladder and is expelled to the exterior by the process of *urination or micturition*.

The kidneys are also endocrine organs, making *kinins and 1,25-dihydroxy-cholecalciferol* and making and secreting *renin*.

The component parts of the Urinary system

1. A pair of kidneys : Form urine.
2. A pair of ureters : Convey urine from kidney to bladder.
3. A urinary bladder : Temporary reserviour of urine.
4. Urethra : Excrete urine from bladder to the exterior.

Nephron

I. *Definition* : It is the structural and functional unit of the kidney.

II. *Parts* : It consists of two parts :
   a. Glomerulus.
   b. Renal tubules : *It consists of-*
      i. Bowman's capsule
      ii. Proximal convoluted tubule
      iii. Loop of Henle
         * Descending limb of the loop of Henle
         * Ascending limb of the loop of Henle
      iv. Distal convoluted tubule
      v. Collecting tubule.

(Ref. Ganong 22th edition, page 699)

III. *Total number of nephron* : Each kidney in the human contains about ***1 million nephrons***, each capable of forming urine. The kidney cannot regenerate new nephrons. Therefore, with renal injury, disease, or normal aging, there is a gradual decrease in nephron number. After age 40, the number of functioning nephrons usually decreases about 10 per cent every 10 years; thus, at age 80, many people have 40 per cent fewer functioning nephrons than they did at age 40. This loss is not life-threatening because adaptive changes in the remaining nephrons allow them to excrete the proper amounts of water, electrolytes, and waste products.

(Ref. Guyton & Hall 11th edition, page 310)

There are approximately 1.3 million nephrons in each human kidney.

(Ref. Ganong 22th edition, page 699)

IV. *Total length of the nephrons* : The total length of the nephrons, including the collecting ducts, ranges from 45 to 65 mm.

(Ref. Ganong 22th edition, page 702)

Parts of the Kidney

Kidney consist of two parts :

1. *Outer cortex :* Reddish colour due to the large blood supply.
2. *Inner medulla :* Pale in colour due to the less blood supply.

Content of the cortex :

i. Renal corpuscles
   a. Glomerulus
   b. Bowman's capsule.
ii. Proximal convoluted tubules (PCT).
iii. Distal convoluted tubules (DCT) .
iv. Collecting tubules (CT).
v. Afferent and efferent arterioles.
vi. Peritubular capillary plexus.
vii. Juxta glomerular apparatus.

Content of the medulla :

i. Loop of Henle.
   a. Thin decending limb of the loop of Henle.
   b. Thick ascending limb of the loop of Henle.
ii. Collecting tubule.
iii. Vasa recta.

(Ref. Ganong 22th edition & Guyton 11th edition)

Renal corpuscle

Renal (Malpigian) corpuscle, are small rounded masses composed of two parts glomerulas and Bowman's capsule.

i. *Glomerulus* : It is about 200 micrometer in diameter. It is formed by the invagination of a tuft of capillaries into the dilated blind end of the nephron (*Bowman's capsule*). The capillaries are supplied by an *afferent arteriole* and drained by slightly smaller *efferent arteriole*.
ii. *Bowman's capsule* : It is the initial dilated part of the renal tubule which contains an invaginated tuft of capillaries- *the glomerulus*.

Glomerular membrane : There are two cellular layers seperating the blood from the glomerular filtrate in Bowman's capsule :

a. *Endothelium of the glomerular capillaries* : The endothelium of the glomerular capillaries is fenestrated, with pores that are 70-90 nm in diameter.
b. *Epithelium of the Bowman's capsule* : The specialized epithelium of the Bowman's capsule that is made up of *podocytes* overlying the capillaries. The cells of the epithelium *(podocytes)* have numerous pseudopodia that interdigitate to form filtration slits along the capillary wall. The slits are approximately 25 nm wide, and each is closed by a thin membrane.
c. *Basal lamina* : The capillary endothelium and the epithelium of the Bowman's capsule are seperated by a basal lamina. The basal lamina does not contain visible gaps or pores. Stellate cells called *mesangial cells* are located between the basal lamina and the endothelium. Mesangial cells are contractile and play a role in the regulation of glomerular filtration. They also secrects various substances, take up immune complexes, and are involved in the production of glomerular disease.

Function of the glomerular membrane : Functionally the glomerular membrane permits the free passage of neutral substances up to 4 nm in diameter and almost totally excludes those with diameters greater than 8 nm. However, the charges on molecules as well as their diameters affect their passage into Bowman's capsule. The total area of glomerular capillary endothelium across which filtration occurs in humans is about 0.8 m^2.

(Ref. Ganong 22th edition, page 699, 700)

Q. **Why proteins cannot pass through the glomerular membrane?**

Ans. The pores of the membrane are larger (80 Å or 8 nanometer) than the molecular diameter of the plasma protein-albumin (6 nanometer), yet the protein can not pass through the membrane. Because the glomerular pores are lined with a complex of glycosylated proteins that have very strong negative electrical charges. The plasma proteins also have strong negative electrical charges. Therefore, electrostatic repulsion of the protein molecules by the pores walls keeps these molecules from passing through.

(Ref. Guyton & Hall 11th Edition; Page 317)

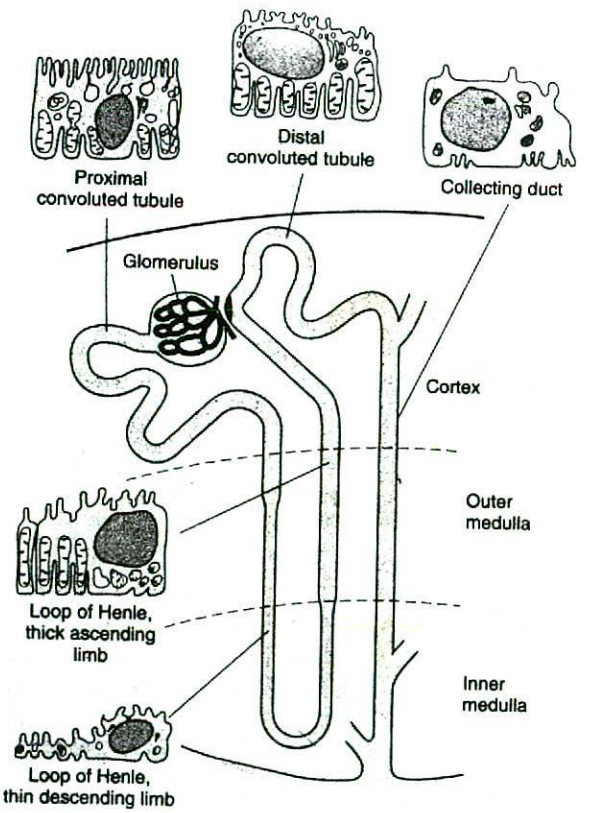


Fig. 13-1. Diagram of a juxtamedullary nephrone. The main histologic features of the cells that make up each prtion of the tubule are also shown.

Proximal convoluted tubule

The human *proximal convoluted tubule* is about 15 micro meter long and 55 micro meter in diameter. Its wall is made up of a single layer of cells that interdigitate with one another and are united by apical tight junctions. Between the bases of the cells, there are extensions of the extracellular space called the *lateral intercellular spaces*. The luminal edges of the cells have a striate *brush border* due to the presence of innumerable 1 x 0.7 micro meter microvilli.

The *convoluted portion of the proxial tubule* (pars convoluta) drains into the straight portion (pars recta), which forms the first part of the loop of Henle.

(Ref. Ganong 22th edition, page 700)

Loops of Henle

The nephrons with glomeruli in the outer portions of the renal cortex have short loops of Henle (*cortical nephrons*), whereas those with glomeruli in the juxtamedullary region of the cortex (juxtamedullary nephrons) have long loops extending down into the medullary pyramids. In humans, only 15% of the nephrons have long loops.

i. *Thin segment of the decending limb of the loop of Henle* : It has an epithelium made up of attenuated, flat cells. The total length of the thin segment of the loop varies from 2 to 14 mm. It ends in the thick segment of the asceding limb.

ii. *Thick segment of the asceding limb of the loop of Henle* : It is about 12 mm in length. The cells of the *thick ascending limb* are cuboid. They have numerous mitochondria, and the basilar portions of their cell membranes are extensively invaginated.

The thick ascending limb of the loop of Henle reaches the glomerulus of the nephron from which the tubule arose and passes close to its afferent arteriole and efferent arteriole. The

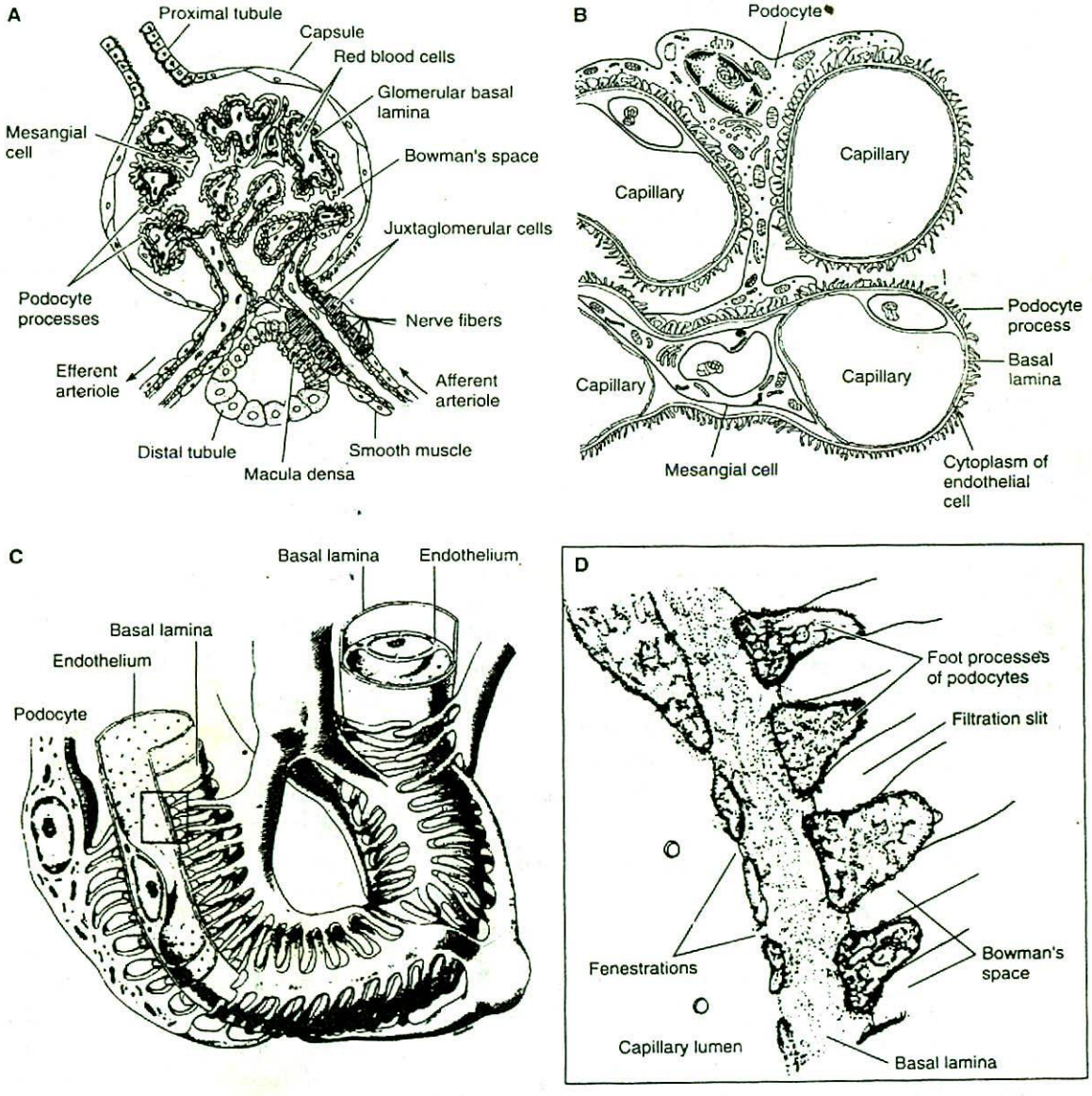


Fig. 13-2. Stuctural details of glomerulus. A: Section through vascular pole, showing capillary loops. B: Relation of mesangial cells and podocytes to glomerular capillaries. C: Detail of the way podocytes form filtration slits on the basal lamina, and the relation of the lamina to the capillary endothelium. D: Enlargement of the rectangle in C to show the podocyte processes.

walls of the afferent arterioles contain the *renin-secreting* juxtaglomerular cells. At this point, the tubular epithe- lium is modified histologically to form the *macula densa*. The juxtaglomerular cells and the macula densa, and the lacis cells near them are known collectively as the *juxtaglomerular apparatus.*

(Ref. Ganong 22th edition, page-700)

Distal convoluted tubule : The *distal convoluted tubule* is about 5 mm long. Its epithelium is lower than that of the proximal tubule, and although there are a few microvilli, there is no distinct brush border.

(Ref. Ganong 22th edition, page-700)

Collecting ducts : The distal tubules coalesce to form *collecting ducts* that are about 20 mm long and pass through the renal cortex and medulla to empty into the pelvis of the kidney at the apexes of the medullary pyramids. The epithelium of the collecting ducts is made up of-

i. *Principal cells (Pcells)* : The P cells, which predominate, are relatively tall and have few organelles.

Function : They are involved in Na^+ reabsorption and vasopressin stimulated water reabsorption.

ii. *Intercalated cells (I cells)* : The I cells, which are present in smaller numbers and are also found in the distal tubules, have more microvilli, cytoplasmic vesicles, and mitochondria.

Function : They are concerned with acid secretion and HCo_3^- transport.

(Ref. Ganong 22th edition, page-700)

N.B.

Cells in the kidneys that appear to have a secretory function include not only the juxtaglomerular cells but also some of the cells in the interstitial tissue of the medulla. These cells are called ***type I medullary interstitial cells***. They contain lipid droplets and probably secrete prostaglandins, predominantly PGE_2. PGE_2 is also secreted by the cells in the collecting ducts, and prostacyclin (PGI_2) , as well as other prostaglandins are secreted by the arterioles and glomeruli.

(Ref. Ganong 22th edition, page-702)

Agents causing contraction or relaxation of mesangial cells

Contraction	*Relaxation*
Endothelins	ANP
Angiotensin II	Dopamin
Vasopressin	PGE_2
Norepinephrine	cAMP
Platelet activating factor	
Platelet derived growth factor	
Thromboxane A_2	
PGE_2	
Leukotriens C_4 and D_4	
Histamine.	

Multiple function of the kidneys in homeostasis

Most people are familiar with one important function of the kidneys- to rid the body of waste materials that are either ingested or produced by metabolism. A second function that is especially critical is to control the volume and composition of the body fluids. For water and virtually all electrolytes in the body, balance between intake (due to ingestion or metabolic production) and output (due to excretion or metabolic consumption) is maintained in large part by the kidneys. This regulatory function of the kidneys maintains the stable environment of the cells necessary for them to perform their various activities.

The kidneys perform their most important functions by filtering the plasma and removing substances from the filtrate at variable rates, depending on the needs of the body. Ultimately, the kidneys "clear" unwanted substances from the filtrate (and therefore from the blood) by excreting them in the urine while returning substances that are needed back to the blood.

Kidneys serve multiple functions, including the following

1. Excretion of metabolic waste products and foreign chemicals.
2. Regulation of water and electrolyte balances.
3. Regulation of body fluid osmolality and electrolyte concentrations.
4. Regulation of acid-base balance.
5. Regulation of arterial pressure.
6. Secretion, metabolism, and excretion of hormones
7. Gluconeogenesis.

(Ref. Guyton & Hall 11th Edition, Page 307)

Description of the kidney functions :

i. *Excretion of metabolic waste products, foreign chemicals, drugs, and hormone metabolites* : The kidneys are the primary means for eliminating waste products of metabolism that are no longer needed by the body. These products include *urea* (from the metabolism of amino acids), *creatinine* (from muscle creatine), *uric acid* (from nucleic acids), the end products of hemoglobin breakdown (such as *bilirubin*), and metaholites of various *hormones*. These waste products must be eliminated from the body as rapidly as they are produced. The kidneys also eliminate most *toxins* and other foreign substances that are either produced by the body or ingested, such as *pesticides, drugs, and food additives.*

ii. *Regulation of water and electrolyte balances* : For maintenance of homeostasis, excretion of water and electrolytes must precisely match intake. If intake exceeds excretion, the amount of that substance in the body will increase. If intake is less than excretion, the amount of that substance in the body will decrease.

Intakes of water and many electrolytes usually are governed mainly by a person's eating and drinking habits, necessitating that the kidneys adjust their excretion rates to match intakes of the various substances.

Response of the kidneys to a sudden 10-fold increase in

sodium intake from a low level of 30 mEq/day to a high level of 300 mEq/day is that within 2 to 3 days after raising sodium intake, renal excretion also increases to about 300 mEq/day, so that a balance between intake and output is re-established. However, during the 2 to 3 days of renal adaptation to the high sodium intake, there is a modest accumulation of sodium that raises extracellular fluid volume slightly and triggers hormonal changes and other compensatory responses that signal the kidneys to increase their sodium excretion.

The capacity of the kidneys to alter sodium excretion in response to changes in sodium intake is enormous. Experimental studies have shown that in many people, sodium intake can be increased to 1500 mEq/day (more than 10 times normal) or decreased to 10 mEq/day (less than 1/10 normal) with relatively small changes in extracellular fluid volume or plasma sodium concentration. This is also true for water and for most other electrolytes, such as chloride, potassium, calcium, hydrogen, magnesium, and phosphate ions.

iii. *Regulation of arterial pressure* : Kidneys play a dominant role in long-term regulation of arterial pressure by excreting variable amounts of sodium and water. In addition, the kidneys contribute to short-term arterial pressure regulation by secreting vasoactive factors or substances, such as renin, that lead to formation of vasoaetive products (for example, angiotensin II).

iv. *Regulation of acid-base balance* : The kidneys contribute to acid-base regulation, along with the lungs and body fluid buffers, by excreting acids and by regulating the body fluid buffer stores. The kidneys are the only means for eliminating from the body certain types of acids generated by metabolism of proteins, such as sulfuric acid and phosphoric acid.

v. *Regulation of erythrocyte production* : The kidneys secrete erythropoietin, which stimulates the production of red blood cells. One important stimulus for erythropoietin secretion by the kidneys is hypoxia. In the normal person, the kidneys account for almost all the erythropoietin secreted into the circulation. In people with severe kidney disease or who have had their kidneys removed and have been placed on hemodialysis, severe anemia result of decreased erythropoietin production.

vi. *Regulation of 1,25-dihydroxy vitamin D_3 production* : The kidneys produce the active form of vitamin D, 1 ,25-dihydroxy vitamin D_3 (*calcitriol*) by hydroxylating this vitamin at the number '1' position. Calcitriol is essential for normal calcium deposition in bone and calcium reabsorption by the gastrointestinal tract.

vii. *Glucose synthesis* : The kidneys synthesize glucose from amino acids and other precursors during prolonged fasting, a process referred to as *gluconeogenesis*. The kidneys' capacity to add glucose to the blood during prolonged periods of fasting rivals that of the liver.

(Ref. Guyton & Hall 11th Edition, Page 307, 308)

With chronic kidney disease or acute failure of the the kidneys, these homeostatic functions are disrupted, and severe abnormalities of body fluid volumes and composition rapidly occur. With complete renal failure, enough accumulation in the body of potassium, acids, fluid and other substances occurs within a few days to cause death, unless clinical interventions such as hemodialysis are initiated to restore, at least partially, the body fluid and electrolyte balances.

(Ref. Guyton & Hall 11th Edition, Page-280)

Hormones of the kidneys

The kidneys produce three hormones :

1. *1,25-dihydroxycholecalciferol* : It increases the absorption of ca^{++}.
2. *Renin* : It Converts angiotensinogen into angiotensinogen-I. Angiotensinogen-I then converted into angiotensinogen-II which increases the systolic and diastolic blood pressure by vasoconstriction.
3. *Erythropoietin* : It increases the synthesis of haemoglobin, and production and release of red blood cells from the bone marrow- during hypoxia or anaemia.

Hormones that act on kidneys

Hormones that act on the kidneys are :

i. Vasopressin or anti-diuretic hormone-ADH
ii. Aldosterone
iii. Parathyroid hormone
iv. Catcitonin
v. Atrial natriuretic peptide-ANP

Vasopressin : Antidiuretic hormone (ADH) or vasopressin is secreted from the posterior pituitary gland due to osmotic stimuli i.e. hyperosmolarity and non-osmotic stimuli i.e hypovolaemia.

i. *Major site of action of ADH* : is the V_2-receptor in the basolateral membrane of the cells of distal tubule, collecting tubule and collecting duct.
ii. *Function* :
   a. Increase H_2O reabsorption from distal tubule, collecting tubule and collecting duct by increasing permeability to H_2O.
   b. Decrease in renal medullary blood flow.

Aldosterone : Aldosterone is a steroid hormone, secreted from the Zona glomerulosa of the adrenal cortex. Renin-angiotensin system regulates aldosterone secretion in addition to hyponatraemia, hyperkalaemia and excessive ACTH.

Physiological effects on renal tubules are :

i. Primary action : Conservation of Na^+ from distal tubule, collecting tubule and collecting ducts by

stimulation of the Na^+-K^+ / Na^+-H^+ cation exchange process.

ii. Secondary effects : Secretion of K^+ and H^+ into the tubules.

iii. On GFR : It has no direct effect on GFR, renal plasma flow or renin production. By stimulating Na reabsorption aldosterone causes passive water retention and the resulting expansion of ECF volume. Then leads to an increase in GFR and renal blood flow and a decrease in renin production.

Parathyroid hormone : It is secreted by the four parathyroid glands. It level rises as serum calcium falls.

Physiological effects on renal tubules are :

i. Increased tubular reabsorption of calcium

ii. Increased excretion of phosphate (by inhibiting reabsorption).

Calcitonin : Calcitonin is produced by thyroid C-cells.

Physiological effects on renal tubules are :

i. Increased excretion of calcium and phosphate

ii. Inhibits renal 1 alpha-hydroxylase activity, which leads to a decrease in the synthesis of calcitriole.

Atrial natriuretic peptide-ANP : ANP is released from atrial cardiocytes. It exerts a hormonal influence on kidneys, which results in changes in intrarenal hemodynamics.

Physiological effects on renal tubules are :

i. Increases GFR

ii. Dilatation of the afferent arterioles

iii. Natriuresis i.e increased urinary Na^+ excretion

iv. Inhibition of renin secretion.

Renal blood supply

Blood flow to the two kidneys is normally about 22 per cent of the cardiac output, or 1100 ml/minute. The ***renal artery*** enters the kidney through the hilum and then branches progressively to form the *interlobar arteries*, *arcuate arteries*, *interlobular arteries* (also called radial arteries), and *afferent arterioles*, which lead to the glomerular capillaries, where large amounts of fluid and solutes (except the plasma proteins) are filtered to begin urine formation. The distal ends of the capillaries of each glomerulus coalesce to form the *efferent arteriole*, which leads to a second capillary network, the *perituhular capillaries*, that surrounds the renal tubules.

The renal circulation is unique in that it has two capillary beds, the *glomerular and peritubular capillaries*, which are arranged in series and separated by the efferent arterioles that help to regulate the hydrostatic pressures in both sets of capillaries. High hydrostatic pressure in the glomerular capillaries (about *60 mm of Hg*) causes rapid fluid filtration, whereas a much lower hydrostatic pressure in the peritubular capillaries (about *13 mm Hg*) permits rapid *fluid reabsorption*. By adjusting the resistances of the afferent and efferent arterioles, the kidneys can regulate the hydrostatic pressures in both the glomerular and the peritubular capillaries, thereby changing the rate of glomerular filtration and/or tubular reabsorption in response to body homeostatic demands.

The peritubular capillaries empty into the vessels of the venous system, which run parallel to the arteriolar vessels and progressively form the *interlobular vein, arcuate vein, interlobar vein, and renal vein*, which leaves the kidney beside the renal artery and ureter.

(Ref. Guyton & Hall 11th edition, page 309)

Blood flow to the two kidneys is about 1.2 - 1.3 L/minute or just under 25% of the cardiac output.

(Ref. Ganong 22th edition, page-702)

Autoregulation of renal blood flow : The process by which the renal blood flow remain near the normal level despite considerable change in the arterial pressure, is called autoregulation of renal blood flow.

(Ref. Guyton & Hall 11th edition, page 323)

Mechanism of autoregulation of renal blood flow : The renal blood flow is autoregulated by the following ways :

a. Afferent arteriolar vasodilator feed back mechanism : Please see autoregulation of GFR.

b. Myogenic mechanism : When arterial pressure rises, it stretches the wall of the ateriole, this inturn causes secondary contraction of arteriole and decreases renal blood flow back toward normal.

(Ref. Guyton & Hall 11th edition, page 325)

Peculiarities of the renal circulation

a. ***Anatomical peculiarities of the renal artery*** :

i. After only a relatively few branching of the renal artery, the glomerular capillaries are formed. The efferent arteriole from the glomerulus is narrower than the afferent. For these reasons, the capillary blood pressure in the renal glomerulus is rather high, about 45 or 60 mm Hg. This high blood pressure in the glomerular capillaries facilitates the filtration.

ii. The efferent arteriole from the glomerulus however offers considerable resistance to the flow of blood and, as a result, the blood pressure falls beyond the efferent arteriole. In the peritubular capillary, it is only 13 or 8 mm Hg or so. This facilitates reabsorption from the tubules.

iii. In the vasa recta, velocity of circulation is very slow. This helps to preserve the medullary gradient.

iv. The direction of the flow of blood in the vasa recta and its U shaped loop, also help to preserve the medullary gradient and conservation of water by the kindey.

v. Mesangial cells can control the diameter of the glomerular capillaries and thus the GFR.

b. ***Functional specialities of the renal artery*** :

i. The renal blood (or plasma) flow is very high, plasma flow being about 650 ml/min.

ii. Renal vessels are constricted by the traditional agents : sympathetic stimulation, adrenaline or noradrenalin administration. Angiotensin II stimulates mainly the afferent arterioles to the glomerulus. Fever, due to most causes, causes renal vasodilatation. Anoxia causes renal vasoconstriction.

iii. Autoregulation of renal blood flow is remarkable. Between say (80-180) mm of Hg of systemic blood pressure, the glomerular flow is not affected.

Difference between glomerular and peritubular capillary

Glomerular capillary	*Peritubular capillary*
i. It opens in the efferent arteriole (Arterial end).	i. It opens in the venules (Venous end).
ii. It is high pressure capillary bed (60 or 45 mm of Hg).	ii. It is low pressure capillary bed (13 or 8 mm of Hg).
iii. Here filtration occurs.	iii. Here reabsorption occurs.
iv. It receives blood from afferent arteriole.	iv. It receives blood from efferent arteriole.
v. It remains invaginated inside the Bowman's capsule.	v. It remains outside the Bowman's capsule & arranged around the PCT, DCT & CT.

Blood pressure in renal vessels

Vessels	*Pressure in vessels (mm of Hg)*	
	Beginning	*End*
1. *Renal artery*	*100*	*100*
2. *Interlobar, arcuate and interlobular arteries*	*100*	*85*
3. Afferent arteriole	85	60
4. Glomerular capillaries	60	59
5. *Efferent arteriole*	*59*	*18*
6. *Peritubular capillaries*	*18*	*08*
7. Interlobar, arcuate and interlobular vein	08	04
8. *Renal vein*	*04*	*~ 04*

(Ref. Guyton. & Hall 11th edition, page 321)

Pressure in the renal tubules

1. Bowman's capsule : 18 mm of Hg
2. Proximal convoluted tubules : 18 mm of Hg
3. Distal convoluted tubules : 10 mm of Hg
4. Colltecting tubules : 02 mm of Hg
5. Renal pelvis : 00 mm of Hg
6. Interstitial fluid : 06 mm of Hg.

(Ref. Guyton & Hall 11th edition).

Glomerular filtration (GF)

Definition : The filtration that occurs through the glomerular capillary is called glomerular filtration.

Causes (Dynamics) of glomerular filtration : Due to the effective filtration pressure glomerular filtration (GF) occurs. The pressure inside the glomerular capillaries promotes glomerular filtration. On the other hand colloidal osmotic pressure in blood and the pressure in the Bowman's capsule opposes the filtration.

1. *Factors favouring filtration (mm of Hg)* :
   a. Glomerular hydrostaticy pressure : 60
   b. Bowman's capsule colloid osmotic pressure : 0
2. *Factors opposing filtration (mm of Hg)* :
   a. Bowman's capsule hydrostatic pressur : 18
   b. Glomerular capillary colloidal osmotic pressure : 32

So net filtration pressure = 60 - (18 + 32) mm of Hg
= + 10 mm of Hg.

So net filtration pressure +10 mm of Hg causes the filtration of glomerular filtrate.

(Ref. Guyton & Hall 11th edition, page 318)

Glomerular filtrate

The fluid that filters through the glomerulus into Bowman's capsule is called glomerular filtrate.

Normal glomerular filtrate = 180 liter/day.
= 7.5 liter/hour
= 125 ml/minute

P^H of glomerular filtrate = 7.4

(Ref. Ganong 22th edition, page 706)

Composition of glomerular filtrate (character) :

Its composition is as the fluid that filters from the arterial ends of the capillaries into the interstitial fluid.

1. It is isotonic to plasma (osmotic pressure- 300 mosm/liter).
2. It is devoid of cellular elements, including red blood cells.
3. It is essentially protein free, may contains about 0.03% protein, or about 1/240, the protein in the plasma.

4. The electrolyte and other solute composition is similar to that of plasma. But-
   a. The concentration of the nonprotein negative ions (Cl^-, HCO_3- etc) are 5% higher than plasma.
   b. The concentration of positive ions are about 5% lower than plasma.
   c. Almost one half of the plasma calcium and most of the fatty acids are bound to proteins, and these bound proteins are not filtered through the glomerular capillaries.

Summary : Glomerular filtrate is the same as the plasma except that it has no significant amount of protein.

(Ref. Guyton & Hall-11th Edition and others)

Difference between glomerular filtrate & Urine

Glomerular filtrate	*Urine*
1. It is alkaline pH- 7.4.	1. It is always acidic pH - 5.5-6.5.
2. It is isotonic to plasma (300 mosm/l).	2. It is hypertonic to plasma.
3. It is about 180 liters /day.	3. It is about 1.2-1.5 liters/ day.
4. Glomerular filtration rate-125ml/min.	4. Urine formation rate - 1ml/min.
5. It's composition is near ly similar to plasma.	5. It is not similar to plasma.

Glomerular Filtration Rate (GFR)

Definition : The quantity of glomerular filtrate formed in each minute by all the nephrones of both kidneys is called glomerular filtration rate (GFR).

Normal values : The GFR in an average-sized normal man is approximately 125 ml/minute.

i. Its magnitude correlates fairly well with surface area, but values in women are 10% lower than those in men even after correction for surface area.

ii. A rate of 125 ml/minute is 7.5 litres/hour or 180 litres/day, where as the normal urine volume is about 1 L/day.

iii. Thus, 99% or more of the filtrate is normally reabsorbed.

iv. At the rate of 125 mL/minute, the kidneys filter in 1 day an amount of fluid equal to 4 times the total body water, 15 times the ECF volume, and 60 times the plasma volume.

(Ref. Ganong 22th edition, page-706)

Control of GFR

The factors governing filtration across the glomerular capillaries are the same as those governing filtration across all other capillaries, ie, the size of the capillary bed, the permeability of the capillaries, and the hydrostatic and osmotic pressure gradients across the capillary wall. For each nephron :

$$GFR = K_f [(P_{GC} - P_T) - (\pi_{GC} - \pi_T)]$$

1. K_f, the glomerular ultrafiltration coefficient, is the product of the glomerular capillary wall hydraulic conductivity (ie. its permeability) and the effective filtration surface area.
2. P_{GC} is the mean hydrostatic pressure in the glomerular capillaries.
3. P_T the mean hydrostatic pressure in the tubule.
4. π_{GC} the osmotic pressure of the plasma in the glomerular capillaries
5. π_T the osmotic pressure of the filtrate in the tubule.

(Ref. Ganong 22th edition, page 706)

Factors affecting the GFR

1. Changes in renal blood flow
2. Changes in glomerular capillary hydrostatic pressure
   i. Changes in systemic blood pressure
   ii. Afferent or efferent arteriolar constriction
3. Changes in hydrostatic pressure in Bowman's capsule
   i. Ureteral obstruction
   ii. Edema of kidney inside tight renal capsule
4. Changes in concentration of plasma proteins : dehydration, hypoproteinemia etc (minor factors)
5. Changes in K_f.
   i. Changes in glomerular capillary permeability
   ii. Changes in effective filtration surface area.

(Ref. Ganong 22th edition)

Renal fraction

The portion of the total cardiac output that passes through the kidneys is called the renal fraction.

i. The total cardiac output of 70 kg adult : 5600 ml/min.
ii. Rate of blood flow through both kidneys : 1200 ml/minute.

$$\text{So, Renal fraction} = \frac{1200 \times 100}{5600}$$

$$= 21\%$$

Range : 12-30 %.

(Ref. Guyton & Hall 11th Edition)

Filtration fraction

Filtration fraction is the ratio of the GFR to the renal plasma flow (RPF).

The normal plasma flow through both kindey = 650 ml/ minute.

The glomerular filtration rate = 125 ml/ min.

So, Filtration fraction $= \frac{125}{650}$

$= 0.19$

(Ref. Ganong 22th edition, page-708; Guyton 11th, Page-346)

Filtration Pressure

The filtration pressure is the net pressure forcing fluid through the glomerular membrane. It is about 10 mm Hg.

Filtration pressure is equal to the sum of glomerular hydrostatic pressure plus Bowman's capsule colloid osmotic pressure minus the sum of glomerular capillary colloidal osmotic pressure and Bowman's capsule hydrostatic pressure, that is -

i. *Factors favouring filtration (mm of Hg)* :
   a. Glomerular hydrostaticy pressure : 60
   b. Bowman's capsule colloid osmotic pressure : 0

ii. *Factors favouring filtration (mm of Hg)* :
   a. Bowman's capsule hydrostatic pressure : 18
   b. Glomerular capillary colloidal osmotic pressure : 32

So net filtration pressure = 60 - (18 + 32) mm of Hg
= + 10 mm of mg.

So net filtration pressure +10 mm of mg causes the filtration of glomerular filtrate.

(Ref. Guyton & Hall 11th edition)

Filtration co-efficient

K_f, the glomerular ultrafiltration coelficient, is the product of the glomerular capillary wall hydraulic conductivity (ie. its permeability) and the effective filtration surface area.

(Ref. Ganong 22th edition, page-706)

The K_f is a measure of the product of the hydraulic conductivity and surface area of the glomerular capillanes. The K_f cannot be measured directly, but it is estimated experimentally by dividing the rate of glomerular filtration by net filtration pressure :

$$K_f = \frac{GFR}{\text{Effective filtration pressure}}$$

$$= \frac{125}{10}$$

$= 12.5$ ml/min./mm of Hg of filtration pressure.

Because total GFR for both kidneys is about 125 ml/min and the net filtration pressure is 10 mm Hg, the normal K_f is calculated to be about 12.5 ml/min/mm Hg of filtration pressure.

When K_f is expressed per 100 grams of kidney weight, it averages about 4.2 ml/min/mm Hg per 100 grams of kidney weight, a value about 400 times as high as the K_f of most other capillary systems of the body; the average K_f of the other tissues in the body is only about 0.01 ml/min/mm Hg per 100 grams. This high K_f for the glomerular capillaries contributes tremendously to their rapid rate of fluid filtration.

Although increased K_f raises GFR, and decreased K_f reduces GFR, changes in K_f probably do not provide a primary mechanism for the normal day-to-day regulation of GFR. Some diseases, however, lower K_f by reducing the number of functional glomerular capillaries (thereby reducing the surface area for filtration) or by increasing the thickness of the glomerular capillary membrane and reducing its hydraulic conductivity. For example, chronic, uncontrolled hypertension and diabetes mellitus gradually reduce K_f by increasing the thickness of the glomerular capillary baesment membrane and, eventually, by damaging the capillaries so severely that there is loss of capillary function.

(Ref. Guyton & Hall 11th Edition, Page 318)

Autoregulation of GFR and renal blood flow

Feedback mechanisms intrinsic to the kidneys normally keep the renal blood flow and GFR relatively constant, despite marked changes in arterial blood pressure. These mechanisms still function in blood-perfused kidneys that have been removed from the body, independent of systemic influences. This relative constancy of GFR and renal blood flow is referred to as *autoregulation.*

The primary function of blood flow autoregulation in most other tissues besides the kidneys is to maintain delivery of oxygen and nutrients to the tissues at a normal level and to remove the waste products of metabolism, despite changes in the arterial pressure. In the kidneys, the normal blood flow is much higher than required for these functions. The major function of auto-regulation in the kidneys is to maintain a relatively constant GFR and to allow precise control of renal excretion of water and solutes.

The GFR normally remains autoregulated (that is, remains relatively constant), despite considerable arterial pressure fluctuations that occur during a person's usual activities. For instance, a decrease in arterial pressure to as low as 75 mm Hg or an increase to as high as 160 mm Hg changes GFR only a few percentage points. In general renal blood flow is autoregulated in parallel with GFR, but GFR is more efficiently autoregulated under certain conditions.

Importance of GFR autoregulation in preventing extreme changes in renal excretion : The autoregulatory mechanisms of the kidney are not 100 per cent perfect, but they do prevent potentially large changes in GFR and renal excretion of water and solutes that would otherwise occur with changes in blood pressure. One can understand the quantitative importance of autoregulation by considering the relative magnitudes of glomerular filtration, tubular reabsorption, and renal excretion and the changes in renal excretion that would occur without autoregulatory mechanisms.

Normally, GFR is about 180 L/day and tubular reabsorption is 178.5 L/day, leaving 1.5 L/day of fluid to be excreted in the urine. In the absence of autoregulation, a relatively small increase in blood pressure (from 100 to 125 mm Hg) would cause a similar 25 per cent increase in GFR (from about 180 to 225 L/day). If tubular reabsorption remained constant at 178.5 L/day, this would increase the urine flow to 46.5 L/day (the difference between GFR and tubular reabsorption), making a total increase in urine of more than 30-fold! Because the total plasma volume is only about 3 liters, such a change would quickly deplete the blood volume.

Mechenism of autoregulation of GFR and renal blood flow : But in reality, such a change in arterial pressure exerts much less of an effect on urine volume for two reasons :

1. Renal autoregulation prevents large changes in GFR that would otherwise occur and
2. There are additional adaptive mechanisms in the renal tubules that allow them to increase their reabsorption rate when GFR rises, a phenomenon referred to as *glomerulotubular balance.*
3. Yet, even with these special control mechanisms, changes in arterial pressure still have significant effects on renal excretion of water and sodium; this is referred to as *pressure diuresis or pressure natriuresis*, and it is crucial in regulation of body fluid volumes and arterial pressure.

(For details Please see Guyton 10th Edition, Page 290)

(Ref. Guyton & Hall 11th Edition, Page 323)

Juxta glomerular complex

The epithelial cells of the distal tubule that come in contact with the atrerioles (afferent and efferent) are more dense than the other tubular cells and are collectively called the macula densa. The macula densa cells appear to secrete some substance toward the arteriole. The smooth muscle cells of both the afferent and efferent arteriole are swollen and contain dark granules where they come in contact with macula densa. These cells are called *juxtaglomerular cells (JG)* and the granules are composed mainly of inactive renin. The whole complex of macula densa and juxta glomerular cells is called the *juxtaglomerular complex or juxtaglomerular apparatus*. The *juxtaglomerular* cells of this complex secrete renin which regulate blood pressure *(fig. 13.2).*

(Ref. Guyton & Hall 11th Edition)

Urinary and plasma concentrations of some physiologically important substances : *(Ref. Ganong 22th edition, page 699)*

	Concentration in		
Substance	*Urine (U)*	*Plasma (P)*	*U/P Ratio*
Glucose((mg/dL)	0	100	0
Na^+ (meq/L)	*90*	*140*	*0.6*
Urea (mg/dl)	900	15	60
Creatinine(mg/dl)	*150*	*1*	*150*

Plasma clearance or renal clearance

Definition : The rates at which different substances are "cleared" from the plasma provide a useful way of quantitating the effectiveness with which the kidneys excrete various substances. By definition, *the renal clearance of a substance is the volume of plasma that is completely cleared of the substance by the kidneys per unit time.* This concept is somewhat abstract because there is no single volume of plasma that is completely cleared of a substance.

Clearance principle : To illustrate the clearance principle, consider the following example : If the plasma passing through the kidneys contains 1 milligram of a substance in each milliliter and 1 milligram of this substance is also excreted into the urine each minute, then 1 ml/min of the plasma is 'cleared" of the substance. Thus, clearance refers to the volume of plasma that would be necessary to supply the amount of substance excreted in the urine per unit time. Stated mathematically,

$$C_s \times P_s = U_s \times V$$

Where C_s is the clearance rate of a substance s, P_s is the plasma concentration of the substance, U_s is the urine concentration of that substance, and V is the urine flow rate.

Plasma clearance of any substance can be determined by the following formula :

$$C_s = \frac{U_s \times V}{P_s}$$

Calculation : Thus, renal clearance of a substance is calculated from the urinary excretion rate (U_s x V) of that substance divided by its plasma concentration.

Plasma clearance =

Conc. of substance in urine x Volume of urine (ml/minute)
Concentration of substance in plasma in ml.

$$C_s = \frac{U_s \times V}{P_s}$$

Use of plasma clearance : However, renal clearance provides a useful way of quantifying the excretory function of the kidneys and can be used to quantify the rate at which blood flows through the kidneys as well as the basic functions of the kidneys : glomerular filtration, tubular reabsorption, and tubular secretion.

(Ref. Guyton & Hall 11th Edition, Page 343, 344)

Plasma clearance value of Urea is 70 ml - *Explain*

We know that the plasma clearance of any substance-

$$= \frac{\text{Conc. of substance in urine x Volume of urine (ml/min.)}}{\text{Concentration of substance in plasma in ml.}}$$

Normal concentration of urea in plasma = 0.26 mg/ml.

Amount of urea excreted in urine =18.2 mg/minute.

$$\text{Plasma clearance of Urea} = \frac{18.2 \times 1}{0.26}$$

$$= 70 \text{ ml.}$$

So, the clearance value of urea is 70 ml/min means-70 ml of plasma contain the amount of urea which is excreted in the urine per minute.

Determination of GFR from plasma clearance *(Inulin clearance)* : If a substance is freely filtered (filtered as freely as water) and is not reabsorbed or secreted by the renal tubules, then the rate at which that substance is excreted in the urine (U_s X V) is eqal to the filtration rate of the substance by the kidneys (GFR x P_s).

Thus,

GFR x Ps = Us x V

The GFR, therefore, can be calculated as the clearance of the substance as follows :

$$GFR = \frac{U_s \times V}{P_s}$$

$$= C_s$$

A substsnce that fits these criteria is inulin, a polysaccharide molecule with a molecular weight of about 5200. Inulin, which is not produced in the body, is found in the roots of certain plants and must be administered intravenously to a patient to measure GFR.

The plasma concentration of inulin is 1 mg/ml, urine concentration is 125 mg/ml, and urine flow rate is 1 ml/min. Therefore, 125 mg/min of inulin passes into the urine. Then, inulin clearance is calculated as the urine excretion rate of inulin divided by the plasma concentration, which yields a value of 125 ml/minute. Thus, 125 milliliters of plasma flowing through the kidneys must be filtered to deliver the inulin that appears in the urine. So, GFR is 125 ml/minute.

(Ref. Guyton & Hall 11th Edition, Page-344)

N.B.

Inulin is not the only substance that can be used for determining GFR. Other substances that have been used clinically to estimate GFR include *creatinine* and *radioactivc iothalamate*. Because creatinine is a by-product of skeletal muscle metabolism, it is present in the plasma at a relatively constant concentration and does not require intravenous infusion into the patient. For this reason, creatininc clearance is perhaps the most widely used method of estimating GFR clinically. However, creatinine is not a perfect marker for GFR because a small amount of it is secreted by the tubules, so that the amount of creatinine excreted in the urine slightly exceeds the amount filtered. There is normally a slight error in measuring plasma creatinine that leads to an overestimate of the plasma concentration and fortuitously, these two errors tend to cancel each other. Therefore, the clearance of creatinine provides a reasonable estimate of GFR.

(Ref. Guyton & Hall 10th Edition, Page-311)

Determination of renal plasma flow from plasma clearance *(PAH clearance)* :

Theoritically, if a substance is *completely* cleared from the plasma, the clearance rate of that substance is equal to the total renal plasma flow. In other words, the amount of the substance delivered to the kidneys (renal plasma flow x Ps) would be equal to the amount excreted in the urine (Us x V).Thus, renal plasma flow (RPF) could be calculated as

$$GFR = \frac{U_s \times V}{P_s}$$

$$= C_s$$

Because the GFR is only about 20 per cent of the total plasma flow, a substance that is completely cleared from the plasma must be excreted by tubular secretion as well as glomerular filtration. There is no known substance that is completely cleared by the kidneys. One substance, However, PAH, is about 90 per cent cleared from the plasma. Therefore, the clearance of PAH can be used as an approximation of renal plasma flow. To be more accurate, one can correct for the percentage of PAH that is still in the blood when it leaves the kidneys. The percentage of PAH removed from the blood is known as the *extraction ratio of PAH* and averages about 90 per cent in normal kidneys. In diseased kidneys, this extraction ratio may be reduced because of inability of damaged tubules to secrete PAH into the tubular fluid.

The calculation of renal plasma flow can be demonstrated by the following example : Assume that the plasma concentration of PAH is 0.01 mg/ml, urine concentration is 5.85 mg/ml, and urine flow rate is 1 ml/min. PAH clearance can be calculated from the rate of urinary PAH excretion (5.85 mg/ml x 1 ml/min) divided by the plasma PAH concentration (0.01 mg/ml). Thus, clearance of PAH calculates to be 585 ml/min.

If the extraction ratio for PAH is 90 per cent, the actual renal plasma flow can be calculated by dividing 585 ml/min by 0.9, yielding a value of 650 ml/min. Thus, total renal plasma flow can be calculated as

Total renal plasma flow = Clearance of PAH/Extraction ratio of PAH.

The extraction ratio (E_{PAH}) is calculated as the difference between the renal arterial PAH(P_{PAH}) and renal venous PAH (V_{PAH}) concentrations, divided by the renal arterial PAH concentration :

$$E_{PAH} = \frac{P_{PAH} - V_{PAH}}{P_{PAH}}$$

(Ref. Guyton & Hall 11th Edition, Page 345)

Determination of total blood flow : We can calculate the total renal blood flow in each minute from the plasma flow and the hematocrit. If the hematocrit is 45% and the renal plasma flow 650 ml/minute.

The total renal blood flow-

$$= \frac{\text{Renal plasma flow}}{1 - \text{hematocrite}}$$

$$= \frac{650}{1 - 45/100}$$

$$= \frac{650 \times 100}{55}$$

= 1182 ml/minute.

(Ref. Guyton & Hall 11th Edition, Page 346)

Plasma Load

The plasma load of a substances means the total amount of that substance present in plasma, that passes through the kindey in each minute.

The plasma concentration of glucose=100 mg/100 ml. and 650 ml of plasma passes through each kidney/min.

So, plasma load of glucose = 650 mg/minute.

Tubular Load : The tubular load of a substance is the total amount of the substance that filters through the glomerular membrane into the tubules in each minute.

If 125 ml of glomerular filtrate is formed in each minute with a glucose concentration of 100 mg percent, the tubular load of glucose is 125 mg per minute.

(Ref. Guyton & Hall 11th Edition)

Renal threshold

Definition : Renal threshold of a substance may be defined as the critical concentration of that substances in plasma below which none of it appears in urine but above which progressively larger quantity of it appears in urine.

Normal value : Renal threshold for glucose 180 mg%.

(Ref. Guyton & Hall 11th Edition)

High threshold substances are :

i. Glucose, Potassium (100%).

ii. Water (99%).

iii. Na^+, Cl^- & Ca^{++} (98 - 99%).

The renal threshold for glucose : Means the threshold concentration of glucose in plasma, below which none of glucose appear in urine but above which progressively larger quantity of it appears in urine. The threshold concentration of glucose in plssma is 180 mg%.

Quantifying renal urine concentration and dilution

Free water and Osmolar clearances : The process of concentrating or diluting the urine requires the kidneys to excrete water and solutes somewhat independently. When the urine is dilute, water is excreted in excess of solutes. Conversely, when the urine is concentrated, solutes are excreted in excess of water.

Osmolar clearances : The total clearance of solutes from the blood can be expressed as the osmolar clearance (C_{osm}); this is the volume of plasma cleared of solutes each minute, in the same way that clearance of a single substance is calculated :

$$C_{osm} = \frac{U_{osm} \times V}{P_{osm}}$$

Where U_{osm} is the urine osmolarity, V is the urine flow rate, and P_{osm} is the plasma osmolarity. For example, if plasma osmolarity is 300 mOsm/L, urine osmolarity is 600 mOsm/L, urine flow rate is 1 ml/min (0.001 L/min), the rate of osmolar excretion is 0.6 mOsm/min (600 mOsm/L x 0.001 L/min) and osmolar clearance is 0.6 mOsm/min divided by 300 mOsm/L, or 0.002 L/min (2.0 ml/min). This means that 2 milliliters of plasma are being cleared of solute each minute.

Free water clearance : Free-water clearance (C_{H_2O}) is calculated as the difference between water excretion (urine flow rate) and osmolar clearance.

$$C_{H_2O} = V - C_{osm}$$

$$= V - \frac{U_{osm} \times V}{P_{osm}}$$

Relative rates at which solutes and water are excreted can be assessed using the concept of 'Free-Water Clear' : The rate of free-water clearance represents the rate at which solute-free water is excreted by the kidneys. When *free-water clearance is positive*, excess water is being excreted by the kidneys; when *free-water clearance is negative*, excess solutes are being removed from the blood by the kidneys and water is being conserved.

Example : Using the example discussed earlier, if urine flow rate is 1 ml/min and osmolar clearance is 2 ml/min, free-water clearance would be- 1 ml/min. This means that instead of water being cleared from the kidneys in excess of solutes, the kidneys are actually returning water back to the systemic circulation, as occurs during water deficits. Thus, *whenever urine osmolarity is greater than plasma osmolarity, free-water clearance will be negative, indicating water conservation.*

When the kidneys are forming a dilute urine (that is, urine osmolarity is less than plasma osmolarity), free-water clearance will be a positive value, denoting that water is being removed from the plasma by the kidneys in excess of solutes. Thus, water free of solutes, called "free water," is being lost from the body and the plasma is being concentrated when free-water clearance is positive.

(Ref. Guyton & Hall 11th Edition; Page-357)

Tubular transport maximum (Tm)

Definition : Almost every actively reabsorbed or secreted substance has a maximum rate at which it can be reabsorbed or secreted in the kidney tubule. The rate at which the substance reabsorbed or secreted in the kidney tubule is called tubular transport maximum.

Example :

Substance	*Transport maximum*
1. Glucose	375 mg/minute
2. Phosphete	0.10 mM/minute
3. Sulphate	0.06 mM/minute
4. Amino acids	1.5 mM/minute
5. Urate	15 mg/minute
6. Lactate	75 mg/minute
7. Plasma protein	30 mg/minute.

Transport maximums for substances that are actively secreted :

Substance	*Transport maximum*
1. Creatinine	16 mg/minute
2. Paraminohippuric acid	80 mg/minute.

Tm of glucose = 375 mg/minute :

Tm of glucose 375 mg/minute means that 375 mg glucose is reabsorbed its maximum rate through the tubules in each minute. If the rate is above this value then glucose is excreted out through urine.

(Ref. Guyton & Hall 11th Edition, page 331)

Glomerulotubular balance

Under normal conditions almost a constant percentage, about 65 percent, of both the sodium and fluid is reabsorbed during passage through the proximal tubules regardless of the rate at which glomerular filtrate enters the tubular system, is called glomerulo tubular balance. That is when GFR increases reabsorption also increases, but when GFR decreases reabsorption also decreases maintaining the proportional balance very near to 65%.

i. *Cause* :
   a. Greater stretch of the tubules.
   b. Higher flow rates.

ii. *Importance* : It helps to prevent overloading of the more distal segments of the tubular system when the GFR increases.

(Ref. Guyton & Hall 11th Edition)

Filtration, reabsorption, and excretion rates of different substances by the kidneys

Some substances, such as glucose and amino acids, are almost completely reabsorbed from the tubules, so that the urinary excretion rate is essentially zero. Many of the ions in the plasma, such as sodium, chloride, and bicarbonate, are also highly reabsorbed, but their rates of reabsorption and urinary excretion are variable, depending on the needs of the body. Certain waste products, such as urea and creatinine, on the other hand, are poorly reabsorbed from the tubules and excreted in reatively large amounts. Therefore, by controlling the rate at which they reabsorb different substances, the kidneys regulate the excretion of solutes independently of one another, a capability that is essential for precise control of the composition of body fluids.

Urinary excretion = Glomerular filtration - Tubular reabsorption + Tubular secretion.

(Ref. Guyton & Hall 11th Edition, page 327)

Example :

	Amount Filtered	*Amount Reabsorbed*	*Amount Excreted*	*% of Filtered Load Reabsorbed*
Glucose(gm/day)	180	180	0	100
Bicarbonate(mEq/day)	4,320	4,318	2	>99.9
Sodium(mEq/day)	25,560	25,410	150	99.4
Chloride(mEq/day)	19,440	19,260	180	99.1
Urea (gm/day)	46.8	23.4	23.4	50
Creatinine(gm/day)	1.8	0	1.8	0

(Ref. Guyton & Hall 11th Edition, page 327)

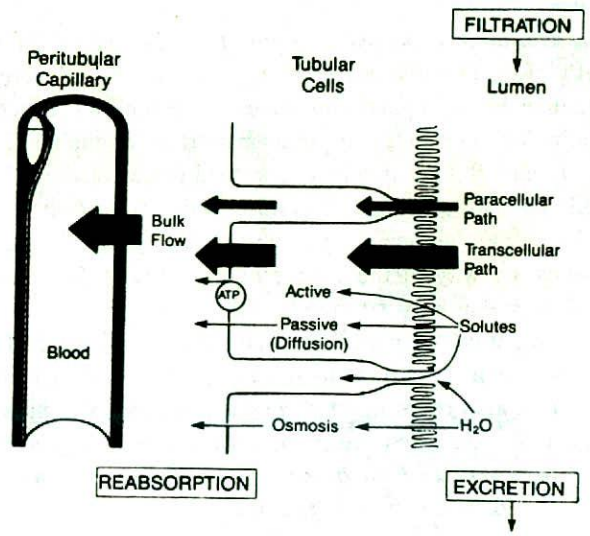


Fig. 13-3. Reabsorption of filtered water and solutes from the tubular lumen across the tubular epithelial cells, through the renal interstitium, and back into the blood. Solutes are transported through the cells (transcellular route) by passive diffusion or active transport or between the cells (paracellular route) by diffusion. Water is transported through the cells and between the tubular cells by osmosis. Transport of water and solutes from the interstitial fluid into the peritubular capillaries occurs by ultrafiltration (bulk flow).

Tubular Reabsorption

Pathway : For a substance to be reabsorbed, it must first be transported -

a. Across the tubular epithelial membranes into the renal interstitial fluid.

b. Through the peritubular capillary membrane back into the blood.

Thus, reabsorption of water and solutes includes a series of transport steps. Reabsorption across the tubular epithelium into the interstitial fluid includes active or passive transport. For instance-

1. *Transcellular route* : Water and solutes can be transported either through the cell membranes themselves.
2. *Paracellular route* : Through the junctional spaces between the cells .
3. *Ultrafiltration (bulk flow)* : After absorption across the tubular epithelial cells into the interstitial fluid, water and solutes are transported the rest of the way through the peritubular capillary walls into the blood by ultrafiltration (bulk flow) that is mediated by hydrostatic and colloid osmotic forces.

The peritubular capillaries behave very much like the venous ends of most other capillaries because there is a net reabsorptive force that moves the fluid and solutes from the interstitium into the blood.

(Ref. Guyton & Hall 11th Edition, Page 328)

Solutes can be transported through epithelial cells or between cells : Renal tubular cells, like other epithelial cells, are held together by tight junctions. Lateral intercellular spaces lie behind the tight junctions and separate the epithelial cells of the tubule. Solutes can be reabsorbed or secreted across the cells by way of the transcellular pathway or between the cells by moving across the tight junctions and intercellular spaces, by way of the paracellular pathway. ***Sodium*** is a substance that moves through both routes, although most of the sodium is transported through the transcellular pathway. In some nephron segments, especially the proximal tubule, ***water*** is also reabsorbed across the paracellular pathway, and substances dissolved in the water, especially ***potassium, magnesium, and chloride ions***, are carried with the reabsorbed fluid between the cells.

(Ref. Guyton & Hall 11th Edition, Page 329)

Tubular reabsorption includes- Active and Passive Transport

Active transport : A good example of *primary active transport* is sodium potassium ATPase pump. Reabsorption of glucose by the renal tubule is an example of *secondary active transport*. Although solutes can be reabsorbed by active and/or passive mechanisms by the tubule, water is always reabsorbed by a passive (nonactive) physical mechanism called *osmosis*, which means water diffusion from a region of low solute concentration (high water concentration) to one of high solute concentration (low water concentration).

(Ref. Guyton & Hall 11th Edition, Page 328)

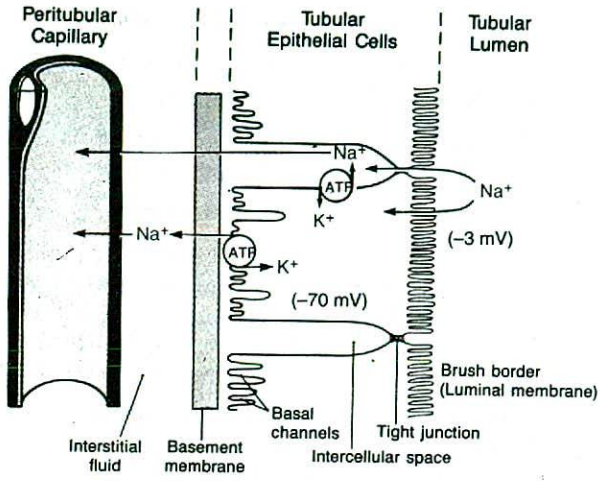


Figure 13-4. Basic mechanism for active transport of sodium through the tubular epithelial cell. The sodium-potassium pump transports sodium from the interior of the cell across the basolateral membrane, creating a low intracellular sodium concentration and a negative intracellular electrical potential. The low intracellular sodium concentration and the negative electrical potential cause sodium ions to diffuse from the tubular lumen into the cell through the brush border.

1. **Primary active transport through the tubular membrane is linked to hydrolysis of ATP** : A good example of a primary active transport system is the ***reabsorption of sodium ions*** across the proximal tubular membrane.

   Active reabsorption of sodium by sodium-potassium ATPase occurs in most parts of the tubule. In certain parts of the nephron, there are additional provisions for moving large amounts of sodium into the cell. In the *proximal tubule*, there is an extensive brush border on the luminal side of the membrane (the side that faces the tubular lumen) that multiplies the surface area about 20-fold. There are also sodium carrier proteins that bind sodium ions on the luminal surface of the membrane and release them inside the cell, providing facilitated diffusion of sodium through the membrane into the cell. These sodium carrier proteins are also important for secondary active transport of other substances, such as glucose and amino acids.

   Thus, the net reabsorption of sodium ions from the tubular lumen back into the blood involves at least three steps :

   i. Sodium is transported across the basolateral membrane against an electrochemical gradient by the *sodium-potassium ATPase pump.*

   ii. Sodium diffuses across the luminal membrane (also

called the apical membrane) into the cell down an electrochemical gradient established by the sodium-potassium ATPase pump on the basolateral side of the membrane.

iii. Sodium, water, and other substances are reabsorbed from the interstitial fluid into the peritubular capillaries by *ultrafiltration*, a passive process driven by the hydrostatic and colloid osmotic pressure gradients.

(Ref. Guyton & Hall 11th Edition, Page 328)

2. **Secondary active reabsorption through the tubular membrane** : Secondary active transport of glucose and amino acids occurs in the proximal tubule. In both instances, a specific carrier protein in the brush border combines with a sodium ion and an amino acid or a glucose molecule at the same time. These transport mechanisms are so efficient that they remove virtually all the glucose and amino acids from the tubular lumen. After entry into the cell, glucose and amino acids exit across the basolateral membranes by *facilitated diffusion*, driven by the high glucose and amino acid concentrations in the cell.

   For ***glucose reabsorption***, *secondary active transport* occurs at the luminal membrane, but *passive facilitated diffusion* occurs at the basolateral membrane, and *passive uptake by bulk flow* occurs at the peritubular capillaries.

   (Ref. Guyton & Hall 11th Edition, Page 329)

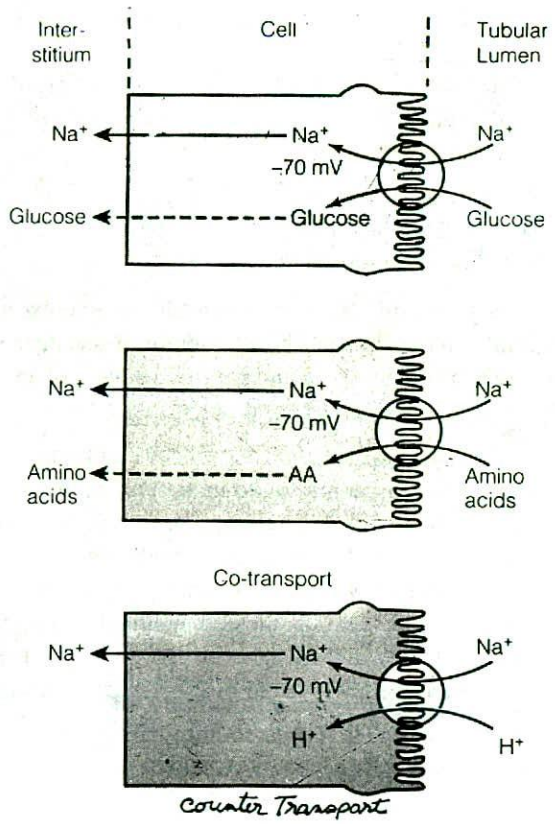


Figure 13-5. Mechanisms of seecondary active transport. The upper two cells show the co-transport of glucose or amino acids along with sodium ions through the brush border of the tubular epithelial cells, followed by facilitated diffusion through the basolateral membranes. The third cell shows the counter-transport of hydrogen ions from the interior of the cell across the brush border member and into the tubular lumen; movement of sodium ions into the cell, down an electrochemical gradient established by the sodium-potassium pump of the basolateral membrane, provides the energy for transport of the hydrogen ions from inside the cell into the tubular lumen

3. **Secondary active secretion into the tubules** : A few substances are secreted into the tubules by secondary active transport. This often involves counter-transport of the substance with sodium ions.

   One example of counter-transport, shown in *figure 10-6*, is the *active secretion of hydrogen ions* coupled to sodium reabsorption in the luminal membrane of the proximal tubule. In this case, sodium entry into the cell is coupled with hydrogen extrusion from the cell by sodium-hydrogen counter-transport. This transport is mediated by a specific protein in the brush border of the luminal membrane. As sodium is carried to the interior of the cell, hydrogen ions are forced outward in the opposite direction into the tubular lumen.

   (Ref. Guyton & Hall 11th Edition, Page 330)

4. **Pinocytosis *(An active transport mechanism for reabsorption of proteins)*** : Some parts of the tubule, especially the proximal tubule, reabsorb large molecules such as ***proteins*** by *pinocytosis*. In this process, the protein attaches to the brush border of the luminal membrane, and this portion of the membrane then invaginates to the interior of the cell until it is completely pinched off and a vesicle is formed containing the protein. Once inside the cell, the protein is digested into its constituent amino acids, which are reabsorbed through the basolateral membrane into the cell.

   (Ref. Guyton & Hall 11th Edition, Page 330)

Reabsorption and Secretion
along different parts of the nephron

Proximal tubular reabsorption : Nomally, about 65 per cent of the filtered load of sodium and water and a slightly lower percentage of filtered chloride are reabsorbed by the proximal tubule before the filtrate reaches the loops of Henle. These pecentages can be increased or decreased in different phsiological conditions.

The proximal tubules have a high capacity for active and passive reabsorption : The high capacity of the proximal tubule for reabsorption results from its special cellular characteristics, as shown in figure . The poximal tubule epithelial cells are highly metabolic and have large numbers of mitochondria to support potent active transport processes. In addition, the proximal tubular cells have an extensive brush border on the

luminal (apical) side of the membrane as well as an extensive labyrinth of intercellular and basal channels, all of which together provide an extensive membrane surface area on the luminal and basolateral sides of the epithelium for rapid transport of sodium ions and other substances.

The extensive membrane surface of the epithelial brush border is also loaded with protein carrier molecules that transport a large fraction of the sodium ions across the luminal membrane linked by way of the co-transport mechanism with multiple organic nutrients such as amino acids and glucose. The remainder of the sodium is transported from the tubular lumen into the cell by counter-transport mechanisms, which reabsorb sodium while secreting other substances into the tubular lumen, especially hydrogen ions. The secretion of hydrogen ions into the tubular lumen is an important step in the removal of bicarbonate ions from the tubule (by combining H^+ with the HCO_3^- to form H_2CO_3, which then dissociates into H_2O and CO_2).

Although the sodium-potassium ATPase pump provides the major force for reabsorption of sodium, chloride, and water throughout the proximal tubule, there are some differences in the mechanisms by which sodium and chloride are transported through the luminal side of the early and late portions of the proximal tubular membrane.In the *first half of the proximal tubule*, sodium is reabsorbed by co-transport along with glucose, amino acids, and other solutes. But in the *second half of the proximal tubule,* little glucose and amino acids remain to be reabsorbed. Instead, sodium is now reabsorbed mainly with chloride ions. The second half of the proximal tubule has a relatively high concentration of chloride (around 140 mEq/L) compared with the early proximal tubule (about 105 mEq/L) because when sodium is reabsorbed, it preferentially carries with it glucose, bicarbonate, and organic ions in the early proximal tubule, leaving behind a solution that has a higher concentration of chloride. In the second half of the proximal tubule, the higher chloride concentration favors the diffusion of this ion from the tubule lumen through the intercellular junctions into the renal interstitial fluid.

(Ref. Guyton & Hall 11th Edition, Page 333)

Concentrations of solutes along the proximal tubule : The amount of sodium in the tubular fluid decreases markedly along the proximal tubule, the *concentration* of sodium (and the total osmolarity) of the proximal tubules is so great that water reabsorption keeps place with sodium reabsorption. Certain organic solutes, such as glucose, amino acids, and bicarbonate are much more avidly reabsorbed than water, so that their concentrations decrease markedly along the length of the proximal tubule. Other organic solutes that are less permeant and not actively reabsorbed, such as urea, increase their concentration along the proximal tubule. The total solute concentration, as reflected by osmolarity, remains essentially the same all along the proximal tubule because of the extremely high permeability of this part of the nephron to water.

(Ref. Guyton & Hall 11th Edition, Page 334)

Secretion of organic acids and bases by the proximal tubule : The *proximal tubule* is also an important site for secretion of organic acids and bases such as *bile salts, oxalate, urate, and catecholamines*. Many of these substances are the end products of metabolism and must be rapidly removed from the body. The *secretion* of these substances into the proximal tubule plus *filtration* into the proximal tubule by the glomerular capillaries and the almost total lack of reabsorption in any portion of the tubular system, all combined, contribute to rapid excretion in the urine.

Another compound that is rapidly secreted by the proximal tubule is *para-aminohippuric acid (PAH)*. PAH is secreted so rapidly that the normal person can clear about 90 per cent of the PAH from the plasma flowing through the kidneys and excrete it in the urine. For this reason, the rate of PAH clearance can be used as an index of the renal plasma flow.

(Ref. Guyton & Hall 11th Edition, Page 334)

Solute and water transport in the Loop of Henle : The loop of Henle consists of three functionally distinct segments :

a. Descendtng thin segment
b. Ascending thin segment
c. Thick ascending segment.

The thin descending and thin ascending segments, as their names imply, have thin epithelial membranes with no brush borders, few mitochondria, and minimal levels of metabolic activity.

The *descending part of the thin segment* is highly permeable to water and moderately permeable to most solutes, including urea and sodium. The function of this nephron segment is mainly to allow simple diffusion of substances through its walls. About 20 per cent of the filtered water is reabsorbed in the loop of Henle, and almost all of this occurs in the descending thin limb because the ascending limb, including both the thin and the thick portions, is virtually impermeable to water, a characteristic that is important for concentrating the urine.

The *thick segment of the loop of Henle,* which begins about half way up the ascending limb, has thick epithelial cells that have high metabolic activity and are capable of active reabsorption of sodium, chloride, and potassium. About 25 per cent of the filtered loads of sodium, chloride , and potassium are reabsorbed in the loop of Henle, mostly in the thick ascending limb. Considerable amounts of other ions, such as calcium, bicarbonate, and magnesium, are also reabsorbed in the thick ascending loop of Henle. The thin segment of the ascending limb has a much lower reabsorptive capacity than the thick

segment, and the descending thin limb does not reabsorb significant amounts of any of these solutes.

An important component of solute reabsorption in the thick ascending limb is the sodium-potassium ATPase pump in the epithelial cell basolateral membranes. As in the proximal tubule, the reabsorption of other solutes in the thick segment of the ascending loop of Henle is closely linked to the reabsorptive capability of the sodium potassium ATPase pump, which maintains a low intracellular sodium concentration. The low intracellular sodium concentration in turn provides a favorable gradient for movement of sodium from the tubular fluid into the cell. In the thick ascending loop, movement of sodium across the luminal membrane is mediated primarily by a *1- sodium, 2-chloride, 1-potassium* co-transporter . This co-transport protein carrier in the luminal membrane uses the potential energy released by downhill diffusion of sodium into the cell against a concentration gradient.

The thick ascending limb also has a sodium-hydrogen counter-transport mechanism in its luminal cell membrane that mediates sodium reabsorption and hydrogen secretion in this segment.
Because the thick segment of the ascending loop of Henle is virtually impermeable to water, most of the water delivered to this segment remains in the tubule, despite reabsorption of large amounts of solute. Thus, the tubular fluid in the ascending limb becomes very dilute as it flows toward the distal tubule, a feature that is important in allowing the kidneys to dilute or concentrate the urine under different conditions.

(Ref. Guyton & Hall 11th Edition, Page 334, 335)

Distal tubule : The thick segment of the ascending limb of the loop of Henle empties into the distal tubule. The *very first portion* of the distal tubule forms part of the *juxtaglomerular complex* that provides feedback control of GFR and blood flow in this same nephron. The *next early part* of the distal tubule is highly convoluted and has many of the same reabsorptive characteristics of the thick segment of the ascending limb of the loop of Henle. That is, it avidly reabsorbs most of the ions, including sodium, potassium, and chloride, but is *virually impermeable to water and urea.* For this reason, it is referred to as the *diluting segment* because it also dilutes the tubular fluid.

(Ref. Guyton & Hall 11th Edition, Page 336)

Late distal tubule & cortical collecting tubule : The *second half of the distal tubule* and the subsequent *cortical collecting tubule* have similar functional characteristics. Anatomically, they are composed of two distinct cell types, the principal cells and the intercalated cells. The *principal cells* reabsorb sodium and water from the lumen and secrete potassium ions into the lumen. The *intercalated cells* reabsorb potassium ions and secrete hydrogen ions into the tubular lumen.

a. ***The principal cells reabsorb sodium and secrete potassium*** : Sodium reabsorption and potassium secretion by the principal cells depend on the activity of a sodium-potassium ATPase pump in each cell's basolateral membrane. This pump maintains a low sodium concentration inside the cell and, therefore, favors sodium diffusion into the cell through special channels. The secretion of potassium by these cells from the blood into the tubular lumen involves two steps :
   1. Potassium enters the cell because of the sodium-potassium ATPase pump, which maintains a high intracellular potassium concentration.
   2. Once in the cell, potassium diffuses down its concentration gradient across the luminal membrane into the tubular fluid.

b. ***The Intercalated cells avidly secrete hydrogen and reabsorb bicarbonate and potassium ions :***
Hydrogen ion secretion by the intercalatd cells is mediated by a hydrogen-ATPase transport mechanism. Hydrogen is generated in this cell by the action of carbonic anhydrase on water and carbondioxide to form carbonic acid, which then dissociates into hydrogen ions and bicarbonate ions. The hydrogen ions are then secreted into the tubular lumen, and for each hydrogen ion secreted, a bicarbonate ion becomes available for reabsorption across the basolateral membrane. The intercalated cells also reabsorb potassium ions, although the mechanisms are not well understood.

The functional characteristics of the late distal tubule and cortical collecting tubule can be summarized as follows :

1. The tubular membranes of both segments are *almost completely impermeable to urea*, similar to the diluting segment of the early distal tubule; thus, almost all the urea that enters these segments passes on through and into the collecting duct to be excreted in the urine, although some reabsorption of urea occurs in the medullary collecting ducts.
2. Both the late distal tubule and the cortical collecting tubule segments *reabsorb sodium ions*, and the rate of reabsorption is controlled by hormones, especially **aldosterone**. At the same time, these segments secrete potassium ions from the peritubular capillary blood into the tubular lumen, a process that is also controlled by aldosterone and by other factors such as the concentration of potassium ions in the body fluids.
3. The intercalated cells of these nephron segments avidly *secrete hydrogen ions* by an active hydrogen-ATPase mechanism. This process is different from the secondary active secretion of hydrogen ions by the proximal tubule because it is capable of secreting hydrogen ions against a large concentration gradient, as much as 1000 to 1. This is in contrast to the relatively small gradient (4 to 10-fold) for hydrogen ions that can be achieved by secondary active

secretion in the proximal tubule. Thus, the intercalated cells play a key role in acid-base regulation of the body fluids.

4. The permeability of the late distal tubule and cortical collecting duct to water is *controlled by the concentration of ADH*, which is also called vasopressin. *With high levels of ADH, these tubular segments are permeable to water, but in the absence of ADH, they are virtually impermeable to water*. This special characteristic provides an important mechanism for controlling the degree of dilution or concentration of the urine.

(Ref. Guyton & Hall 11th Edition, Page 336, 337)

Medullary collecting duct : Although the medullary collecting ducts reabsorb less than 10 per cent of the filtered water and sodium, they are the final site for processing the urine and, therefore, play an extremely important role in determining the final urine output of water and solutes.

The epithelial cells of the collecting ducts are nearly cuboidal in shape with smooth surfaces and relatively few mitochondria.

Special characteristics of this tubular segment are as follows :

a. The permeability of the medullary collecting duct to water is controlled by the level of ADH. With high levels of ADH, *water* is avidly reabsorbed into the medullary interstitium, thereby reducing the urine volume while at the same time concentrating most of the solutes in the urine.

b. Unlike the cortical collecting tubule, the medullary collecting duct is permeable to *urea*. Therefore, some of the tubular urea is reabsorbed into the medullary interstitium, helping to raise the osmolality in this region of the kidneys and contributing to the kidneys' overall ability to form a concentrated urine.

c. The medullary collecting duct is capable of *secreting hydrogen ions* against a large concentration gradient, as also occurs in the cortical collecting tubule. Thus, the medullary collecting duct also plays a key role in regulating acid-base balance.

(Ref. Guyton & Hall 11th Edition, Page 337, 338)

Summary of urine concentrating mechanism and changes in osmolarity in different segments of the tubules :

1. ***Proximal tubule*** : About 65 per cent of the filtered electrolytes are reabsorbed in the proximal tubule. However the tubular membranes are highly permeable to water, so that whenever solutes are reabsorbed, water also diffuses through the tubular membrane by osmosis. Therefore, the osmolarity of the fluid remains about the same as the glomerular filtrate, 300 mOsm/L.

2. ***Decending Loop of Henle*** : As fluid flows down the decending loop of Henle, water is absorbed into the medulla. The descending limb is highly permeable to water but much less permeable to sodium chloride and urea. Therefore, the osmolarity of the fluid flowing through the descending loop gradually increases until it is equal to that of the surrounding interstitial fluid, which is about 1200 mOsm/L when the blood concentration of ADH is high. When a dilute urine is being formed, owing to low ADH concentrations, the medullary interstitial osmolarity is less than 1200 mOsm/L; consequently the descending loop tubular fluid osmolarity also becomes less concentrated. This is due partly to the fact that less urea is absorbed into the medullary interstitium from the collecting ducts when ADH levels are low and the kidney is forming a large volume of dilute urine.

3. ***Thin ascending Loop of Henle*** : The thin ascending limb is essentially impermeable to water but reabsorbs some sodium chloride. Because of the high concentration of sodium chloride in the tubular fluid, owing to water removal from the descending loop of Henle, there is some passive diffusion of sodium chloride from the thin ascending limb into the medullary interstitium. Thus, the tubular fluid becomes more dilute as the sodium chloride diffuses out of the tubule and water remains in the tubule. Some of the urea absorbed into the medullary interstitium from the collecting ducts also diffuses into the ascending limb, thereby returning the urea to the tubular system and helping to prevent its washout from the renal medulla. This urea recycling is an additional mechanism that contributes to the hyperosmotic renal medulla.

4. ***Thick ascending loop of Henle*** : The thick part of the ascending loop of Henle is also virtually impermeable to water, but large amounts of sodium, chloride, potassium, and other ions are actively transported from the tubule into the medullary interstitium. Therefore, fluid in the thick ascending limb of the Loop of Henle becomes very dilute, falling to a concentration of about 100 mOsm/L.

5. ***Early distal tubule*** : The early distal tubule has properties similar to those of the thick ascending loop of Henle, so that further dilution of the tubular fluid occurs as solutes are reabsorbed while water remains in the tubule.

6. ***Late distal tubule and cortical collecting tubules*** : In the late distal tubule and cortical collecting tubules, the osmolarity of the fluid depends on the presence or absence of ADH. With high levels of ADH, these tubules are highly permeable to water, and significant amounts of water are reabsorbed. Urea, however, is not very permeant in this part of the nephron, resulting in increased urea concentration as water is reabsorbed. This allows most of the urea delivered to the distal tubule and collecting tubule to pass into the inner medullary collecting ducts, from which it is eventually reabsorbed or excreted in the urine. In the absence of ADH, little water is reabsorbed in the late distal tubule and cortical collecting tubule; therefore, osmolarity decreases even

further because of continued active reabsorption of ions from these segments.

7. ***Inner medullary collecting ducts*** : The concentration of fluid in the inner medullary collecting ducts also depends on- i. ADH and ii. the osmolarity of the medullary interstitium established by the countercurrent mechanism. In the presence of large amounts of ADH, these ducts are highly permeable to water, and water diffuses from the tubule into the interstitium until osmotic equilibrium is reached, with the tubular fluid having about the same concentration as the renal medullary interstitium (1200 to 1400 mOsm/L). Thus, a very concentrated but small volume of urine is produced when ADH levels are high. Because water reabsorption increases urea concentration in the tubular fluid, and because the inner medullary collecting ducts are highly permeable to urea, much of the highly concentrated urea in the ducts diffuses out of the tubular lumen into the medullary interstitium. This absorption of the urea into the renal medulla contributes to the high osmolarity of the medullary interstitium and the high concentrating ability of the kidney.

There are several important points to consider that may not be obvious from this discussion :

i. *First*, although sodium chloride is one of the principal solutes that contributes to the hyperosmolarity of the medullary interstitium, *the kidney can, when needed, excrete a highly concentrated urine that contains little sodium chloride*. The hyperosmolarity of the urine in these circumstances is due to high concentrations of other solutes, especially of waste products such as urea and creatinine. One condition in which this occurs is dehydration accompanied by low sodium intake. Low sodium intake stimulates formation of the hormones angiotensin II and aldosterone, which together cause avid sodium reabsorption from the tubules while leaving the urea and other solutes to maintain the highly concentrated urine.

ii. *Second, large quantities of dilute urine can be excreted without increasing the excretion of sodium*. This is accomplished by decreasing ADH secretion, which reduces water reabsorption in the more distal tubular segments without significantly altering sodium reabsorption.

iii. *Finally*, we should keep in mind that there is an *obligatory urine volume*, which is dictated by the maximum concentrating ability of the kidney and the amount of solute that must be excreted. Therefore, if large amounts of solute must be excreted, they must be accompanied by the minimal amount of water necessary to excrete them. For example, if 1200 milliosmoles of solute must be excreted each day, this requires at least 1 liter of urine if maximal urine concentrating ability is 1200 mOsm/L.

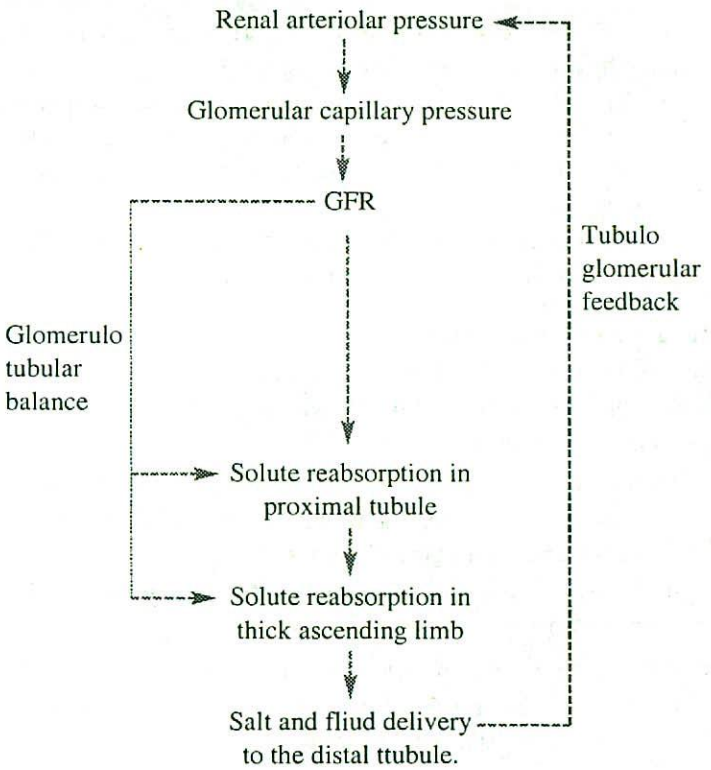
(Ref. Guyton & Hall 11th Edition, Page 355)

Reabsoption & Secretion in the renal tubule

1. Reabsorbed substances : Na^+, K^+, Ca^{++}, Mg^{++}, glucose,amino acids, vitamins, acetoacetone ion, Cl^-, HCo_3^-, So_4^{--}, NO_3^-, PO_4^{-3}, urea etc.
2. Secreted substances : K^+, H^+, ammonia, creatinine, P-aminohippuric acid, penicillin, bromsulphthelin, diodrast etc.
3. Completely reabsorbed substances are : Glucose, proteins, amino acids, acetoacetate ions, and vitamins.
4. Non-reabsorbed substances are : Creatinine, inulin, manitol and sucrose.

(Ref. Guyton & Hall 11th Edition)

Mechanisms of glomerulotubular balance and tubuloglomerular feedback



(Ref. Ganong 22th Edition; Page 713)

Reabsorbtion of water

Passive water reabsorption by osmosis is coupled mainly to sodium reabsorption : When solutes are transported out of the tubule by either primary or secondary active transport, their concentrations tend to decrease inside the tubule while increasing in the renal interstitium. This creates a concentration difference that causes osmosis of water in the same direction that the solutes are transported, from the tubular lumen to the renal interstitium. Some parts of the renal tubule, especially the proximal tubule, are highly permeable to water, and water reabsorption occurs so rapidly that there is only a small concentration gradient for solutes across the tubular membrane.

A large part of the osmotic flow of water occurs through the so-called tight junctions between the epithehal cells as well as through the cells themselves. The reason for this is that the junctions between the cells are not as tight as their name would imply, and they allow significant diffusion of water and small ions. This is especially true in the proximal tubules, which have a high permeability for water and a smaller but significant permeability to most ions, such as sodium, chloride, potassium, calcium, and magnesium.

(Ref. Guyton & Hall 11th Edition, Page 332)

Reabsorbtion of water takes place through out the tubule except ascending limb of loop of Henle by passive diffusion :

i. In the *proximal convoluted tubule*, obligatory reabsorbtion of water takes place along with the active reabsorption of Na.

ii. In *descending limb of loop of Henle* water reabsorption takes place by diffusion.

iii. In *distal convoluted tubule*, facultative water reabsorption occurs. Here anti-diuretic hormone (ADH) increase the permeability of distal convoluted tubular cell which causes water reabsorption.

iv. In *collecting tubule* water reabsorption takes place under the influence of antidiuretic hormone(ADH).

Renal handling of water

Normally about 99.3% of the filtered load of water is reahsorhed in the renal tubular system with excretion of averages 1 ml/minute urine.

I. *Mechanisms* :
   i. Passive reabsorption along the osmotic gradients set up by the active transport of solutes.
   ii. Anti-diuretic-hormone (ADH) dependent H_2O reabsorption.

II. *Reabsorption at different parts of the tubules* :
   i. *PCT* : About 65 - 80% of the filtered water is reabsorbed. Osmolarity : isotonic (300 mosmol/L).
   ii. *Descending limb of loop of Henle* : About 15% water is reabsorhed passively with no solute reabsorption. This makes the isosmotic tubular fluids into hyperosmotic solution.
   Osmolarity : At the tip of the LH the osmolarity reaches to some 1200 to 1400 mosmole/ L.
   iii. *Ascending limb of loop of Henle* : Is impermeable to H_2O but highly permeable to Na^+, Cl^- and urea. This makes the hyperosmotic tubular fluid into hyposmotic solution.
   Osmolarity :
      a. Thin segment- tonicity gradually decreases
      b. Thick segment- hypotonic- 100 mosmol/L.
   iv. *Diluting segment of the distal tubule* : Is impermeable to H_2O but highly permeable to Na^+, Cl^- and urea.
   Osmolarity : More hypotonic.
   v. *Late distal tubule and collecting system* :
      a. Late distal tubule : 5-10% of H_2O is reabsored. H_2O reabsorption depends on the presence of circulating ADH.
      b. Collecting system : 14.7% water is reabsored. H_2O reabsorption depends on the presence of circulating ADH. Thus only 0.5 to 1.5 liters of urine is excreted per day. About 2% is reabsorbed in the absence of ADH.
      Osmolarity :
         a. Hypertonic (upto 1400 mosmol/L) in presence of ADH
         b. Hypotonic (below to 30 mosmol/L) in absence of ADH.

Among 125 ml/min. of glomerular filtrate : Water that is reabsorbed in each segment of the tubules as follows :

a. Proximal tubules : 65%
b. Loop of Henle : 15%
c. Distal tubules : 10%
d. Collecting ducts : 9.3%
e. Passing into the urine : 0.7%

Difference between obligatory and facultative water reabsorption.

Obligatory	*Facultative*
i. It takes place in the PCT.	i. It takes place in the DCT and CT.
ii. It occurs along with the reabsorption of (electrolyte) Na^+.	ii. It occurs under the influence of ADH.
iii. Rate of reabsorption is proportional to GF of the iso-osmotic condition.	iii. Rate of reabsorption is proportional to the ADH secretion.

Obligatory water reabsorption : When the water reabsorption occurs at such a rate that the iso-osmotic condition of glomerular filtrate is maintained in the proximal convoluted tubles, reabsorption of Na^+ from the tubules into in the peritubular fluid of intercellular spaces increases its osmotic pressure while that in the tubules decreases. Since the proximal tubular membrane is highly permeable to water, osmosis of water occur into peritubular fluid from the tubules. It is called obligatory reabsorption of water.

Facultative reabsorption of water : When water reabsorbtion occurs under the influence of Anti-diuretic hormone (ADH).

The distal and collecting tubules are normally impermeable to water. Here water reabsorbtion takes place under the influence of ADH. Anti diuretic hormone itself acts not on the luminal membrane of the tubular epithelial cells but instead on the basolateral membrane of the these cells. It activates the enzyme adenyl cyclase in the membrane, which then causes formation of cyclic adenosine monophosphate (cyclic AMP) in the cell cytoplasm. The cyclic AMP then diffuses to the luminal membrane of the cells where it greatly increases the permeability to water, causes osmosis of water. This is called facultiative water reabsorption.

(Ref. Guyton & Hall 11th Edition)

Tubular handling of sodium

The filtered load of Na^+ is approximately 25,200 mmol per day. About 99.3% of this filtered load is reabsorbed in the renal tubular system with only excretion of 200 - 250 mmol daily in the urine.

The reabsorption of Na^+ occurs by the following mechanism :

i. *Active transport process (co-transport and antiport)* : In the PCT, the thick segment of ALLH, the DTs and the CDs Na^+ moves by co-transport (with glucose, amino acids) process. Na^+ reabsorption is equivalent to Cl^- reabsorption plus H^+ and K^+ secretion into the tubular fluid.

The transport mechanism in the thick ALLH depends on a carrier that transports one Na^+ one K^+ and 2 Cl^- from the tubular lumen into the cells. Na^+-K^+ ATPase actively transports the Na^+ out of the cells into the interstitium.

ii. *Passive reabsorption of Na+* : In the thin segment of the ALLH NaCl is passively reabsorbed.

iii. *Cation exchange process* : In the distal tubules and collecting system Na^+ is reabsorbed by two electrically linked cation exchange processes :

a. Na^+- H^+ exchange involves Na^+ reabsorption and H^+ secretion

b. Na^+-K^+ exchange involves Na^+ reabsorption and K^+ secretion.

These cation exchange processes is competitive (i.e. K^+ competes with H^+ for Na^+). Both cation exchange processes, however, are enhanced by hormone aldosterone.

Mechanism of tubular reabsorption of Na^+ :

Site of reabsorption	*Mechanism*
a. Proximal tubule	a. Active transport
b. ALLH (thick)	b. Co- transport (Na^+-K^+-2Cl)
c. ALLH (thin)	c. Passive transport
d. Distal tubule	d. Aldosterone induced
e. Collecting ducts	e. Countertrausport.

Aldosterone induced Na^+ reabsorption

It enhances the reabsorption of Na^+ from the distal tubule and the collecting system (only 2- 3%). Of the amount of filtered Na^+ only 2- 3% are actively reabsorbed via an aldosterone-dependent cation exchange mechanism in the distal nephron. Aldosterone acts by the following way in this regard :

a. Formation of hormone receptor complex : Upon entering into the tubular epithelial cells aldosterone binds with cytoplasmic receptors to form hormone receptor complex

b. DNA activation and messenger RNA formation : Hormone receptor complex activates DNA and form mRNA by transcription process.

c. Formation of biologically active protein by mRNA : Messenger RNA comes out of the nucleus and form active protein by the process of translation.

d. Protein molecule increases Na^+ permeability by the following ways :

i. *Permease hypothesis* : Protein increases passive permeability of the cell to Na^+.

ii. Metabolic hypothesis : Protein increases the oxidation of substrate to provide ATP.

iii. Pump hypothesis : Protein acts directly to increase the activity of the pump. In any case the effect is increased active transport of Na from the tubular lumen to interstitial space.

Salt appetite mechanism for controlling ECF sodium concentration and volume : Maintenance of normal extracellular fluid volume and sodium concentration requires a balance between sodium excretion and sodium intake. In modern civilizations, sodium intake is almost always greater than necessary for homeostasis. In fact, the average sodium intake for individuals in industrialized cultures eating processed foods usually ranges between 100 and 200 mEq/day, even though humans can survive and function normally on 10 to 20 mEq/day. Thus, most people cat far more sodium than is necessary for homeostasis, and there is evidence that our usual high sodium intake may contribute to cardiovascular disorders such as *hypertension*.

Salt appetite is due in part to the fact that animals and humans like salt and eat it regardless of whether they are salt-deficient. There is also a regulatory component to salt appetite in which there is a behavioral drive to obtain salt when there is sodium deficiency in the body. This is particularly important in herbivores, which naturally eat a low-sodium diet, but salt craving may also be important in humans who have extreme deficiency of sodium, such as occurs in Addison's disease. In this instance, there is deficiency of aldosterone secretion, which causes excessive loss of sodium in the urine and leads to decreased extracellular fluid volume and decreased sodium concentration; both of these changes elicit the desire for salt.

In general, *the two primary stimuli that are believed to excite salt appetite are* :

i. Decreased extracellular fluid sodium concentration
ii. Decreased blood volume or blood pressure, associated with circulatory insufficiency.

These are the common major stimuli that elicit thirst.

The neuronal mechanism for salt appetite is analogous to that of the thirst mechanism. Some of the same neuronal centers in the AV3V region of the brain seem to be involved, because lesions in this region frequently affect both thirst and salt appetite simultaneously in animals. Also, circulatory reflexes elicited by low blood pressure or decreased blood volume affect both thirst and salt appetite at the same time.

(Ref. Guyton 10th Edition; page 363)

Quantitative aspects of Na^+ reabsorption in a normal man on a normal Na^+diet

GFR	125 ml/min	
Plasma HCO_3	27 meq/L	
Plasma Na^+	145 meq/L	
Na^+ filtered per minute	18,125 peq	
Reabsorbed with Cl	14,585 peq	
Reabsorbed while reabsorbing 3375 peq of HCO_3		3,375 peq
Reabsorbed in association with formation of titratable acidity and ammonia		50 peq
Reabsorbed in association with K		50 peq
Total Na^+ reabsorbed per minute		13,000 peq

Table 13-2. Changes in Na^+ excretion that would occur as a result of changes in GFR if there were no concomitant changes in Na^+ reabsorption.

GFR (ml/min)	*Plasma Na^+ (peq/mL)*	*Amount Filtered (peq/min)*	*Amount Reabsorbed (peq/min)*	*Amout Excreted (peq/min)*
125	145	18,125	18,000	125
127	145	18,415	18,000	415
124	145	18,000	18,000	0

Renal handling of urea

Normal plasma level : 2.5 - 6.7 mmol/litre (8-25 mg/dl).

The GFR is normally 125 ml/minute, so daily filtered load of urea is approximately 870 mmol. About 460 mmol is reabsorbed. The daily excretion rate depending upon circumstances ranges 30-70% of the filtered load. Therefore the clearance ratio for urea may vary from 0.3 to 0.7. Urea is both reabsorbed from and secreted into renal tubules.

Thus tubular handling of urea is important for the following facts :

1. Urea increases urine osmolarity i.e formation of concentrated urine by its contribution in the establishment of the osmotic gradient in the medullary pyramids.
2. Urea clearance is a measure of GFR.

Urea reabsorption :

a. *Mechenism* : Reabsorption of urea is always passive, from higher concentration in the urine to a lower concentration in plasma.
b. *Site of reabsorption* :
   i. Proximal convoluted tubule
   ii. Inner portion of the medullary collecting duct (especially in the presence of ADH).
   iii. The decending limb of loop of Henle and thin segment of ascending limb of loop of Henle is permeable to urea.
b. *Site of reabsorption* : Some urea reenters the ALLH.

Renal handling of creatinine

Creatinine derives from muscle cells.

i. Normal serum creatinine value : 0.06 to 0.12 mmol/litre (0.6-1.5 mg/dl).
ii. So daily filtered load of creatinine : 12-15 mmol.
iii. Daily reabsorption : No amount of creatinine is reabsorbed from the renal tubules.
iv. Daily excretion : The clearance of creatinine is 160 ml/minute. A typical adult male excretes about 15 mmol of creatinine per day. Creatinine excretion is, however by both glomerular filtration + tubular secretion (relatively small amount).
v. Significance :
   a. Creatinine clearance is a good measure of GFR.
   b. Creatinine content of the urine falls when body muscle decreases for any reason (for example, from paralysis or muscular dystrophy).
   c. Any rise in serum creatinine is a sensitive indicator of malfunction.

Renal handling of para-aminohippuric acid-PAH

PAH is a derivative of hippuric acid.

i. PAH entered into the tubular fluid by glomerular filtration and tubular secretion. The filtered load of PAH is a linear function of the plasma level, but PAH secretion increases as plasma PAH rises only until a maximal secretion rate is reached.
ii. *Mechenism of secretion* : PAH is secreted actively; an active pump at the peritubular cells help to uptake of PAH from blood to tubular cell.
ii. *Transfer from tubular cell to tubular lumen* : Probably by facilitated diffusion.

Ammonia secretion

Ammonia is produced within the renal tubular epithelial cells

and secreted into tubular lumen. 60% secreted ammonia are derived from metabolism of glutamine and 40% are derived from other amino acids or amines i.e alanine, glycine.

Tubular handling of HCO_3^-

The daily filtered load of HCO_3^- is approximately 4300 to 4500 mmol ($P_{HCO_3^-}$ x GFR). About 99.9 to 100% of the filtered load of HCO_3^- is reabsorbed. The renal threshold for HCO_3^- is around 28 mmol/litre. HCO_3^- appears in the urine and urine becomes alkaline when plasma HCO_3^- concentration ($P_{HCO_3^-}$) exceeds the renal threshold. Reabsorption of HCO_3^- alone cannot maintain normal acid base balance. Therefore kindey can capable of generating new HCO_3^- as well.

HCO_3^- reabsorption : Bicarbonate filtered at the glomerulus must be reabsorbed. Reabsorption of HCO_3^- occurs throughout the nephron except in the descending limb of the loop of Henle. HCO_3^- reabsorption in the proximal tubule is complicated because HCO_3^- cannot diffuse freely across the membrane of the tubular cell, whereas CO_2 diffuses freely. Therefore from the tubular fluid HCO_3^- is entered into the tubular epithelial cells in the form of CO_2.

Process of HCO_3^- reabsorption :

i. Formation of H_2CO_3 in the tubular fluid by combination of secreted H^+ with filtered HCO_3^-.

$$H^+ + HCO_3^- \rightarrow H_2CO_3$$

ii. Dehydration of H_2CO_3 by cabonic anhydrase enzyme.

$$H_2CO_3 \rightarrow H_2O + CO_2$$

iii. Entrance of CO_2 into the tubular epithelial cells.

iv. Formation of H_2CO_3 by cellular carbonic anhydrase.

$$H_2O + CO_2 \rightarrow H_2CO_3$$

v. Dissociation of H_2CO_3.

HCO_3^- is transported into blood across basolateral membrane by a secondary active transport system. H^+ is secreted again into the tubular lumen.

About 90% of the filtered HCO_3^- is reabsorbed into the proximal tubule and 10-15% is reabsorbed in the distal tubule and collecting tubules. Normally 2-3 mmol of HCO_3^- is excreted daily in urine.

i. *HCO_3^- regeneration* : The kidneys generate new HCO_3^- in the renal tubular cell via the hydration of CO_2 and dissociation of H_2CO_3. The amount of new HCO_3^- formed per day is approximately 70-100 mEq. The HCO_3^- that is generated within the tubular cell does not represent filtered HCO_3^-.

ii. *HCO_3^- secretion* : The entire segments of the neprone normally reabsorb HCO_3^- except for the cortical collecting ducts. The type B cells of the collecting ducts secrete HCO_3^- into the tubular lumen by the HCO_3-Cl^- exchange mechanism. This HCO_3^- secreting mechanism is important in metabolic alkalosis.

Tubular handling of K^+

K^+ is the only plasma electrolyte that is both secreted into the renal tubules.

i. The normal plasma value : 3.5 - 5.0 mmol/L.

ii. Daily filtered load : About 600 mmol.

iii. *Daily secretion into tubules* : About 50 mmol. The secretion of K^+ is a function of distal tubule. Secretion is influenced by aldosterone and involves an active transport and a passive diffusion process. The steps of K^+ secretion and the role of aldosterone in K^+ secretion may be summarized as follows :

a. Active transport of K^+ from the interstitial fluid into tubular epithelial cells via the Na^+-K^+ATPase pump.

b. Aldosterone increases the activity of the Na^+-K^+ ATase pump in the basolateral membrane of the distal tubular cells.

* Elevation of the intracellular (K^+) favors the net K^+ diffusion at the luminal membrane down a concentration gradient into the tubular lumen. Aldosterone increases the permeability of the luminal membrane to K^+.

* In the distal tubules, K^+ secretion is generally coupled with Na^+ reabsorption in the presence of aldosterone. Since Na^+ is also reabsorbed in association with H^+ secretion, there is competition between K^+ and H^+ for Na^+. When the total body K^+ is high (i.e. hyperkalaemia), H^+ secretion is inhibited; K^+ secretion and excretion are therefore facilitated. Conversely, in hypokalaemia, K^+ secretion declines.

iv. Reabsorption : About 93-94% of the filtered load of K^+ is reabsorbed fron renal tubules. The tubular reabsorption occurs by a transport in the PCT, ALLH, DT, CD.

iv. Daily excretion : 90 mmol. The excretion increased in :

a. Hyperaldosteronaemia (excess K~ secretion)

b. Metabolic alkalosis

c. Uncontrolled diabetes mellitus

Relationship between plasma K^+ and HCO_3^- reabsorption

HCO_3^- reabsorption depends on H^+ secretion. An increase in intracellular H^+ causes increase tubular H^+ secretion - thus favors HCO_3^- reabsorption. Plasma K^+ concentration affects the intracellular H^+ concentration, therefore, influences HCO_3^- reabsorption. There is an inverse relationship between plasma K^+ and HCO_3^- reabsorption.

i. In hypokalaemia : Low plasma $K^+ \rightarrow$ K^+ efflux with influx of Na^+ & $H^+ \rightarrow$ intracellular acidosis $\rightarrow$ more H^+ secretion $\rightarrow$ more reabsorption of HCO_3^-.

ii. In hyperkalaemia : High plasma $K^+ \rightarrow K^+$ influx with efflux of H^+ & $Na^+ \rightarrow$ intracellular alkalosis $\rightarrow$ less H^+ secretion $\rightarrow$ reduce HCO_3^- reabsorption.

Tubular secretion of H^+

I. *The daily filtered load of H^+* : is very negligible i.e only < 0.1 mmol per day.

II. *Tubular secretion* : Is the main source of H^+ in the tubular fluid. Approximately 43-75 mmol H^+ is secreted into the tubular fluid each day.

III. *Reabsorption* : 98-99% of the secreted H^+ is reabsorbed daily.

IV. *Secretion* : About 5 -60 mmol H^+ is excreted daily.

i. *The significance of secretion into renal tubule* :
   a. To maintain normal plasma HCO_3^-
   b. To maintain normal acid-base status of the body.

ii. *Site of secretion* : H^+ secretion occurs in all parts of the nephron except DLLH. Approximate proportions are :
   a. Proximal convulated tubules : 85%
   b. ALLH and distal tubule : 18%
   c. Collecting ducts : 5%

iii. *Mechanism of H^+ secretion* : H^+ is secreted into the tubular lumen by active transport. The primary reaction that is responsible for the H^+ secretion in the different parts of nephrons is :
   a. Proximal tubule : Na^+-H^+ exchange
   b. Distal tubule : Hormone (aldosterone) induced cation exchange i.e Na^+-H^+ exchange.
   c. Collecting ducts : Na^+-H^+ exchange, H^+-K^+ ATPase pump.

iv. *Fate of secreted H^+ in the tubular fluid* : Within the tubular system three important reactions remove free H^+, permitting continuous H^+ secretion in the tubular fluid is mandatory to maintain acid base homeostasis :
   a. Secreted H^+ reacts with HCO_3^- in the proximal and distal tubular fluid- causing HCO_3^- reabsorption
   b. Secreted H^+ reacts with dibasic phosphate ($HPO4^{--}$) in the distal tubules and collecting ducts- causing formation of monobasic phosphate.
   c. Secreted H^+ reacts with NH_3 to form NH_4^+ in the priximal and distal tubules.

The majority of the secreted H^+ is used to bring about HCO_3^- reabsorption and, therefore is not excreted. The most of the H^+ that is excreted occurs in the form of monobasic phosphate and NH_4^+.

Summary of reabsorption and secretion in different parts of the renal tubules

I. *Proximal convulated tubule* :
   i. Reabsorption in proximal tubule :
      a. Glucose and amino acids: 100%
      b. Sodium : 65%
      c. Water : 65%
      d. Urea : 50%
      e. All filtered potassium
      f. Other electrolytes
   ii. Secretion in proximal tubule :
      a. Variable proton secretion for acid-base regulation
      b. Organic ion secretion.

II. *Distal convulated tubule* :
   i. Reabsorption in distal tubule :
      a. Sodium : Variable, controlled by aldosterone
      b. Chloride : follows passively
      c. Water : Variable,controlled by ADH
   ii. Secretion in distal tubule :
      a. Proton secretion : Variable for acid-base regulation
      b. Potassium : Variable, controlled by aldosterone

II. *Collecting duct* :
   a. Water : Variable, reabsorption controlled by ADH
   b. Proton : Variable secretion for acid-base regulation.

Renal tubular buffer system

a. *Buffer systems* : The continuous secretion of H^+ in the tubular fluid is maintained by the operation of the three important buffer systems :

i. *Bicarbonate buffer* : The concentration of HCO_3^- in plasma, and consequently in the glomerular filtrate, normally about 24 mEq/litre. Therefore, in the proximal tubule, most of the secreted H^+ reacts with HCO_3^- to form H_2CO_3, which dissociates into CO_2 and H_2O.

ii. *Phosphate buffer* : The concentration of HPO_4^{--} in the glomerular filtered is only 1.5 meq/litre, but in the distal tubular fluid it is greatly concentrated due to H_2O reabsorption. Thus phosphate buffer is mainly acts in distal tubule. In the urine hydrogen ions are buffered mainly by the phosphate buffer system.

$$H^+A^- + HPO_4^{--} = A + H_2PO_4$$

iii. *Ammonia buffer* : Renal tubular cells secrete NH_3 in the tubular fluid (own urinary buffer). NH_3 reacts with secreted H^+ to form NH_4^+.

b. *Buffer systems acting in renal tubules* :

Buffer system	*Site of action*
i. Bicarbonate (HCO_3^-/CO_2)	i. Proximal and distal tubule
ii. Phosphate ($HPO_4^{--}/H_2PO_4^-$)	ii. Distal tubule and collecting ducts

iii. Ammonia (NH_3/NH_4^+) and distal tubule. iii. Proximal tubule

c. *Importance of renal tubular buffers* :

i. Maintaining continual H^+ secretion in the tubular fluid : Buffer systems *tied up* H^+ in the urine. If there are no buffers, the limiting pH of urine (4.5) would be reached rapidly, and H^+ secretion would stop. Thus urinary buffers facilitate the H^+ excretion without touching the minimum pH of urine.

ii. Acidification of urine.

iii. Maintenance of acid-base homeostasis.

Buffering in Vivo : Buffering in vivo is of course not limited to the blood. The principal buffers in the blood, interstitial fluid, and intracellular fluid are listed in *Table*. The principal buffers in cerebrospinal fluid and urine are the bicarbonate and phosphate systems.

In metabolic acidosis, only 15-20% of the acid load is buffered by the H_2CO_3-HCO_3 system in the ECF, and most of the remainder is buffered in cells.

In metabolic alkalosis, about 30-35% of the OH^- load is buffered in cells.

In respiratory acidosis and *alkalosis*, almost all the buffering is intracellular.

(Ref. Ganong 22th Edition; Page 733)

Principle buffers in body fluids :

i. Blood : a. $H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$

b. $HProt \rightleftharpoons H^+ + Prot^-$

c. $HHb \rightleftharpoons H^+ + Hb^-$

ii. Interstitial fluid : a. $H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$

iii. Intracellular fluid : a. $HProt \rightleftharpoons H^+ + Prot^-$

b. $H_2PO_4^- \rightleftharpoons H^+ + HPO_4^{2-}$

(Ref. Ganong 22th Edition; Page 733)

When a strong acid is added to the blood, the major buffer reactions are driven to the left. The blood levels of the three 'buffer anions"- Hb^- (hemoglobin), $Prot^-$ (protein), and HCO_3^- -consequently drop. The anions of the added acid are filtered into the renal tubules. They are accompanied ('covered") by cations, particularly Na^+, because electrochemical neutrality is maintained. The renal tubules replace the Na^+ with H^+ and in so doing reabsorb equimolar amounts of Na^+ and HCO_3^-, thus conserving the cations, eliminating the acid, and restoring the supply of buffer anions to normal.

When CO_2 is added to the blood, similar reactions occur, except that since it is H_2CO_3 that is formed, the plasma HCO_3^- rises rather than falls.

(Ref. Ganong 22th Edition; Page 733, 734)

Clinical evaluation of acid-base status

In evaluating disturbances of acid-base balance, it is important to know the pH and HCO_3^- content of arterial plasma. Reliable pH determinations can be made with a pH meter and a glass pH electrode. The HCO_3^- content of plasma cannot be measured directly, but the Pco_2 can be measured with a CO_2 electrode and the HCO_3^- concentration calculated. The Pco_2 is 7-8 mm Hg higher and the pH 0.03-0.04 unit lower in venous than arterial plasma because venous blood contains the CO_2 being carried from the tissues to the lungs. Therefore, the calculated HCO_3^- concentration is about 2 mmol/L higher. However, if this is kept in mind, free-flowing venous blood can be substituted for arterial blood in most clinical situations.

A measurement that is of some value in the differential diagnosis of metabolic acidosis is the **anion gap**. This gap which is something of a misnomer, refers to the difference between the concentration of cations other than Na^+ and the concentration of anions other than Cl^- and HCO_3^- in the plasma. It consists for the most part of proteins in the anionic form, HPO_4^{2-}, SO_4^{2-}, and organic acids, and a normal value is about 12 meq/L. It is increased when the plasma concentration of K^+, Ca^{2+}, or $Mg2+$ is decreased; when the concentration of or the charge on plasma proteins is increased; or when organic anions such as lactate or foreign anions accumulate in blood. It is decreased when cations are increased or when plasma albumin is decreased. The anion gap is increased in metabolic acidosis due to ketoacidosis, lactic acidosis, and other forms of acidosis in which organic anions are increased. It is not increased in hyperchloremic acidosis due to ingestion of NH_4CI or carbonic anhydrase inhibitors.

(Ref. Ganong 22th Edition; Page 736)

N.B.

Plasma anion gap :

Law of neutrality : Cations = Anions

i.e $Na^+ + K^+$ + unmeasured cations (UC)

$= Cl^- + HCO_3^-$ + unmeasured anions (UA)

$(Na^+ + K^+) - (Cl^- + HCO_3^-)$

= Unmeasured anions - unmeasured cations

= UA - UC

= Anion gap

UC : Ca++, Mg++, gama globulin

UA : Plasma protein, SO_4, PO_4, lactate, others

Normal value : 12 (+/-) 4 meq/L.

Causes of increased anion gap :

i. Renal failure

ii. Lactic acidosis

iii. Ketoacidosis

iv. Intoxication of aspirin, alcohol poisoning.

N.B. End product of alcohol metabolism → organic acid → anion of that organic acid → increase anion gap).

Plasma pH, HCO_3^-, and P_{CO_2} values in varios typical disturbances of acid base balance : *(Arterial plasma)*

Condition	*pH*	*HCO_3^- (meq/L)*	*P_{CO_2} (mmHg)*	*Cause*
Normal	7.40	24.1	40	
Metabolic	*7.28*	*18.1*	*40*	*NH_4Cl ingestion*
acidosis	*6.96*	*5.0*	*23*	*Diabetic acidosis*
Metabolic	7.50	30.1	40	$NaHCO_3$ ingestion
alkalosis	7.56	49.8	58	Prolonged vomitting
Respiratory	*7.34*	*25.0*	*48*	*Breathing 7% CO_2*
acidosis	*7.34*	*33.5*	*64*	*Emphysema*
Respiratory	7.53	22.0	27	Voluntary hyperventilation
alkalosis	7.48	18.7	26	Three-week residence at 4000-maltitude

(Ref. Ganong 22th Edition; Page 736)

Acid base disorder

Types of acid base disorder :

1. *Simple acid base disorder* :
   - i. *Metabolic*
     - a. Acidosis (decrease HCO_3^-)
     - b. Alkalosis (increase HCO_3^-)
   - ii. *Respiratory*
     - a. Acidosis (increase PCO_2)
     - b. Alkalosis (decrease PCO_2)
2. *Complex acid base disorder* : If both component vary. Any combination of 4 simple acid base disorder, but all four can not persist in a body.

Acid base parameters

1. Classical acid base parameters
   - i. pH (7.4)
   - ii. PCO_2 (40 mm of Hg)
2. Non classical acid base parameters
   - i. Plasma anion gap
   - ii. Electrolytes.

Respiratory Acidosis

A rise in arterial P_{CO_2} due to decreased ventilation causes *respiratory acidosis*. The CO_2 that is retained is in equilibrium with H_2CO_3, which in turn is in equilibrium with HCO_3^-, so that the plasma HCO_3^- rises and a new equilibrium is reached at a lower pH.

Conversely, a decline in P_{CO_2} causes *respiratory alkalosis*.

(Ref. Ganong 22th Edition; Page-734)

Causes of respiratory acidosis :

i. Physiological :
   a. Alveolar hypoventilation.
   b. Increased CO_2 in atmosphere.

ii. Pathological :
   a. Chronic obstructive pulmonary disease (COPD)
   b. Asthma, pneumonia, emphysema, chronic bronchitis
   c. Poliomyelitis
   d. Neuromuscular causes
   e. Chest deformities- kyphosis, iordosis etc
   f. Depression of respiratory centre- morphine poisoning.

Renal compensation of respiratory acidosis : HCO_3^- reabsorption in the renal tubules depends not only on the filtered load of HCO_3^-, which is the product of the GFR and the plasma HCO_3^- level, but also on the rate of H^+ secretion by the renal tubular cells, since HCO_3^- is reabsorbed by exchange for H^+. The rate of H^+ secretion and hence the rate of HCO_3^- reabsorption is proportionate to the arterial P_{CO_2}, probably because the more CO_2 that is available to form H_2CO_3 in the cells, the more H^+ can be secreted. Furthermore, when the P_{CO_2} is high, the interior of most cells becomes more acidic.

In respiratory acidosis, renal tubular H^+ secretion is therefore increased, removing H^+ from the body; and even though the plasma HCO_3^- is elevated, HCO_3^- reabsorption is increased, further raising the plasma HCO_3^-. Cl^- excretion is increased, and plasma Cl^- falls as plasma HCO_3^- is increased.

(Ref. Ganong 22th Edition; Page-734)

In respiratory acidosis :

$$= \frac{HCO_3^-}{\textit{increased } PCO_2}$$

$$\textit{Compensation} = \frac{\text{increase } HCO_3^-}{\text{increased } PCO_2}$$

→ pH becomes normal, but total body CO_2 increases due to * *HCO_3^- generation* by the kidney *(Kidney system managed).*

Respiratory Alkalosis

A decline in P_{CO_2} causes *respiratory alkalosis.*

Causes of respiratory alkalosis :

a. Hyperventilation
b. Hysteria
c. Hyperapnoea at high altitude

d. Salicylate poisoning
e. Lobar pneumonia
f. Meningitis
g. Enchephalitis
h. Hepatic failure.

Renal compensation in respiratory alkalosis, the low P_{CO_2} hinders renal H^+ secretion, HCO_3^- reabsorption is depressed, and HCO_3^- is excreted, further reducing the already law plasma HCO_3^- and lowering the pH towards normal.

(Ref. Ganong 22th Edition; Page-734)

Respiratory alkalosis :

$$= \frac{HCO_3^-}{\textit{decreased } PCO_2}$$

$$\textit{Compensation} = \frac{\text{decrease } HCO_3^-}{\text{decreased } PCO_2}$$

→ pH becomes normal,
but total body CO_2 decreases due to * *increase HCO_3^- excretion* by the kidney
(Kidney sysrem managed).

Metabolic acidosis

When acids stronger than HHb and the other buffer acids are added to blood, *metabolic acidosis* is produced. If, for example, H_2SO_4 is added, the H^+ is buffered and the Hb^-, $Prot^-$, and HCO_3^- levels in plasma drop. The H_2CO_3 formed is converted to H_2O and CO_2, and the CO_2 is rapidly excreted via the lungs. This is the situation in uncompensated metabolic acidosis. Actually, the rise in plasma H^+ stimulates respiration, so that the P_{CO_2}, instead of rising or remaining constant, is reduced. This *respiratory compensation* raises the pH even further.

(Ref. Ganong 22th Edition, Page 734)

Causes :

a. Diarrhea
b. Diabetic mellitus
c. Renal failure (failure of excretion of metabolic acid)
d. Ingestion of acids
e. Formation of excessive quantities of metabolic acid in the body
f. Loss of excessive alkali from the body
g. Intravenous administration of metaoolic acid
h. Acidic poisoning i.e acetyl salicylates (aspirin) and methyl alcohol.

Renal compensation : The *renal compensatory* mechanisms then bring about the excretion of the extra H^+ and return the buffer systems to normal.

The anions that replace HCO_3^- in the plasma in metabolic acidosis are filtered, each with a cation (principally Na^+), thus maintaining electrical neutrality. The renal tubular cells secrete H^+ into the tubular fluid in exchange for Na^+; and for each H^+ secreted, one Na^+ and one HCO_3^- are added to the blood. The limiting urinary pH of 4.5 would be reached rapidly and the total amount of H^+ secreted would be small if there were no buffers in the urine that tied up H^+. However secreted H^+ reacts with HCO_3 to form CO_2 and H_2O (bicarbonate reabsorption); with HPO_4^{2-} to form $H_2PO_4^-$ and with NH_3 to form NH_4^+. In this way large amounts of H^+ can be secreted, permitting correspondingly large amounts of HCO_3^- to be returned to (in the case of bicarbonate reabsorption) or added to the depleted body stores and large numbers of the cations to be reabsorbed. It is only when the acid load is very large that cations are lost with the anions, producing diuresis and depletion of body cation stores. In chronic acidosis, glutamine synthesis in the liver is increased, using some of the NH_4^+ that usually is converted to urea, and the glutamine provides the kidneys with an additional source of NH_4^+. NH_3 secretion increases over a period of days, further improving the renal compensation for acidosis. In addition, the metabolism of glutamine in the kidneys produces alpha-ketoglutarate, and this in turn is decarboxylated, producing HCO_3^- which enters the bloodstream and helps buffer the acid load.

Metabolic acidosis :

$$= \frac{\textit{decreased } HCO_3^-}{PCO_2}$$

$$\textit{Compensation} = \frac{\text{decreased } HCO_3^-}{\text{decrease } PCO_2}$$

→ pH becomes normal,
but total body CO_2 decreases due to * *hyperventilation*
(Respiratory sysrem managed).

The overall reaction in blood when a strong acid such as H_2SO_4 is added is

$$2NaHCO_3 + H_2SO_4 \qquad Na_2SO_4 + 2H_2CO_3$$

For each mole of H^+ added, 1 mole of $NaHCO_3$ is lost. The kidney in effect reverses the reaction :

$$Na_2SO_4 + 2H_2CO_3 \qquad 2NaHCO_3 + 2H^+ + SO_4^{2-}$$

and the H^+ and SO_4^{2-} are excreted. Of course, H_2SO_4 is not excreted as such, the H^+ appearing in the urine as titratable acidity and NH_4^+.

In *metabolic acidosis*, the respiratory compensation tends to inhibit the renal response in the sense that the induced drop in P_{CO_2}, hinders acid secretion, but it also decreases the filtered load of HCO_3^- and so its net inhibitory effect is not great.

(Ref. Ganong 22th Edition, Page 734, 735)

Metabolic Alkalosis

When the free H^+ level falls as a result of addition of alkali or removal of acid, *metabolic alkalosis* results. In metabolic alkalosis, the plasma HCO_3^- level and pH rise.

Causes :

a. Administration of diuretics
b. Excess aldosterone secretion
c. Vomiting of gastric contents- rich in HCI
d. Ingestion of alkaline drugs i.e $NaHCO_3$ for gastritis or peptic ulcer.

Respiratory compensation : The respiratory compensation is a decrease in ventilation produced by the decline in H^+ concentration, and this elevates the Pco_2. This brings the pH back toward normal while elevating the plasma HCO_3^- level still further. The magnitude of this compensation is limited by the carotid and aortic chemoreceptor mechanisms, which drive the respiratory center if there is any appreciable fall in the arterial Po_2. In metabolic alkalosis, more renal H^+ secretion is expended in reabsorbing the increased filtered load of HCO_3^- and if the HCO_3^- level in plasma exceeds 26-28 meq/L, HCO_3^- appears in the urine. The rise in Pco_2 inhibits the renal compensation by facilitating acid secretion, but its effect is relatively slight.

(Ref. Ganong 22th Edition, Page 735)

Metabolic alkalosis :

$$= \frac{\textit{increased } HCO_3^-}{PCO_2}$$

$$\text{Compensation} = \frac{\text{increased } HCO_3^-}{\text{increase } PCO_2}$$

→ pH becomes normal,
but total body CO_2 increases due to * *hypoventilation*
(Respiratory sysrem managed).

Q.03. **Define alkalosis? Classify it. What is the effects of alkalosis on the body.**

i. *Definition* : It may be defined as a pathological condition in which H^+ is decreased below 43.6 rnEq/L of blood or pH is increased above 7.4 due to the accumulation of base or the loss of acid in the body.

ii. *Types* :

a. Respiratory alkalosis : A decreased arterial PCO_2 below normal resulting in increase pH is called respiratory alkalosis.

b. Metabolic alkalosis : An increased pH due to increase HCO_3^- concentration is called metabolic alkalosis.

iii. *Effects* :

a. Over excitation of nervous system.

b. Muscles go into a state of tetany i.e a state of tonic spasm.

c. Tetany usually appears first in the muscles of forearm, then spreads rapidly to the muscles of the face and finally all over the body.

d. Extremely alkaline patients may die for tetany of respiratory muscles.

(Q. Write short notes on- Alkalosis)

In compensatory mechenism of acid baes disorder :

4 sequele occurs :

1. Total body CO_2 decreases in-
   i. Metabolic acidosis
   ii. Respiratory alkalosis
   iii. Metabolic acidosis + Respiratory alkalosis.
2. Total body CO_2 increases in-
   i. Metabolic alkalosis
   ii. Respiratory acidosis.
3. Total body CO_2 normal with acid baes disorder in-
   i. Metabolic acidosis + Respiratory acidosis
   ii. Metabolic alkalosis + Respiratory alkalosis.
4. Total body CO_2 normal with acid baes disorder in-
   i. Metabolic acidosis + Metabolic alkalosis.

Q.00. **Define acidosis. Classify it.**

i. *Definition* : It may be defined as a pathological condition in which H^+ is increased above 43.6 mEq/L of blood or pH is decreased below 7.4 due to accumulation of acid or loss of base in the body.

ii. *Types* :

a. Respiratory acidosis : An increased arterial PCO_2 above normal resulting in decrease pH is called respiratory acidosis.

b. Metabolic acidosis : Decreased pH due to HCO_3^- deficit is called metabolic acidosis.

Q.02. **What is the effects of acidosis on the body?**

Ans. Effects of acidosis : The major effect of acidosis is depression of the CNS. The nervous system becomes so depressed that the person becomes disoriented and latter comatose. Therefore patients dying of diabetic acidosis, uraemic acidosis and other types of actdosis usually die in state of coma.

(Q: Write short notes on-Acidosis. Ans. Definition + Types + Effects on body)

Renal handling of various plasma constituents in a normal adult human on an average diet.

Substance	Per 24 Hours				Percentage Reabsorbed	Location
	Filtered	Reabsorbed	Secreted	Excreted		
Na^+ (meq)	26,000	25,850		150	99.4	P, L, D, C
K^+ (meq)	600	560[2]	50[2]	90	93.3	P, L, D, C
Cl^- (meq)	18,000	17,850		150	99.2	P, L, D, C
HCO_3^-(meq)	4,900	4,900		0	100	P, D
Urea (mmol)	870	460[3]		410	53	P, L, D, C
Creatinine (mmol)	12	1[4]	1[4]	12		
Uric acid (mmol)	50	49	4	5	98	P
Glucose (mmol)	800	800		0	100	P
Total solute (mosm)	54,000	53400	100	700	87	P, L, D, C
Water (mL)	180,000	179,000		1000	99.4	P, L, D, C

[1] *P, proximal tubules; L, loops of Henle; D, distal tubules; C, collecting ducts.* [2] *K^+ is both reabsorbed and secreted.*
[3] *Urea diffuses into as well as out of some portions of the nephron.*
[4] *Variable secretion and probable reabsorption of creatinine in humans.*

(Ref. Ganong 22th Edition, Page 710)

Urine

Mechanism of formation of urine

Urine formation takes place by the following three mechanism.

i. Formation of glomerular filtrate.
ii. Reabsorption of glomerular filtrate from tubule.
iii. Tubular secretion.

Formation of glomerular filtrate : Due to the effective filtration pressure glomerular filtrate is formed through the glomerular membrane. Total amount of glomerular filtrate is 180 liter/ day.

Tubular reabsorption : Please see page 13.24

Tubular secretion :

a. *In proximal tubule :* H^+, K^+& NH_3 is secreted.
b. *In thin segment :* Na^+ by the passive diffusion .
c. *In thick segment :* Urea by passive diffusion.
d. *In distal tubule :* NH_3 is secreted and also K^+ & H^+ with the help of exchange pump.

In these way urine is formed.

Mechanism of formation of dilute urine

When the glomerular filtrate is initially formed, its osmolarity is about the same as plasma (300 mOsm/L). To excrete excess water, it is necessary to dilute the fiirate as it passes along the tubule. This is achieved by reabsorbing solutes to a greater extent than water.

i. *Tubular fluid remains isosmotic in the proximal tubule* : As fluid flows through the proximal tubule, solutes and water are reabsorbed in equal proportions, so that little change in osmolarity occurs; that is, the proximal tubule fluid remains isosmotic to the plasma, with an osmolarity of about 300 mOsm/L.

ii. As fluid passes down the *descending loop of Henle*, water is reabsorbed by osmosis and the tubular fluid reaches equilibrium with the surrounding interstitial fluid of the renal medulla, which is very hypertonic- about two to four times the osmolarity of the original glomerular filtrate. Therefore, the *tubular fluid becomes more concentrated as it flows into the inner medulla.*

iii. *Tubular fluid becomes dilute in the ascending loop of Henle* : In the ascending limb of the loop of Henle, especially in the thick segment, sodium, potassium, and chloride are avidly reabsorbed. However, this portion of the tubular segment is impermeable to water, even in the presence of large amounts of ADH. Therefore, the tubular fluid becomes more dilute as it flows up the ascending loop of Henle into the early distal tubule, with the *osmolarity decreasing progressively to about 100 mOsm/L* by the time the fluid enters the early distal tubular segment. Thus, *regardless of whether ADH is present or absent, fluid leaving the early distal tubular segment is hypo-osmotic, with an osmolarity of only about one third the osmolarity of plasma.*

iv. *Tubular fluid in the distal and collecting tubules is further diluted in the absence of ADH* : As the dilute fluid in the

early distal tubule passes into the late distal convoluted tubule, cortical collecting duct, and collecting duct, there is additional reabsorption of sodium chloride. *In the absence of ADH, this portion of the tubule is also impermeable to water, and the additional reabsorption of solutes causes the tubular fluid to become even more dilute, decreasing its osmolarity to as low as 50 mOsm/L.* The failure to reabsorb water and the continued reabsorption of solutes lead to a large volume of dilute urine.

N.B. To summarize, *the mechanism for forming a dilute urine* is to continue reabsorbing solutes from the distal segments of the tubular system while failing to reabsorb water. In healthy kidneys, *fluid leaving the ascending loop of Henle and early distal tubule is always dilute, regardless of the level of ADH.* In the *absense of ADH, the urine is further diluted in the late distal tubule and collecting ducts*, and a large volume of dilute urine is excreted.

(Ref. Guyton & Hall 11th Edition; Page 348, 349)

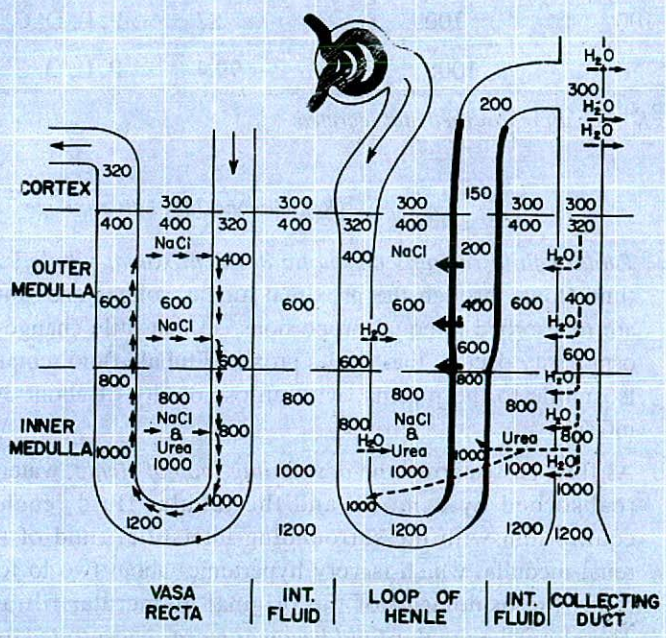


Fig. 13-7 . The countercurent mechanism for concentrating the urine (numerical value are in milliosmoles per liter)

Counter current hypothesis : A small change of osmolarity at any level of fluid flowing in counter direction in the two parallel tubules connected each other in hair pin manner can be multiplied several times along the length of the tubules.

Counter current mechanism

When a fluid passes through two parallel stem of 'U' shaped tube in opposite direction with close proximity is called counter current mechanism . During this counter current flow tremendous concentration of solute can be build up at the top of the loop.

U shaped vasa recta is called the counter current exchanger.
U shaped loop of Henle is called counter current multiplier.

Counter current exchange mechanism

There are two special features of the renal medullary blood flow that contribute to the preservation of the high solute concentrations:

i. *The medullary blood flow is low*, accounting for only 1 to 2 per cent of the total renal blood flow. This sluggish blood flow is sufficient to supply the metabolic needs of the tissues but helps to minimize solute loss from the medullary interstitium.

ii. *The vasa recta serve as countercurrent exchangers*, minimizing washout of solutes from the medullary interstitium.

The countercurrent exchange mechanism operates as follows :
Blood enters and leaves the medulla by way of the vasa recta at the boundary of the cortex and renal medulla. The vasa recta, like other capillaries, are highly permeable to solutes in the blood, except for the plasma proteins. As blood descends into the medulla toward the papillae, it becomes progressively more concentrated, partly by solute entry from the interstitium and partly by loss of water into the interstitium. By the time the blood reaches the tips of the vasa recta, it has a concentration of about 1200 mOsm/L, the same as that of the medullary interstitium. As blood ascends back toward the cortex, it becomes progressively less concentrated as solutes diffuse back out into the medullary interstitium and as water moves into the vasa recta.

Thus, although there is a large amount of fluid and solute exchange across the vasa recta, there is little net dilution of the concentration of the interstitial fluid at each level of the renal medulla because of the U shape of the vasa recta capillaries, which *act as countercurrent exchangers*. Thus, *the vasa recta do not create the medullary hyperosmolarity, but they do prevent it from being dissipated.*

Function : Thus, under steady-state conditions, the vasa recta carry away only as much solute and water as is absorbed from the medullary tubules, and *the high concentration of solutes established by the countercurrent mechanism is maintained.*

(Ref.Guyton & Hall 11th Edition; Page 354)

Counter current multiplier mechanism

Definition : The repetitive reabsorption of sodium chloride by the thick ascending loop of Henle and continued inflow of new sodium chloride from the proximal tubule into the loop of Henle is called the *countercurrent multiplier*.

The sodium chloride reabsorbed from the ascending loop of Henle keeps adding to the newly arrived sodium chloride, thus *'multiplying' its concentration in the medullary interstitium.*

Steps involved in causing the hyperosmotic renal medullary interstitium :

First, assume that the loop of Henle is filled with fluid with a

concentration of 300 mOsm/L, the same as that leaving the proximal tubule.

Step 2 : Next, the active pump of the thick ascending limb on the loop of Henle is turned on, reducing the concentration inside the tubule and raising the interstitial concentration; this pump establishes a 200-mOsm/L concentration gradient between the tubular fluid and the interstitial fluid (*step 2*). The limit to the gradient is about 200 mOsm/L because paracellular diffusion of ions back into the tubule eventually counterbalances transport of ions out of the lumen when the 200-mOsm/L concentration gradient is achieved.

Step 3 is that the tubular fluid in the descending limb of the loop of Henle and the interstitial fluid quickly reach osmotic equilibrium because of osmosis of water out of the descending limb. The interstitial osmolarity is maintained at 400 mOsm/L because of continued transport of ions out of the thick ascending loop of Henle. Thus, by itself, the active transport of sodium chloride out of the thick ascending limb is capable of establishing only a 200-mOsm/L concentration gradient, much less than that achieved by the countercurrent system.

Step 4 is additional flow of fluid into the loop of Henle from the proximal tubule, which causes the hyperosmotic fluid previously formed in the descending limb to flow into the ascending limb. Once this fluid is in the ascending limb, additional ions are pumped into the interstitium, with water remaining behind, until a 200-mOsm/L osmotic gradient is established, with the interstitial fluid osmolarity rising to 500 mOsm/L *(step 5)*. Then, once again, the fluid in the descending limb reaches equilibrium with the hyperosmotic medullary interstitial fluid *(step 6)*, and as the hyperosmotic tubular fluid from the descending limb of the loop of Henle flows into the ascending limb, still more solute is continuously pumped out of the tubules and deposited into the inedullary interstitium.

These steps are repeated over and over, with the net effect of adding more and more solute to the medulla in excess of water, with sufficient time, *this process gradually traps solutes in the medulla and multiplies the concentration gradient established by the active pumping of ions out of the thick ascending loop of Henle, eventually raising the interstitial third osmolarity to 1200 to 1400 mOsm/L.*

(Ref. Guyton & Hall 11th Edition; Page 351)

Concentrated urine

Mechanism of formation of concentrated urine : The ability of the kidney to form a urine that is more concentrated than plasma is essential for survival of mammals that live on land, including humans. The basic requirements for forming a concentrated urine are-

1. *A high level of ADH*, which increases the permeability of the distal tubules and collecting ducts to water, thereby allowing these tubular segments to avidly reabsorb water.
2. *A high osmolarity of the renal medullary interstitial fluid*, which provides the osmotic gradient necessary for water reabsorption to occur in the presence of high levels of ADH.

   The major factors that contribute to the buildup of solute concentration into the renal medulla are as follows :

   i. Active transport of sodium ions and co-transport of potassium, chloride, and other ions out of the thick portion of the ascending limb of the loop of Henle into the medullary interstitium.

   ii. Active transport of ions from the collecting ducts into the medullary interstitium.

   iii. Passive diffusion of large amounts of urea from the inner medullary collecting ducts into the medullary interstitium.

   iv. Diffusion of only small amounts of water from the medullary tubules into the medullary interstitium, far less than the reabsorption of solutes into the medullary interstitium

(Ref. Guyton & Hall 11th Edition; Page 350, 351)

Acidification of urine

The ability of the renal tubules to reduce urinary pH is called acidification of urine. The major sites of urine acidification are the distal and collecting tubules. Acidification of urine requires following processes :

i. *H^+ secretion in the tubular fluid* : H^+ that are secreted into tubular fluid is generated by metabolism. Approximately 4300 mEq H^+ is secreted daily. Since the lowest pH attainable in urine is 4.5 i.e H^+ is $40x10^{-6}$ Eq/L and the plasma H^+ is $40x10^{-9}$ Eq/L., kidney can cause a 1000 fold H^+ gradient between plasma and urine. The majority of secreted H^+ is used to bring about HCO_3^- reabsorption, and therefore is not excreted. Only 50-70 mEq is excreted daily.

ii. *Bicarbonate buffering* i.e. reabsorption of filtered HCO_3^- : The filtered HCO_3^- is reabsorbed in the form of CO_2 from the tubular lumen. The CO_2 returns to the tubular cell to form another H^+ ($CO_2 + H_2O \quad H_2CO_3 \quad H^+ + HCO_3^-$) and therefore no net H^+ secretion occurs. For each mole of HCO_3^- removed from the tubular fluid, 1 mol of HCO_3^- diffuses from the tubular cells into the blood. HCO_3^- absorption does not contribute urinary excretion of acid.

iii. *Non-bicarbonate buffering* i.e. formation of titratable acid and NH_4^+.

Physical characteristics of normal urine

i.	Appearance	: Straw or yellow amber
ii.	Smell	: Paint aromatic
iii.	Volume	: 800-2500 ml

iv. Specific gravity : 1015-1030
v. Osmolality : 800-1200 mosm/L
vi. pH : 4.5-8.0 (average 6.0).

Composition of urine :

i. *The normal daily constituents of urine* :

Constituents	*Amount (average)*
a. H_2O	: 1.2 liters
b. Na^+	: 150-200 mmol
c. K^+	: 90-100 ml
d. Cl^-	: 100-150 ml
e. HCO_3^-	: 2-3 mmol
f. Urea	: 410 mmol
g. Uric acid	: 5 mmol
h. Creatinine	: 12-15 mmol
i. Foreign substances	: Variable amount

ii. *In additian to these substances the normal urine contains* :

a. Glucose	: No
b. Protein	: 150-200 mg daily
c. Albumin	: <20 mg/litre urine
d. RBC	: No red blood cells (the presence of single RBC is abnormal)
e. WBC	: 0-2 per cubic millimeter of urine
f. Casts	: hyaline or granular.

Applied

Anuria : The presence of no urine in 24 hours is called anuria. It suggests urinary tract obstruction until proved otherwise.

Oliguria : Oliguria usually defined as the excretion of less than 300 ml of urine per day.

Causes :
a. Hypovolaenia
b. Cardiac failure
c. Septicaemia
d. Acute glomerulonephritis
e. Acute tubular necrosis

Polyuria : Polyuria is a persistent, large increase in urine output usually associated with nocturia.

Causes :
a. Excessive intake of water
b. Increased osmotic load as in hyperglycaemia and glycosunia.
c. Defective renal concentrating ability or failure of production of ADH

Proteinuria : The presence of protein in the urine, which is detectable by dipstrix, (usually > 200 mg daily) is called proteinuria.

Common causes :
a. Pyrexia
b. Exercise
c. Nephrotic syndrome (>3 gm/day)
d. Acute glomerulonephritis
e. Multiple myeloma
f. Diabetic nephropathy.

Glycosuria : The presence of glucose in urine is called glycosuria. The normal urine contains no glucose.

Causes :
a. Diabetes mellitus
b. Pregnancy : due to fall in the renal threshold for glucose.
c. Alimentary glycosuria.

Haematuria : The presence of blood in the urine is called haeinaturia. The urine appears smoky, brighl red or reddish brown.

Causes :
a. Glornerulonephritis
b. Pyelonephritis
c. Hypoplasia of kidney and bladder
d. Stone in the urinary tract
e. Trauma
f. Cystitis.

Micturition

Anatomic considerations : The smooth muscle of the bladder, like that of the ureters, is arranged in spiral, longitudinal, and circular bundles. Contraction of this muscle, which is called the detrusor muscle, is mainly responsible for emptying the bladder during urination (micturition). Muscle bundles pass on either side of the urethra, and these fibers are sometimes called the *internal urethral sphincter*, although they do not encircle the urethra. Farther along the urethra is a sphincter of skeletal muscle, the sphincter of the *membranous urethra (external urethral sphincter)*. The bladder epithelium is made up of a superficial layer of flat cells and a deep layer of cuboidal cells.

(Ref. Ganong 22th Edition)

Innervation of the urinary bladder

The principal nerve supply of the bladder is by way of the *pelvic nerves*, which connect with the spinal cord through the *sacral plexus*, mainly connecting with cord segments S-2 and S-3. Coursing through the pelvic nerves are both *sensory nerve fibers* and *motor nerve fibers*.

The *sensory fibers detect* the degree of stretch in the bladder wall. Stretch signals from the posterior urethra are especially strong and are mainly responsible for initiating the reflexes that cause bladder emptying.

The *motor nerves* transmitted in the pelvic nerves are

parasympathetic fibers. These terminate on ganglion cells located in the wall of the bladder. Short postganglionic nerves then innervate the detrusor muscle.

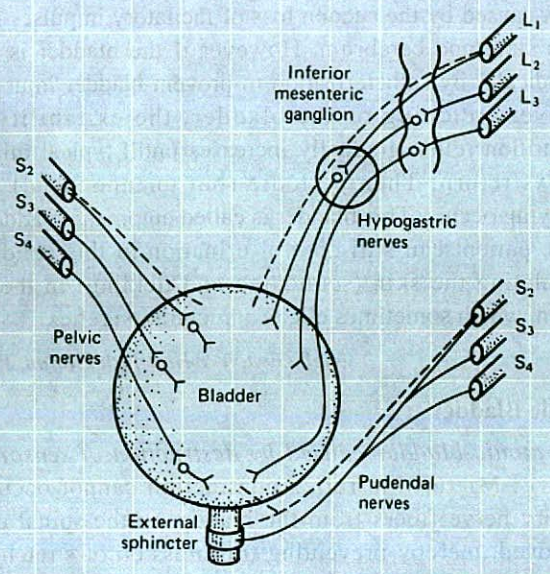


Fig. 13-8.Innervation of the bladder. Dashed lines indicate sensory nerves. Parasympathetic innervation is shown at the left, sympathetic at the upper right, and somatic at the lower right.

In addition to the pelvic nerves, two other types of innervation are important in bladder function. Most important are the *skeletal motor fibers* transmitted through the *pudendal nerve to the external bladder sphincter.* These are *somatic nerve fibers* that innervate and control the voluntary skeletal muscle of the sphincter. Also, the bladder receives *sympathetic innervation* from the sympathetic chain through the hypogastric nerves, connecting mainly with the L-2 segment of the spinal cord. These sympathetic fibers stimulate mainly the blood vessels and have little to do with bladder contraction. Some sensory nerve fibers also pass by way of the sympathetic nerves and may be important in the sensations of fullness and, in some instances, pain.

(Ref. Guyton & Hall 11th Edition, Page 312)

Micturition : Micturition is fundamentally a spinal reflex facilitated and inhibited by higher brain centers and, like defecation, *subject to voluntary facilitation and inhibition.* Urine enters the bladder without producing much increase in intravesical pressure until the viscus is well filled. In addition, like other types of smooth muscle, the bladder muscle has the property of plasticity; when it is stretched, the tension initially produced is not maintained.

(Ref. Ganong 22th Edition, Page 726

Micturation reflex

Mticturition contractions are the result of a stretch reflex initiated by *sensory stretch receptors* in the bladder wall, especially by the receptors in the posterior urethra when this area begins to fill with urine at the higher bladder pressures. Sensory signals from the bladder stretch receptors are conducted to the sacral segments of the cord through the pelvic nerves and then reflexively back again to the bladder through the *parasympathe tic nerve* fibers by way of these same nerves.

When the bladder is only partially filled, these micturition contractions usually relax sponta- neously after a fraction of a minute, the detrusor muscles stop contracting, and pressure falls back to the baseline. As the bladder continues to fill, the rnicturition reflexes become more frequent and cause greater contractions of the detrusor muscle.

Once a micturition reflex begins, it is 'self-regenerative'. That is, initial contraction of the bladder further activates the stretch receptors to cause still further increase in sensory impulses to the bladder and posterior urethra, which causes further increase in reflex contractiwn of the bladder; thus, the cycle is repeated again and again until the bladder has reached a strong degree of contraction. Then, after a few seconds to more than a minute, the self-regenerative reflex begins to fatigue and the regenerative cycle of the micturition reflex ceases, permitting the bladder to relax.

Thus, *the micturition reflex is a single complete cycle of-* i. *progressive and rapid increase of pressure.* ii. *a period of sustained pressure* and iii. *return of the pressure to the basal toneof the bladder.* Once a micturition reflex has occurred but has not succeeded in emptying the bladder, the nervous elements of this reflex usually remain in an inhibited state for a few minutes to 1 hour or more before another micturition reflex occurs. As the bladder becomes more and more filled, micturition reflex occur more and more often and more and more powerfully.

Once the micturition reflex becomes powerful enough, causes another reflex, which passes through the *pudendal nerves* to the external sphincter to inhibit it. If this inhibition is more potent in the brain than the voluntary constrictor signals to the external sphincter, urination will occur. If not, urination will not occur until the bladder fills still further and the micturition reflex becomes more powerful.

(Ref. Guyton & Hall 11th Edition, Page 313)

Facilitation or inhibition of micturition by the brain

The micturition reflex is a completely autonomic spinal cord reflex. but it can be inhibited or facilitated by centers in the brain. These centers include- i. *strong facilitorv and inhibitory centers in the brain stem, located mainly in the pons*, and ii. *several centers, located in the cerebral contex* that are mainly inhibitory but can become excitatory.

The micturition reflex is the basic cause of micturition. but the higher centers normally exert final control of micturition as follows :

1. The higher centers keep the micturition reflex partially inhibited except when micturition is desired.

2. The higher centers can prevent micturition; even if the micturition reflex does occur, by continual tonic contraction of the external bladder sphincter until a convenient time presents itself.
3. When it is time to urinate, the cortical centers can facilitate the sacral micturition centers to help initiate a micturition reflex and at the same time inhibit the external urinary sphincter so that urination can occur.

Voluntary urination is usually initiated in the following way : *First*, a person voluntarily contracts his or her abdominal muscles, which increases the pressure in the bladder and allows extra urine to enter the bladder neck and posterior urethra under pressure, thus stretching their walls. This stimulates the stretch receptors, which excites the micturition reflex and simultaneo-usly inhibits the external urethral sphincter. *Ordinarily, all the urine will be emptied, with rarely more than 5 to 10 milliliters left in the bladder.*

(Ref. Guyton & Hall 11th Edition, Page 313)

Stages of micturation

a. Set up of micturation reflex due to accumulation of urine into urinary bladder.
b. Relaxation of perineal muscle except sphincter urethrae.
c. Contraction of muscles of abdominal wall.
d. Firm contraction of detrusor muscle and relaxation of sphincter vesicae.
e. Ultimately relaxation of sphincter of urethrae due to flow of urine as a result of relaxation of sphincter vesicae.
f. Bladder become empty by the contraction of detrusor muscle and muscle of the abdominal wall.
g. As act is completed, the reversal phenomena happens.

Some conditions

Aneurea	:	Cessation of urine flow due to sever kidney disease.
Oligurea	:	Marked reduction of urinary output is called oligurea.
Polyurea	:	Increased in urinary output is called polyurea.
Glucosurea	:	Presence of glucose in urine.
Albuminurea	:	Presence of Albumin in urine.
Proteinurea	:	Presence of abnormal quantity of protein in urine.
Haematurea	:	Presence of blood in urine.
Nocturea	:	Passage of more urine at night.
Ketonurea	:	Presence of keton bodies in urine.

Automatic bladder

If the spinal cord is damaged above the sacral region but the sacral segments are still intact, typical micturation reflexs can still occur. However, they are no longer controlable by the brain. During the first few days to several weeks after the damage to the cord has occured, the micturation reflexes are completely suppressed because of of the state of state of *spinal shock* caused by the sudden loss of facilatory impulses from the brain stem and cerebrum. However if the bladder is emptied periodically by catheterization to prevent bladder injury caused by overstretching of the bladder, the exitability of the micturition reflex gradually increases untill typical micturition reflexs return; Then periodic (but unannounced) bladder emptying occurs. This bladder is called automatic bladder.

Some patient can still control urination in this condition by stimulating the skin (scratching and tickling) in the genital region, which sometimes elicits a micturation reflex.

(Ref. Guyton & Hall 11th Edition, Page 314)

Atonic Bladder

(The atonic bladder caused by destruction of sensory nerve fibers) : Micturition reflex contraction cannot occur if the sensory nerve fibers from the bladder to the spinal cord are destroyed, thereby preventing transmission of stretch signals from the bladder. When this happens, a person loses bladder control, despite intact efferent fibers from the cord to the bladder and despite intact neurogenic connections within the brain. Instead of emptying periodically, the bladder fills to capacity and overflows a few drops at a time through the urethra. This is called *overflow incontinence.*

A *common cause of atonic bladder* is crush injury to the sacral region of the spinal cord. Certain diseases can also cause damage to the dorsal root nerve fibers that enter the spinal cord. For example, syphilis can cause constrictive fibrosis around the dorsal root nerve fibers, destroying these fibers. This condition is called *tobes dorsalis*, and the resulting bladder condition is called *tabetic bladder.*

(Ref. Guyton & Hall 11th Edition, Page 313)

Un-inhibited Neurogenic Bladder

It results in frequent and relatively uncontrolable micturation. This condition is drives from the partial damage in the spinal cord or the brain stem that interrupts most of the inhibitory signals. Therefore, facilitatory impulses passsing continually down the cord keep the sacral centers so excitable that even a small quantity of urine will elicit an uncontrollable micturition reflex, and thereby promote frequent urination.

(Ref. Guyton & Hall 11th Edition, Page 314)

Abnormalities of micturation

Disorders of micturation may results from neural lesions. The pattern of neurogenic bladder dysfunction are :

i. Atonic bladder with overflow incontinence.
ii. Hypertonic bladder with urge incontinence
iii. Abnormality due to cortical lesions.

Lower motor neuron lesions- LMNL : It causes a flaccid, atonic bladder, which overflows without warning. It must be bilateral to cause urinary symptoms.

Bilateral upper motor neuron lesions (UMNL) : It causes frequency of micturation and incontinence. The bladder is small and usually sensitive to small change in intravesicle pressure.

Effects of deafferentation : When the sacral dorsal roots are cut in experimental animals or interrupted by diseases of the dorsal roots such as *tabes dorsalis* in humans, all reflex contractions of the bladder are abolished. The bladder becomes distended, thin-walled, and hypotonic, but there are some contractions because of the intrinsic response of the smooth muscle to stretch.

(Ref. Ganong 22th Edition; page 728)

Effects of denervation : When the afferent and efferent nerves are both destroyed, as they may be by tumors of the cauda equina or filum terminale, the bladder is flaccid and distended for a while. Gradually, however, the muscle of the *decentralized bladder* becomes active, with many contraction waves that expel dribbles of urine out of the urethra. The bladder becomes shrunken and the bladder wall hypertrophied. The reason for the difference between the small, hypertrophic bladder seen in this condition and the distended, hypotonic bladder seen when only the afferent nerves are interrupted is not known. The hyperactive state in the former condition suggests the development of denervation hhpersensitization even though the neurons interrupted are preganglionic rather than postganglionic.

(Ref. Ganong 22th Edition; page 728)

Effects of spinal cord transection : During spinal shock, the bladder is flaccid and unresponsive. It becomes overfilled, and urine dribbles through the sphincters (*overflow incontinence*). After spinal shock has passed, the voiding reflex returns, although there is, of course, no voluntary control and no inhibition or facilitation from higher centers when the spinal cord is transected. Some paraplegic patients train themselves to initiate voiding by pinching or stroking their thighs, provoking a mild mass reflex. In some instances, the voiding reflex becomes hyperactive. Bladder capacity is reduced, and the wall becomes hypertrophied. This type of bladder is some times called the *spastic neurogenic bladder*. The reflex hyperactivity is made worse by, and may be caused by, infection in the bladder wall.

(Ref. Ganong 22th Edition; page 728)

Kidney function tests

A. *Routine examination of urine* :
   i. Physical examination
      a. Quantity
      b. Colour
      c. Appearance
      d. Presence of sediment
      e. Specific gravity
      f. Osmolarity
   ii. *Chemical examination* :
      a. pH
      b. Protein (mainly albumin)
      c. Glucose
      d. Ketone bodies
      e. Bilirubin
      f. Urobilinogen
      g. Bile salts
      h. Blood
      i. Chyle
         True chyle (fat particles)
         Pseudochyle (a lecithin component of globulin)
      j. Porphyrins
   iii. *Microscopic examination* :
      a. Organized deposits
         1. Cells
            * Epithe.lial cell
            * RBC
            * Pus cell
         2. Casts
            * Cellular
            * Granular
            * Hyaline
            * Pigmented
         3. Bacteria
         4. Mucous, animal parasites, spermatozoa.
      b. Unorganized deposits :
         1. Crystals & amorphous chemicals.

B. Blood analysis :
   i. Blood urea level
   ii. BUN (blood urea nitrogen)
   iii. Plasma uric acid
   iv. Plasma creatinine
   v. Plasma electrolytes.

C. Clearance tests :
   i. Creatinine clearance test (usually used)
   ii. Inulin clearance test

D. Special tests :
   i. Water loading test
   ii. Water deprivation test 5 Acidification test

E. Immaging tests :
   i. Plain X- ray of KUB region

ii. Intravenous urography (IVU)
iii. Ultrasonogram
iv. CT scan
v. Pyelograph
vi. Renal biopsy.

Protein test : Protein coming from glomerulus or urinary tract can be identified by examination of urine.

i. If protein is more than 300mg/day : Proteinuria
ii. If protein is 30 mg/day : Bleeding from lower urinary tract.
iii. If protein is between 300 : 30 mg/day it is called microprotein.
iv. More than 200 mg/day : Abnormal
v. Less than 200 mg/day : Normal.

Creatinine clearance test : It is usually used to measure glomerular filtration rate because it is easy to determine and approximates inulin clearance.

Normal :

i. Male : 90-1 10 mI/mm
ii. Female : 80-125 mI/mm

Q.00. **Do you think determination of specific gravity of urine is a kidney function test? If so why?**

Ans. Yes, determination of specific gravity of urine is one of the kidney function test. Because depending on the types of substances cleared by kidneys, specific gravity of urine vary tremendiously from 1.045 to 1.002.

Specific gravity of urine indicates the concentrating power of kidney. So fall of specific gravity indicates fall of concentrating power of kidney. That is kidney excrets more dilute urine.

Diuresis

i. *Definition* : Diuresis means excretion of large vloume of dilute urine i.e hypotonic urine.

ii. *Types* : It is of 2 types :
   a. Water diuresis
   b. Osmotic diuresis.

Difference between the water and osmolar diuresis

Water diuresis	*Osmotic diuresis*
1. It is the increased loss of excessive water in urine due to increase water intake or lack of ADH.	1. It is the increased loss of water in urine due to the presence of the osmotically active substance which prevent tubular reabsorption of water.
2. Reabsorption of water is normal in PCT.	2. Reabsorption of water decreases from PCT.
3. Water is not reabsorbed from DCT and collecting tubule due to lack of ADH.	3. Water is not reabsorped from DCT and collecting tubule due to presence of osmotically active particle.
4. Electrolytes are not lost.	4. Significant amount of electrolytes lost in the urine.
5. Counter-current mechanism does not affected.	5. Counter current mechanism is affected.

Mechanism of action of various diuretics.

Agent	*Mechanism of action*
Water	Inhibits vasopressin secretion.
Ethanol	Inhibits vasopressin secretion.
Antagonists of V_2 vasopressin on receptors	Inhibit action of vasopressin collecting duct.
Large quantities of osmotically active substances such as mannitol and glucose	Produce osmotic diuresis.
Xanthines such as caffeine and theophylline	Decrease tubular absorption of Na^+ and increase GFR.
Acidifying salts such as $CaCl_2$ NH_4CI	Supply acid load; H^+ is and buffered, an anion is excreted with Na^+ when the ability other kidneys to replace Na^+ with H^+ is exceeded.
Carbonic anhydrase inhibitors such as acetazolamide (Diamox)	Decrease H^+ secretion, with resultant increase in Na^+ and K^+ excretion.
Metolazone (Zaroxolyn), thiazides such as chlorothiazide (Diuril)	Inhibit Na^+ and K^+ reabsorption in the early portion of the distal tubule.
Loop diuretics such as furosemide (Lasix), ethacrynic acid (Edecrin), and bumetanide	Inhibit Na^+-K^+-$2CI^-$ cotransport in the medullary thick ascending limb of the loop of Henle.
K^+- retainining natriuretics such as spironolactone (Aldactone), triamterene (Dyrenium), and amiloride (Colectril).	Inhibit Na^+-K^+ "exchange" in the distal portion of the distal tubule & the collection duct by inhibiting the action of aldosterone (spirono lactone) or by inhibiting Na^+ reabsorption (triamterene, amiloride).

(Ref.Ganong 22th Edition; Page-725)

Dialysis

Definition : Dialysis is the treatment of renal failure by dialysis with an artificial kidney.

i. *Introduction* : Dialysis causes removal of toxic waste products and restoration of body fluid volume and composition toward normal. Dialysis cannot maintain completely normal body fluid composition and cannot replace all the multiple functions performed by the kidney. Thousands of people with irreversible renal failure or even total kidney removal are being maintained for 15 to 20 years by dialysis with artificial kidneys.

ii. *Indication* : Acute or chronic severe loss of kidney function

iii. *Basic principles of dialysis* : The basic principle of the artificial kidney is to pass blood through minute blood channels bounded by a thin membrane. On the other side of the membrane a *dialyzing fluid* into which unwanted substances in the blood pass by diffusion.

In addition to diffusion of solutes, mass transfer of solutes and water can be produced by applying a hydrostatic pressure to force the fluid and solutes by the process of filtration across the membranes of the dialyzer, such filtration is called *bulk flow*.

To prevent coagulation of blood in the artificial kidney, a small amount of heparin is infused into the blood as it enters the artificial kidney.

iv. The *rate of movement of solute* across the dialyzing membrane depends on :

a. The concentration gradient of the solute between the two solutions
b. The permeability of the membrane to the solute.
c. The surface area of the membrane
d. The length of time that the blood and fluid remain in contact with the membrane.

(Ref. Guyton & Hall 11th Edition; page 414)

Q. 01. **What is the relationship of hypertension and kidneys disease?**

Ans. Renal diseases i.e glomerulonephritis, pyelonephritis, polycystic kidney disease may lead to *secondary hypertension.*

Specific tubular disorders

i. ***Renal Glycosuria***- *Failure of the kidneys to reabsorb glucose* : The blood glucose concentration may be normal, but the transport mechanism for tubular reabsorption of glucose is greatly limited or absent. Consequently, despite a normal blood glucose level, large amounts of glucose pass into the urine each day. Because diabetes mellitus is also associate with the presence of glucose in the urine, renal glycosuria, which is a relatively benign condition, must be ruled out before making a diagnosis of diabetes mellitus.

(Ref. Guyton & Hall 11th Edition; page 413)

ii. ***Aminoaciduria***- *Failure of the kidneys to reabsorb amino acids)* : Some amino acids share mutual transport systems for reabsorption, whereas other amino acids have their own distinct transport systems.

Rarely, a condition called *generalized aminoaciduria* results from deficient reabsorption of all amino acids; more frequently, deficiencies of specific carrier systems may result in-

a. Essential cystinura, in which large amounts of cystine fail to be reabsorbed and often crystallize in the urine to form renal stones.
b. *Simple glycinuria*, in which glycine fails to be reabsorbed
c. Beta-aminoisobutyric-aciduria, which occurs in about 5 percent of all people but apparently has no major clinical significance.

(Ref. Guyton & Hall 11th Edition; page 413)

iii. ***Renal hypophosphatemia***- *Failure of the kidneys to reabsorb phosphate* : The renal tubules fail to reabsorb large enough quantities of phosphate ions when the phosphate concentration of the body fluids falls very low.

a. *Effects* : This condition usually does not cause serious immediate abnormalities because phosphate concentration of the extracellular fluids can vary widely without causing major cellular dysfunction. Over a long period, a low phosphate level causes diminished calcification of the bones, thus causing the person to develop rickets.

This type of rickets is refractory to vitamin D therapy in contrast to rapid response of the usual type of rickets.

(Ref. Guyton & Hall 11th Edition; page 413)

iv. ***Renal tubular acidosis***- *Failure of the tubules to secrete hydrogen ions* : The renal tubules are unable to secrete adequate amounts of hydrogen ions.

a. *Effects* : Large amounts of sodium bicarbonate are continually lost in the urine. This causes a continued state of *metabolic acidosis.*
b. Cause : Hereditary disorders or it can occur as a result of widespread injury to the renal tubules.

(Ref. Guyton & Hall 11th Edition; page 413)

v. ***Nephrogenic diabetes insipidus***- *Failure of the kidneys to respond to antidiuretic hormone* : Occasionally, the renal tubules do not respond to antidiuretic hormone, causing large quantities of dilute urine to be excreted. As long as the person is supplied with plenty of water, this condition seldom causes severe difficulty. However, when adequate quantities of water are not available, the person rapidly becomes dehydrated.

(Ref. Guyton & Hall 11th Edition; page 414)

vi. ***Fanconi's Syndrome-*** *A generalized reabsorptive defect of the renal tubules* :

Causes : There are multiple causes of Fanconi's syndrome, which results from a generalized inability of the renal tubular cells to transport various substances. Some of these causes include-

a. Hereditary defects in cell transport mechanisms.
b. Toxins or drugs that injure the renal tubular epithelial cells.
c. Injury to the renal tubular cells as a result of ischemia.

Effects : The proximal tubular cells are especially affected in Fanconi's syndrome caused by tubular injury because these cells reabsorb and secrete many of the drugs and toxins that can cause damage.

Manifestation : Fanconi's syndrome is usually associated with increased urinary excretion of virtually all amino acids, glucose, and phosphate.

In *severe cases*, other manifestations are also observed, such as-

a. Failure to reabsorb sodium bicarbonate, which results in *metabolic acidosis*.
b. Increased excretion of potassium and sometimes calcium.
c. Nephrogenic diabetes insipidus.

(Ref. Guyton & Hall 11th Edition; page 414)

Thirst

The conscious desire for water intake is called thirst.

Thirst stimuli :

i. Intracellular dehydration.
ii. Stimulation of thirst by angiotensin.
iii. Haemorrhage and low cardiac output.
iv. Dryness of the mouth.

(Ref. Guyton & Hall 11th Edition)

Dehydration

Dehydration is a condition resulting from excessive loss of body fluid.

Causes of dehydration :

i. Excessive loss of water from body such as sweating, cholera, diarrhoea, haemorrhage etc.
ii. Reduction of total quantity of clectrolytes
iii. Injection of hypertonic solution.

Sign of dehydration :

1. Sunken of eye ball
2. Dryness of tongue
3. Wrinkles of skin
4. Dryness and rough of skin
5. Prominence of supra orbital margin, zygomatic arch etc.

Urinary System

Directions : Write 'T' for true & 'F' for false against each of the filling statement.

Introduction

Q. 01. **Primary functions of the kidney are**
- T a. tubular reabsorption
- T b. tubular secretion
- T c. glomerular filtration
- F d. glomerular reabsorption
- F e. tubular absorption.

Q. 02. **Functions of the Kidney are**
- T a. regulate blood volume and composition
- T b. help to regulate blood pressure
- T c. release erythropoietin.
- F d. participate in the synthesis of vit C
- F e. stimulate production of WBC

Q. 03. **Endocrine functions of kidney is mediated through**
- T a. renin
- T b. erythropoietin
- T c. 1, 25-dihydroxycholecalciferol
- F d. epinephrine
- F e. aldosterone.

Q. 04. **Each kidney contains about .... nephrons**
- T a. One million
- F b. Two million
- F c. Four million
- F d. 1/2 million
- F e. Three million

Q. 05. **True about nephron is**
- T a. 60 to 70% of GFR is absorbed in proximal tubule
- F b. Na is absorbed actively in descending loop of Henle
- F c. Absorption of water occurs in ascending loop of Henle
- F d. The filtrate reaching distal convoluted tubule is hypertonic with respect to surroundings.
- F e. All.

Q. 06. **Nephrons are**
- T a. are the functional units of the kindey
- T b. are constant from birth
- T c. have three basic functions.
- F d. are not microscopic structure
- F e. when injured, get regenerated

Q. 07. **Regarding nephron**
- T a. it is the functional unit of kidney
- T b. its loss is not life threatening.
- T c. consist of glomerulus.
- F d. total number in each kidney is about one trillion
- F e. it can regenerate.

Q. 08. **The length of distal convulated tubule is**
- T a. 5 mm
- F b. 2 mm
- F c. 8 mm
- F d. 12 mm
- T e. 3 mm

Q. 09. **Juxtamedullary nephrons in kidney are what percentage of total nephrons**
- T a. 15
- F b. 50
- F c. 70
- F d. 90
- F e. 30

Q. 10. **Waste products removed by kidneys are**
- T a. urea - metabolic products of amino acids.
- T b. bilirubin end products of hemoglobin
- T c. food additives.
- F d. creatinine from nucleic acid
- F e. uric acid from muscle

Q. 11. **Kidneys regulate acid-base balance by**
- T a. eliminating sulfuric acid
- T b. eliminating phosphoric acid
- T c. body fluid buffers.
- F d. generating acids
- F e. without help of lungs

Q. 12. **The osmolarity of the fluid in the**
- T a. collecting duct rises when vasopressin is secreted.
- T b. medullary interstitium can exceed 1 osmol/litre.

F c. tip of the loop of Henle is less than that of plasma.
F d. Bowman's capsules is less than that in the distal tubules.
F e. proximal convoluted tubule rises along its length.

Q. 13. **Which of the following hormones are acting on the proximal tubule?**
T a. bradykinin.
T b. prostaglandin
F c. aldosteron
F d. angiotensin II
F e. ADH

Q. 14. **The Kidney secretes**
T a. renin.
T b. erythropoietin
T c. 1,25- dihydroxycholecalciferol
F d. gastrin
F e. vasopressin.

Q. 15. **Erythropoietin is secreted by**
T a. kidney
F b. liver
F c. bone malTow
F d. adrenal cortex
F e. capillary endotheliurn.

Q. 16. **Erythropoietin level is raised by**
T a. Decreased PO_2
F b. Decreased PCO_2
F c. Decreased Hb
F d. Decreased pH
F e. None.

Q. 17. **Erythropoietin is secreted by**
T a. Kidney
F b. Lrver
F c. Adrenal cortex
F d. Bone marrow
F e. None.

Q. 18. **Site of ADH action is**
T a. Collecting tubule
F b. Proximal tubule
F c. Loop of Henle
F d. Vasa recta
F e. None.

Q. 19. **Site of ADH action is**
T a. thick ascending limb of loop of Henle
T b. collecting tubule.
F c. proximal tubule
F d. vasa recta
F e. loop of Henle

Q. 20. **Administration of ADH**
T a. increases active reabsortion of by distal tubule.
T b. decreases water loss by kidney
F c. decreases water loss by lung
F d. increases perspiration
F e. decreases active reabsorbtion of Na^+ by proximal tubule.

Q. 21. **Renin secretion is stimulated by all except**
T a. High Na^+ in proximal tubule
F b. Cardiac failure
F c. Low Na^+ in proximal tubule
F d. Sympathetic stimulation
F e. None.

Q. 22. **Renin secretion is stimualted by**
T a. hypoxia.
T b. cardiac failure
T c. low Na^+ in the proximal tubule
T d. sympathetic stimulation
F e. high Na^+ in proximal tubule

Q. 23. **The renin angiotensin aldosterone system regulates**
T a. K^+ balance
T b. Na^+ balance
T c. fluid volume
T d. blood pressure
F e. nitrogen balance.

Q. 24. **Agents causing contraction of mesangial cells are**
T a. angiotensin-II.
T b. endothelins
T c. vasopressin
F d. ANP
F e. dopamine

Q. 25. **Relaxation of mesangial cells of kidney is brought about by**
T a. cAMP
F b. Endothelin
F c. PGF2 vasopressin
F d. ANP
F e. dopamine

Renal Circulation

Q. 26. **In resting state the renal blood flow per minute is**
T a. 1200 - 1300 ml
F b. 200 - 500 ml
F c. 400 - 500 ml
F d. 500 - 600 ml
F e. 600 - 100 ml.

Q. 27. **The renal blood flow (in ml/minute) is :**
T a. 1260
F b. 250

F c. 800
F d. 1500
F e. 1060

Q. 28. **In humans, effective renal blood flow is :**
T a. 625
F b. 425
F c. 525
F d. 725
F c. 225

Q. 29. **Renal blood flow falls**
T a. during emotional stress
T b. after moderate hemorrhage
F c. about 10% when arterial pressure falls 10% below normal.
F d. about 5% when metabolic activity in the kindney falls by 5% below normal
F e. gradually from the inner medulla to outer cortex per unit weight of tissue.

Q. 30. **Renal blood flow is increased when**
T a. glucocorticoids increases
T b. high protein diet intake increased
T c. hyperglycemia occurs
F d. hypoglycemia occurs
F e. aging occurs.

Q. 31. **Renal plasma flow is 600 ml/minute andthe hematocrit is 40%. What is the renal blood flow in ml/minute?**
T a. 1000
F b. 1500
F c. 900
F d. 1800
F e. 950.

Q. 32. **Effective renal plasma flow is**
T a. 630 ml/minute.
T b. measured by C_{PAH}
F c. measured by Tm of PAH
F d. 125 ml/minute.
F e. measured by C_{IN}

Q. 33. **Hydrostatic pressure in renal glomerular capillaries**
T a. is higher than in most other capillaries at heart level..
T b. falls as the oncotic pressure rises along the length of the capillary.
F c. is lower than pressure in efferent arteriole
F d. rises when afferent arterioles constrict.
F e. falls by 10% when arterial pressure falls by 10%

Q. 34. **Approximate pressure in renal circulation**
T a. renal artery : 100 mm of Hg.
T b. afferent arteriole : 85 mm of Hg.
T c. renal vein : 4 mm of Hg.
F d. glomerular capillaries : 10 mm of Hg.
F e. efferent arteriole : 60 mm of Hg

Q. 35. **Glomerular capillary hydrostatic pressure**
T a. reduces by afferent arteriolar resistance.
T b. is higher than that in efferent arteriole
T c. regulates GFR
F d. is normally 32 mm of Hg
F e. is increased if GFR is decreased

Q. 36. **Filterability of substance by glomerular capillaries**
T a. albumin : 0.005
T b. water : 1.0
F c. sodium : 0.8
F d. glucose : 0.75
F e. inulin : 0 .75

Q. 37. **Autoregulation of renal blood flow**
T a. is seen when the kidney is prefused at pressures between 90-220 mm of Hg
T b. is present in denervated kidney
T c. is partly due to direct contractile response of the efferent arteriole to stretch.
F d. does not occur in the kidney
F e. can be prevented by the administration of drugs that excites the vascular smooth muscles.

Q. 38. **Autoregulation is seen in**
T a. Muscles
T b. Kidneys
T c. Brain
F d. Liver
F e. All.

Q. 39. **Kidneys regulate arterial pressure by**
T a. excreting water and sodium
T b. secreting renin
T c. renin angiotensin mechanism
F d. excreting vasoactive factors
F e. G cells in the efferent arterioles.

Q. 40. **When a patient's mean arterial blood pressure falls by 50%**
T a. there is an increase in the circulating aldosterone level.
T b. renal vesoconstriction occurs.
T c. urinary output may cease.
F d. renal blood flow falls by less than 10%
F e. glomerular filtration falls by about 50%

Q. 41. **Factors favouring filtration across the glomerular capillaries are**
T a. increase in the size of the glomerular capiliary bed.
T b. low colloidal osmotic pressure within the glomerular capillaries
T c. efferent arteriolar constriction.

F d. high colloidal osmotic pressure within the glomerular capillaries.
F e. low hydrostatic pressure within the glomerular capillaries.

GFR

Q. 42. **What is the glomerular filtration rate?**
T a. 125 ml/min
F b. 100 ml/min
F c. 150 ml/min
F d. 175 ml/min
F e. 200 ml/min

Q. 43. **Filtration barrier in the glomerular capilaries is produced by**
T a. basal lamina
F b. slit pore
F c. podocytes
F d. juxtaglomerular cells
F e. endothelial cells.

Q. 44. **One of the following does not form filtration barrier in nephrons**
T a. Mesangium
F b. Podocytes
F c. Endothelial cell
F d. Basement membrane
F e. None.

Q. 45. **Two substances that can probably be usedto determine filtration fraction are**
T a. Inulin and PAH
F b. Insulin and mannitol
F c. Urea and diodrast
F d. PAH and phenol red
F e. None.

Q. 46. **GFR is**
T a. relatively constant.
T b. increased by prostaglandin.
F c. dereased by bradykinin.
F d. increased by nitric oxide.
F e. increased by angiotesin II.

Q. 47. **The normal glomerular filtration rate is apporximately**
T a. 125 m1/minute
T b. 7.5 L/hour
T c. 180 L/day
F d. 100 ml/minute
F e. 180 L/minute

Q. 48. **Glomerular filtration rate**
T a. tends to increase in hypoproteinemia
T b. can be measured by inulin clearance test.
F c. is 60 ml/min
F d. increases during strenuous exercises
F e. tends to decrease when the efferent arteriole is constricted.

Q. 49. **Following substances are filtered by kidney**
T a. glucose :180 gm day
F b. bicarbonate : 4310 mEq/day
F c. sodium : 16420 mEq/day
F d. chloride : 19440 mEq/L
F e. urea : 12120 gm/day.

Q. 50. **Normal kidney does not allow passage of**
T a. β-globulin
F b. Lysozyme
F c. IgG
F d. Albumin
F e. None.

Q. 51. **Factors that can increase GFR**
T a. decreased plasma proteins
T b. decreased arterial pressure
F c. increase glomerular coefficient.
F d. urinary tract obstruction.
F e. increased afferent arteriolar resistance.

Q. 52. **GFR is increased when**
T a. renal blood flow is increased.
T b. glomerular capillary hydrostatic pressure increased.
F c. plasma oncotic prssure is increased.
F d. glomerular hydrostatic pressure is increaed.
F e. tubular hydrostatic pressure is increased.

Q. 53. **GFR is increased when**
T a. renal blood flow is increased
F b. plasma oncotic pressure is increased
F c. glomerular hydostatic pressure is increased
F d. tubular hydrostatic pressure is increased
F e. when blood pressure is decreased.

Q. 54. **GFR is decreased when**
T a. glomerular capillary filtration coefficient (Kf) is decreased.
T b. bowman's capsule pressure increased.
T c. glomerular capillary colloid osmotic pressure is increased.
F d. renal blood flow is increased.
F e. glomerular capillary hydrostatic pressure is increased.

Q. 55. **Renal GFR can be estimated by**
T a. Tc^{99} DTPA
F b. Tc^{99} DMCA
F c. Tc^{99} DMSA
F d. Tc^{99}
F e. Tc^{99} DT.

Q. 56. **GFR can be measured by**
- T a. C_{IN}
- T b. C_{Cr}
- F c. C_{PAH}
- F d. C_G
- F e. C_U

Q. 57. **Criteria to be fulfilled by a substance to be used for the measurement of GFR include**
- T a. to be freely filtered and neither reasorbed or secreted.
- T b. nontoxic
- T c. not metabolized in the body.
- F d. to be freely filtered only
- F e. to be freely filtered and secreted

Q. 58. **GFR is regulated by**
- T a. glomerular capillary pressure
- T b. glomerular capillary flood flow
- T c. plasma collidal osmotic pressure
- T d. effective filtration pressure
- T e. normal blood pressure.

Q. 59. **Which of the following is truly physiological**
- T a. Increased GFR
- F b. Albuminuria
- F c. Increased blood pressure
- F d. Mild pedal edema
- F e. None.

Q. 60. **Major portion of glomerular filtrate is absorbed in**
- T a. Proximal segment
- F b. Loop of Henle
- F c. Distal convoluted tubule
- F d. Collecting duct
- F d. Sprouting

Absorption & Secretion

Q. 61. **The major differences between the plasma and inter stitial fluid are in**
- T a. the concentration of Na^+
- T b. the protein content.
- F c. the concentration of Ca^+
- F d. the HCO_3^- concentration.
- F e. the organic acid concentration.

Q. 62. **Following cells are responsible for acid secretion in kidney**
- T a. I cells
- F b. P cells
- F c. Mesangial cells
- F d. Pericytes
- F e. None.

Q. 63. **The part of the nephron least permeable to water are**
- T a. ascending limb of loop of Henle
- T b. collecting tubule
- T c. collecting duct.
- F d. proximal tubule
- F e. descending limb of loop of Henle

Q. 64. **Substances that are freely filtered but not reabsorbed by the kidney include**
- T a. creatinine
- F b. urea
- F c. glucose
- F d. bicarbonate
- F e. chloride.

Q. 65. **Renal tubules normally reabsorb**
- T a. about 99% of the glomerular filtrate
- T b. all filtered HCO_3 in respiratory acidosis
- T c. all filtered amino acids.
- T d. all filtered plasma proteins.
- F e. more K^+ than $C1^-$

Q. 66. **Tubular reabsorption**
- T a. is highly selective
- T b. is very large relative to excretion
- F c. is only by passive mechanism
- F d. of water is active process
- F e. of water is passive process.

Q. 67. **Substances completely reabsorbed only in the proximal tubule are**
- T a. uric acid
- T b. glucose
- F c. water
- F d. Na^+ ions
- F e. PAH.

Q. 68. **The proximal convoluted tubules**
- T a. reabsorb most of the sodium ions in glomerular filtrate
- T b. reabsorb most of the chloride ions in glomelular filtrate.
- T c. reabsorb most of the potassium ions in glomerular filtrate.
- F d. contain juxtaglomerular cells which secrete renin.
- F e. contain the main target cells for antid uretic hormone.

Q. 69. **Proximal tubule**
- T a. shows highly selective reabsorption.
- T b. is one of the important parts of nephron.
- F c. receives fluid from glomerulus.
- F d. is in the medulla.
- F e. is connected with connective tubules.

Q. 70. **The cells of the distal convoluted tubule**
- T a. secrete hydrogen ions into the tubular lumen
- T b. form NH_4^+
- T c. reabsorb sodium in exchange for hydrogen or potassium ions
- F d. reabsorbs about 50% of water filtered by the golmeruli
- F e. determine the final composition of urine.

Q. 71. **Active reabsorption from proximal tubule are**
- T a. bicarbonate
- T b. water.
- T c. sodium
- F d. carbonic acid
- F e. hydrogen

Q. 72. **Reabsorption in the first half of proximal tubules are**
- T a. sodium
- T b. glucose
- T c. amino acid
- F d. chloride
- F e. bicarbonate.

Q. 73. **Secretion from proximal tubule are**
- T a. bile salt
- T b. oxalate
- T c. urate
- F d. amino acid
- F e. sodium.

Q. 74. **In proximal convoluted tubule**
- T a. glucose is completely reabsorbed under normal conditions
- T b. K^+ is reabsorbed.
- F c. about 90% of filtered water is reabsorbed.
- F d. renin is produced
- F e. PAH is actively reabsorbed.

Q. 75. **The loop of Henle**
- T a. actively transports Na^+ in the thick ascending limb.
- T b. is responsible for high medullary osmolarity
- T c. returns fluid of low osmolarity to the distal convoluted tubule
- F d. has a high permeability to water in the thick ascending limb of the loop of Henle.
- F e. actively pumps ions across the epithelium of the descending limb

Q. 76. **Filtration fraction**
- T a. is normally 0.16 - 0.20
- T b. is the ratio of GFR to RPF
- T c. rises when there is a fall in systemic blood pressure because of the efferent arteriolar constriction and less reduction in GFR compared to RPF
- F d. is the ratio of RPF to GFR
- F e. normally 0.60 - 0.80.

Q. 77. **Thin segment of loop of Henle is highly permeable to**
- T a. water
- T b. glucose
- T c. amino acid.
- F d. sodium
- F b. urea.

Q. 78. **The hyperosmolarity of the renal medulla is due to increased concentration of**
- T a. Na^+
- T b. urea
- F c. K^+
- F d. glucose
- F e. Cl^-.

Q. 79. **The reabsortion of water in distal convoluted tubule is under control of**
- T a. ADH
- F b. aldosterone
- F c. ACTH
- F d. cotisol
- F e. insulin.

Q. 80. **Active reabsorption of glucose occurs in the**
- T a. proximal tubule
- F b. loop of Henle
- F c. distal tubule
- F d. collecting duct
- F e. thick ascending limb of loop of Henle.

Q. 81. **Where in the kidney tubule does active reabsorbtion of Na^+ occur**
- T a. collecting duct
- T b. distal tubule
- T c. ascending limb of loop of Henle
- T d. proximal tubule
- F e. thin segment of loop of Henle.

Q. 82. **Where in the kidney, does active reabsorption of sodium ions occur?**
- T a. Collecting duct
- T b. Distal tubule
- T c. Ascending limb of Henle
- T d. All of the above
- F e. Only b and c

Q. 83. **K^+ reabsorption of the kidney tubules occurs**
- T a. being coupled with Na^+ loss
- T b. only in proximal tubule
- T c. under the influence of aldosterone.
- F d. partly in the proximal and distal tubule
- F e. under the influce of ADH

Q. 84. **Potassium reabsorption in kidneys occur**
- T a. Coupled with sodium ions
- F b. Partly in POT and OCT
- F c. Under the influence of ADH
- F d. Only in POT
- F e. All.

Q. 85. **Ammonia in the Kidney tubules is excreted in exchange for**
- T a. HCO_3
- F b. Na^+
- F c. Cl^-
- F d. PO_4^{--}
- F e. All.

Q. 86. **Extracellular fluid volume is maintained by**
- T a. ADH.
- T b. aldoesterone.
- T c. osmolarity of plasma.
- T d. plasma K^+ level.
- F e. oxytocin.

Formation of urine

Q. 87. **Urine formation results from**
- T a. reabsorption from renal tubules.
- T b. glomenular filtration.
- T c. secretion from peritubular capillaries.
- F d. ultrafiltration of afferent arteriole.
- F e. dialysis of collecting tubules.

Q. 88. **In normal healthy subjects, urinary**
- T a. pH falls as dietary protein is increased
- F b. specific gravity ranges from 1.002 to 1.010
- F c. osmolarity ranges from 200 to 400 mOsmo/L
- F d. volume is SLIday
- F e. calcium excretion is increased by parathormone.

Q. 89. **Abnormal urinary constituents are**
- T a. acetone.
- T b. albumin
- T c. amino acid
- F d. creatinine
- F e. urea

Q. 90. **Abnormal urinary constituents include**
- T a. ketone bodies
- T b. glucose.
- T c. albumin
- T d. amino acid
- F e. creatinine

Q. 91. **Urea**
- T a. may cause diumsis when its blood conctration is increased.
- T b. has similar molar concentration in plasma as glucose.
- T c. concentration rises in tubular fluid as the glomerular filtrate passes down the nephron.
- F d. is actively secreted by the renal tubular cells into the tubular fluid.
- F e. concentration in blood may rise ten fold after a high protein meal.

Q. 92. **True about creatine**
- T a. Measures GFR
- F b. It is a muscle protein
- F c. High energy compound
- F d. None
- F e. All.

Q. 93. **Normal levels of creatinine in serum is**
- T a. 0.6 to 1.2 mg%
- F b. 1 to 2 mg%
- F c. 0.01 to 0.04 mg%
- F d. 0.04 to 0.1 mg%
- F e. 0.14 to 0.2 mg%

Q. 94. **The normal non-fasting blood ketone level is**
- T a. 2-10 mg%
- F b. 0.1-0.5 mg%
- F c. 0.5-2 mg%
- F d. 100-500 mg%
- T c. 20-25 mg%

Q. 95. **U/P ratio of creatinine (mg/dl) is**
- T a. 150
- F b. 0
- F c. 0.6
- F d. 60
- F e. 300.

Q. 96. **The renal clearance of**
- T a. pAH continues to rise as the plasma concentration of pAH rises.
- F b. Creatinine indicates glomerular filtration rate
- F c. Insulin is lower than that of urea
- F d. Chloride increases after an injection of aldosterone
- F e. All.

Q. 97. **When the clearance ratio of a substance is 1, the substance may be**
- T a. inulin
- F b. glucose
- F c. amino acids
- F d. sodium
- F e. PAH.

Q. 98. **What is the urea clearance?**
- T a. 44 ml/min
- F b. 4.4 ml/min

F c. 88 ml/min
F d. 440 ml/min
F e. 22 ml/min

Q. 99. **Inulin clearance closely resembles**
T a. GFR
F b. Renal plasma flow
F c. Creatinine clearance
F d. PAH clearance
F e. None.

Q. 100. **Inulin clearance is equal to**
T a. 125 ml/min
F b. 55 ml/min
F c. 625 ml/min
F d. 40 ml/min
F c. 105 ml/min

Q. 101. **True statement regarding creatinine clearance is**
T a. Represents GFR
F b. 80 ml/mm
F c. Most accurate renal function test
F d. Represents tubular function
F e. None.

Q. 102. **Transport maximum (Tm) means**
T a. Maximum reabsorption & secretion
F b. Maximum amount of glomerular filtration /min
F c. Substance cleared from plasma /min
F d. Amount of toxic substances excreted /min.
F e. None.

Q. 103. **The maximum amount of each substance that can be trasported in each minute by kidney tubules is called**
T a. tubular maximum
F b. transport maximum
F c. secretion maximum
F d. tubular load
F e. filtered load.

Q. 104. **Transport Maximum of**
T a. phosphate : 0.10 mM/min
T b. lactate : 75 mg/min.
F c. glucose : 180 mg/min
F d. amino acids : 15 rmM/min
F e. plasma protein : 90 mg/min

Q. 105. **Regarding transport maximum (Tm) of glucose**
T a. when the TmG is exceeded glucose appears in the urine
T b. it is about 375 mg/min
F c. it is about 650 ml/min
F d. it is high in diabetes mellitus
F e. it is low in diabetes insipidus.

Q. 106. **Which of the following has no Tm value?**
T a. Urea
F b. Albumin, arginine
F c. Betahydroxybutyrate, glucose
F d. Glucose, haemoglobin, phosphate,
F e. Sulfate, uric acid

Q. 107. **Substances that have no transport maxmum include**
T a. chloride
T b. Urea.
F c. amino acid
F d. plasma protein
F e. creatinjne

Q. 108. **Tubular maximum for kidney in practice and is actually less than the calculated value because**
T a. it depends on renal threshold
T b. different nephron have different reabsorp tion capacities
F c. it depends on GFR
F d. it depends on renal blood flow
F e. its depends on decrease blood pressure.
T c. reabsorbtion is complete below a certain threshold value.

Q. 109. **Tm (Transport maximum) limited reabsorption of a substance implies that**
T a. excretion rate is zero until Tm value is reached.
T b. reabsorbtion is active
F c. reabsortion is critically related to tubular transit time
F d. renal clearance falls with its plasma concentration
F e. All.

Q. 110. **Tubular maximum for kidney in practice is actually less than the calculated value because**
T a. Different nephrons have different lengths
F b. Depends on GFR
F c. Depends of Renal blood flow
F d. Depends on blood pressure
F e. All.

Concentration of urine

Q. 111. **Hyperosmolarity of the renal medullary interstium during countercurrent mechnism is due to**
T a. active transport of Na^+ from thick segment.
T b. co-transport of K^+ & $C1^-$ from thick segment.
T c. active transport of ions from the collecting duct.
T d. passive diffusion of urea from inner medullary collecting duct
F e. active transport of K^+ from colleting duct.

Q. 112. **The hyperosmolarity of the renal medulla is due to increased content of**
- T b. Na
- F a. K
- F c. Glucose
- F d. Na^+
- F e. Cl

Q. 113. **The ability of the kidney to concentrate urine is due to**
- T a. presence of juxtamedullary nephrons
- T b. presence of countercurrent multiplier (long loop of Henle)
- T c. presence of countercurrent exchanger (vasa recta)
- T d. presence of ADH
- F e. presence of aldosterone.

Q. 114. **Which one of the following is not responsible for concentration of urine in the kidneys?**
- T a. Aldosterone
- T b. Angiotensin II
- T c. Vasopressin
- F d. Epinephrine
- F d. Norepinephrine

Q. 115. **Which one of the following is not responsible for concentration of urine in the kidneys?**
- T a. Epinephrine.
- F b. Aldosterone
- F c. Angiotensin II
- F d. Vasopressin
- F e. All.

Q. 116. **The excretion of sodium (meq) in 24 hours is**
- T a. 150
- F b. Zero
- F c. 50
- F d. 250
- F e. 75

Q. 117. **In addition to kidney, counter current multiplier system is present in**
- T a. Crypts of gastric submucosa
- F b. Bone
- F c. Muscles
- F d. Skin
- F e. All.

Micturation

Q. 118. **The urge for micturition is felt when the bladder is filled with**
- T a. 300 - 400cc of urine
- F b. 700 - 800cc of urine
- F c. 100 - 200cc of urine
- F d. 500 - 700cc of urine
- F e. 70 - 80cc of urine

Q. 119. **True statement among the following is**
- T a. Bladder emptying cannot occur if volume < 100 ml
- F b. Bladder muscle contains intrafusal fibres
- F c. Pressure increases in bladder vary linearly with time
- F d. One litre of fluid intake results in complete excretion in 1 hour
- F e. All.

Q. 120. **In a normal adult the desire for micturition is felt**
- T a. When about 300-400 cc of urine has collected in the bladder
- F b. When about 100-200 cc of urine has collected in the bladder
- F c. When about 600-800 cc of urine has collected in the bladder
- F d. When about 1000 cc of urine has collected in the bladder
- F e. When about 100-150 cc of urine has collected in the bladder.

Applied

Q. 121. **Factors that increase renal calcium excretion are**
- T a. decreased PTH
- T b. increased PTH
- F c. increased plasma phosphate
- F d. metabolic acidosis
- F e. decreased blood pressure.

Q. 122. **A long standing increase in arterial PCO_2 (respiratory acidosis) leads to an increase in**
- T a. renal bicarbonate formation
- T b. urinary ammonium salts
- T c. plasma potassium concentration
- F d. the ratio of monohydrogen to dihydrogen phosphate in urine
- F e. urinary bicarbonate excretion.

Q. 123. **When pH of the blood is too low, the ions that secrete into the nephon from the surounding capillaries are**
- T a. H^+
- T b. NH^{4+}
- F c. Na^+
- F d. HCO_3^-
- F e. Cl^-.

Q. 124. **Alkalosis accurs whenever pH is above:**
- T a. 7.40
- T b. 7.04
- F c. 7.000

F d. 7.24
F e. 7.36

Q. 125. **Respiratory acidosis can cause**
T a. Increased PCO_2 and decreased P^H
F b. Decreased PCO_2 and decreased P^H
F c. Increased PCO_2 and increased P^H
F d. Decreased PCO_2 and increased P^H
F e. All.

Q. 126. **Metabolic alkalosis associated with prolonged vomiting is due to primarily to loss of**
T a. Chloride
F b. Sodium
F c. Potassium
F d. Hydrogen ion
F e. All.

Q. 127. **At high altitude one will develop**
T a. tetany.
T b. respiratory alkalosis
F c. respiratory acidosis
F d. metabolic acidosis
F e. metabolic alkalosis.

Q. 128. **A patient with chronic renal failure usually has an increased**
T a. blood urea
T b. blood uric acid
T c. acid-base problem on a high protein diet.
F d. creatinine clearance
F e. acid-base disturbance when he or she vomits.

Q. 129. **Dialysis fluid used in the treatment of renal failure should not contain**
T a. urea
T b. creatinine
T c. phosphate
F d. glucose
F e. Na^+.

Q. 130. **Diuresis is caused by**
T a. Mannitol
T b. Glycerol
T c. Urea
T d. All of the above
F e. None.

Q. 131. **Which is seen in high altitude**
T a. Respiratory alkalosis
F b. Metabolic alkalosis
F c. Respiratory acidosis
F d. Metabolic acidosis
F e. None.

Q. 132. **Injection of hypertonic saline into which area causes diuresis**
T a. Supraoptic nucleus
F b. Paraventricular nucleus
F c. Preoptic nucleus
F d. Posterior pituitary
F e. None.

Q. 133. **Addis test is used for :**
T a. Urinary sediment
F b. Urinary sugar
F c. Blood lacted
F d. Serum magnesium
F e. All.

Q. 134. **Renal calculi is seen in**
T a. Hyperparathyroidism
F b. Hyperthyroidism
F c. Cushing disease
F d. Addisons disease
F e. All.

Q. 135. **In renal glycosuria, the renal threshold for glucose is**
T a. Low
F b. High
F c. Same
F d. Greatly increased
F e. All.