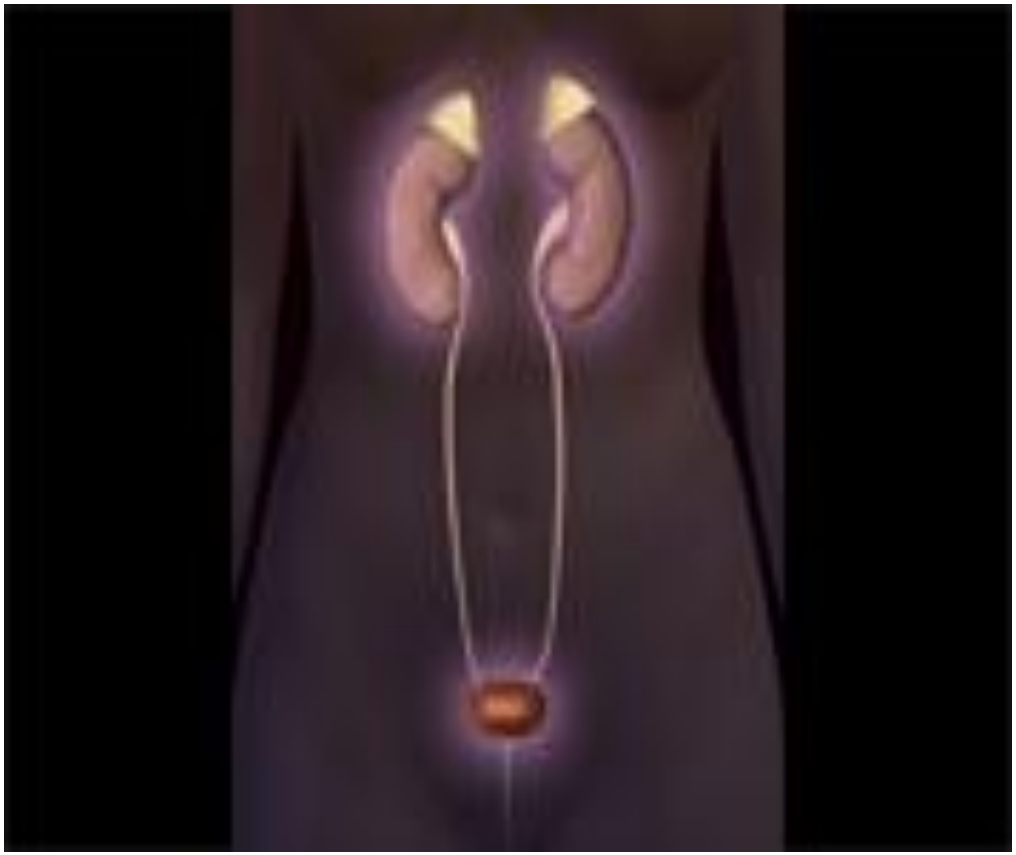
WELCOME



HISTOLOGY OF NEPHRON &URINE FORMATION

Presented by
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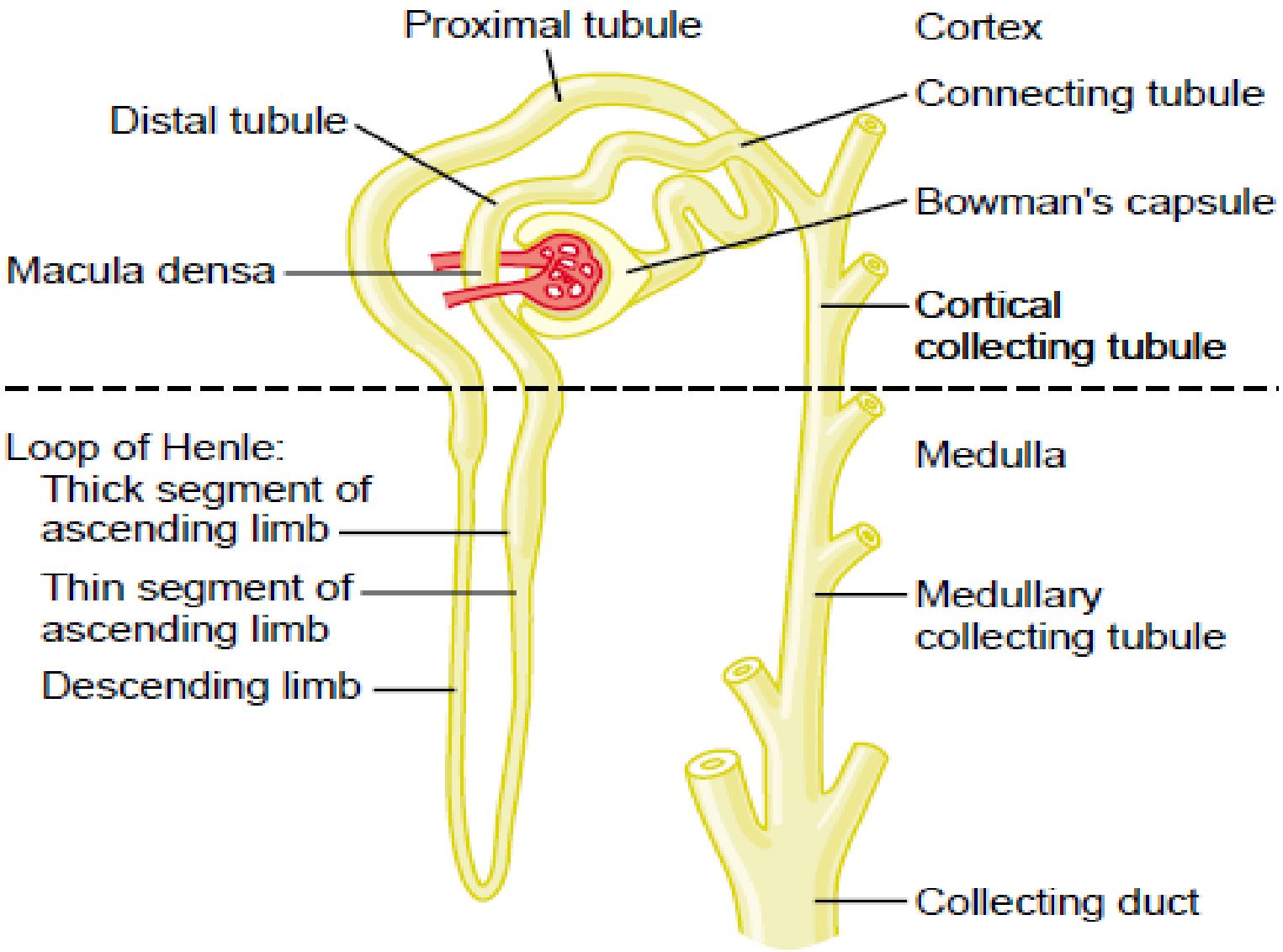
1 MD(organon)

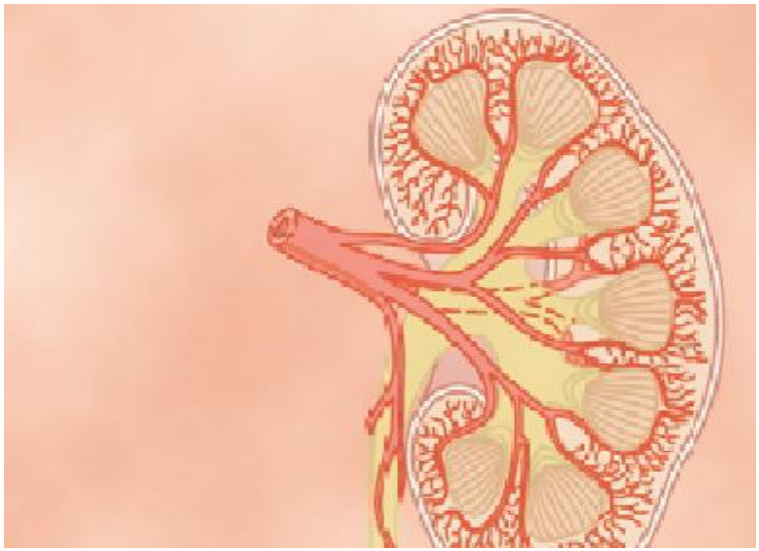
The Nephron

Each individual renal tubule and its glomerulus is a unit **(nephron).** The size of the kidneys in various species is determined largely by the number of nephrons they contain. **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.

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.


Proximal tubule
Cortex
Distal tubule
Connecting tubule
Bowman's capsule
Macula densa
Cortical collecting tubule
Loop of Henle:
Thick segment of ascending limb
Thin segment of ascending limb
Descending limb
Medulla
Medullary collecting tubule
Collecting duct

FUNCTIONAL ANATOMY



Each nephron contains

(1) a tuft of glomerular capillaries called the ***glomerulus***, through which large amounts of fluid are filtered from the blood

(1) a long ***tubule*** in which the filtered fluid is converted into urine on its way to the pelvis of the kidney

Regional Differences in Nephron Structure: Cortical and Juxtamedullary Nephrons.

Those nephrons that have glomeruli located in the outer cortex are called ***cortical nephrons***; they have short loops of Henle that penetrate only a short distance into the medulla

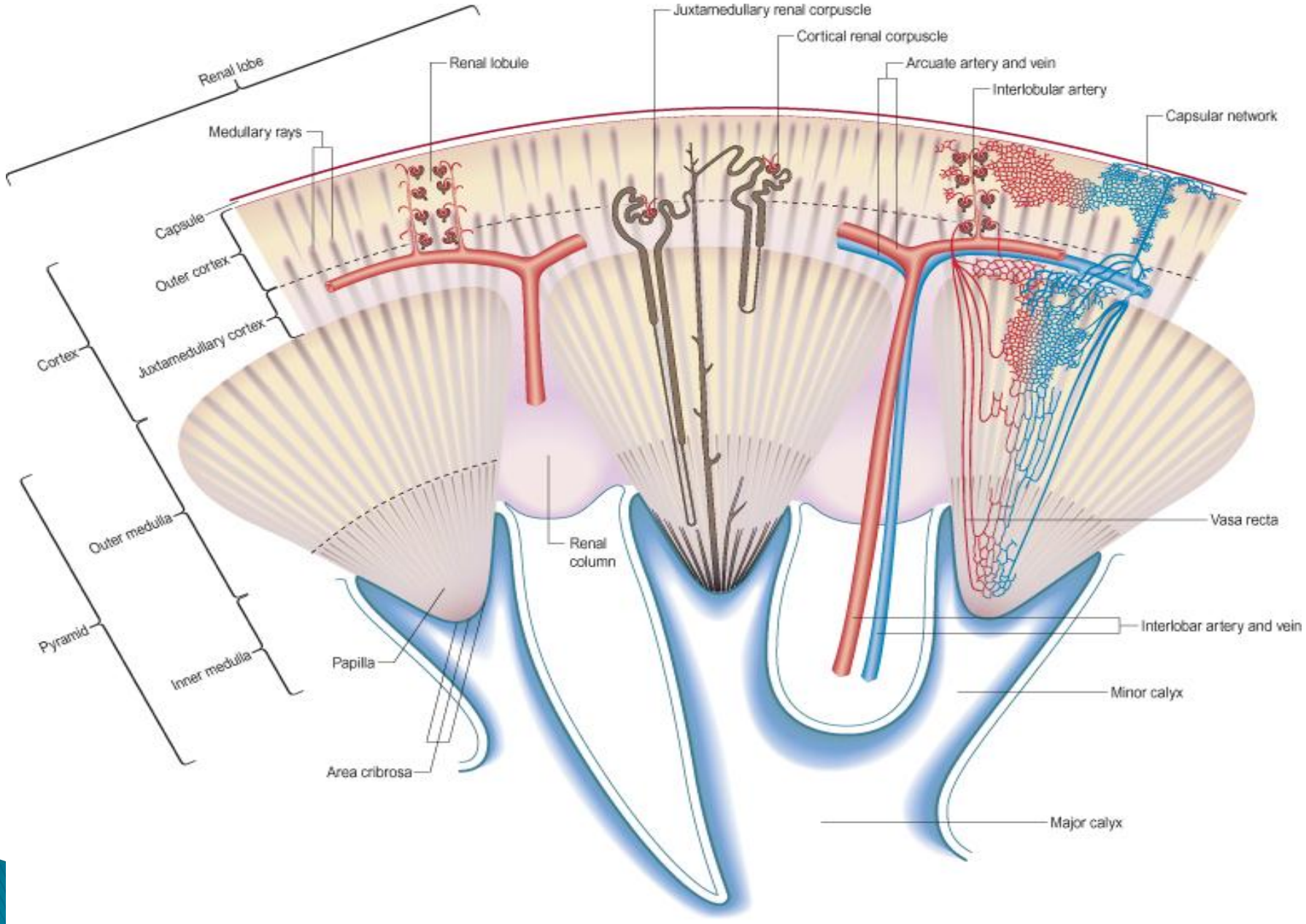
About 20 to 30 per cent of the nephrons have glomeruli that lie deep in the renal cortex near the medulla and are called ***juxtamedullary nephrons***.These nephrons have long loops of Henle that dip deeply into the medulla.

The vascular structures supplying the juxtamedullary nephrons also differ from those supplying the cortical nephrons. For the cortical nephrons, the entire tubular system is surrounded by an extensive network of peritubular capillaries.

For the juxtamedullary nephrons, long efferent arterioles extend from the glomeruli down into the outer medulla and then divide into specialized peritubular capillaries called ***vasa recta*** that extend downward into the medulla, lying side by side with the loops of Henle.Like the loops of Henle, the vasa recta return toward the cortex and empty into the cortical veins. This specialized network of capillaries in the medulla plays an essential role in the formation of a concentrated urine.

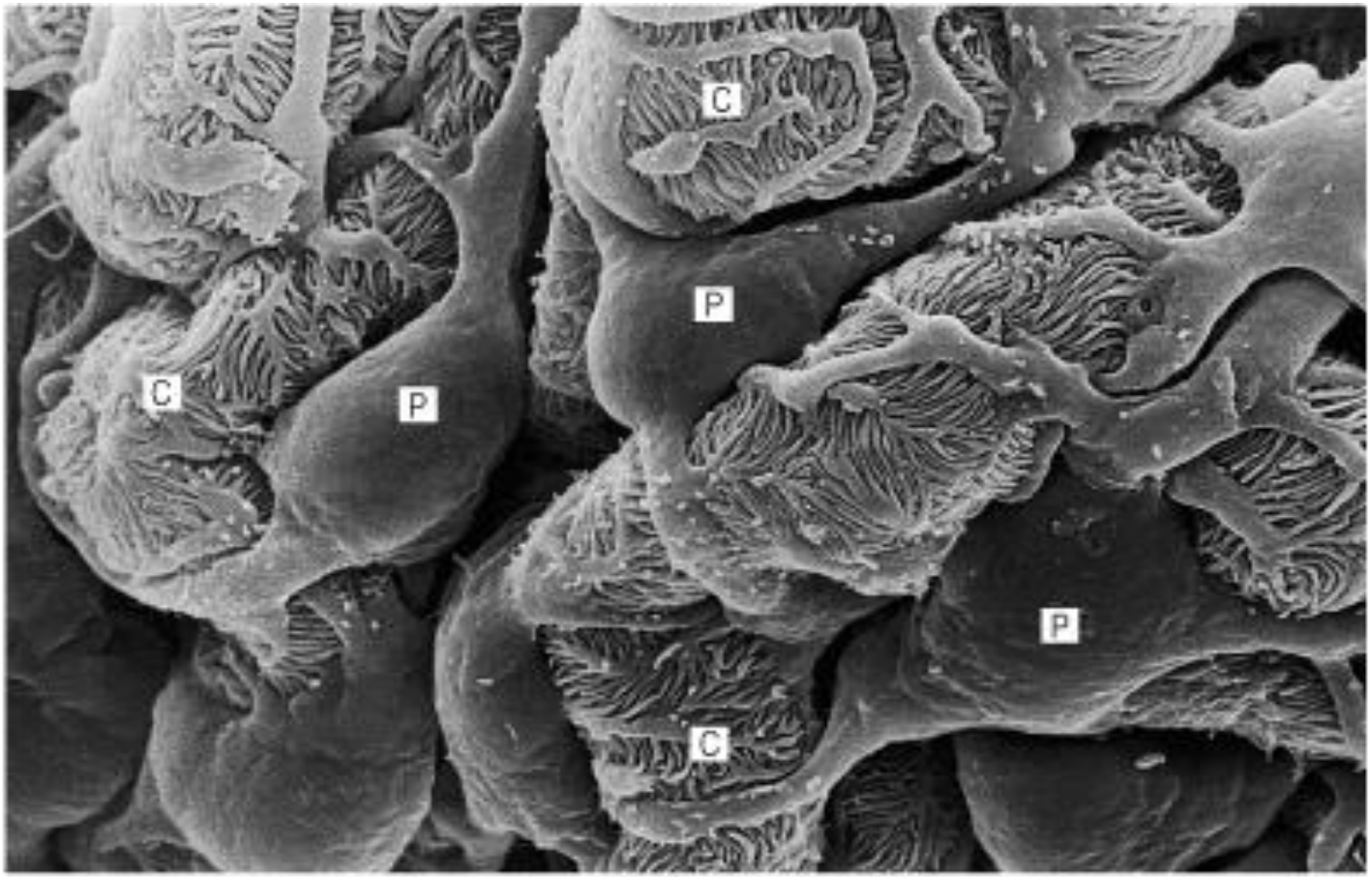
The glomerulus

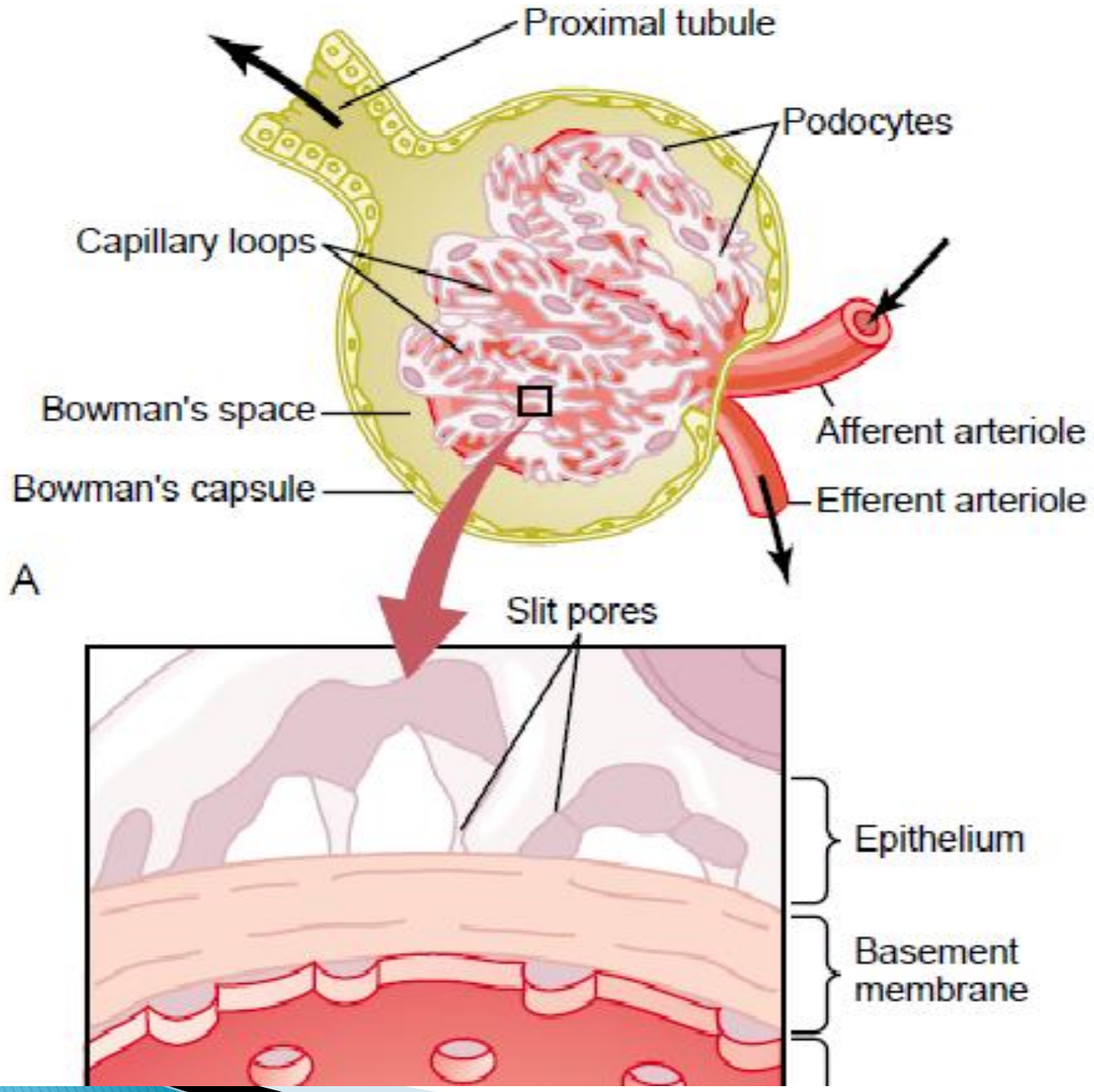
The glomerulus, which is about 200 um in diameter, is formed by the invagination of a tuft of capillaries have high hydrostatic pressure (about 60 mm Hg) into the dilated, blind end of the nephron **(Bowman's capsule).** The capillaries are supplied by an **afferent arteriole** and drained by a slightly smaller **efferent arteriole** . There are two cellular layers separating the blood from the glomerular filtrate in Bowman's capsule: the capillary endothelium and the specialized epithelium of the capsule that is made up of **podocytes** overlying the glomerular capillaries .



These layers are separated by a basal lamina. Stellate cells called **mesangial cells** are located between the basal lamina and the endothelium. Mesangial cells are especially common between two neighboring capillaries, and in these locations the basal membrane forms a sheath shared by both capillaries . The mesangial cells are contractile and play a role in the regulation of glomerular filtration . They also secrete various substances, take up immune complexes, and are involved in the production of glomerular disease.

The endothelium of the glomerular capillaries is fenestrated, with pores that are 70–90 nm in diameter. 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. The basal lamina does not contain visible gaps or pores.

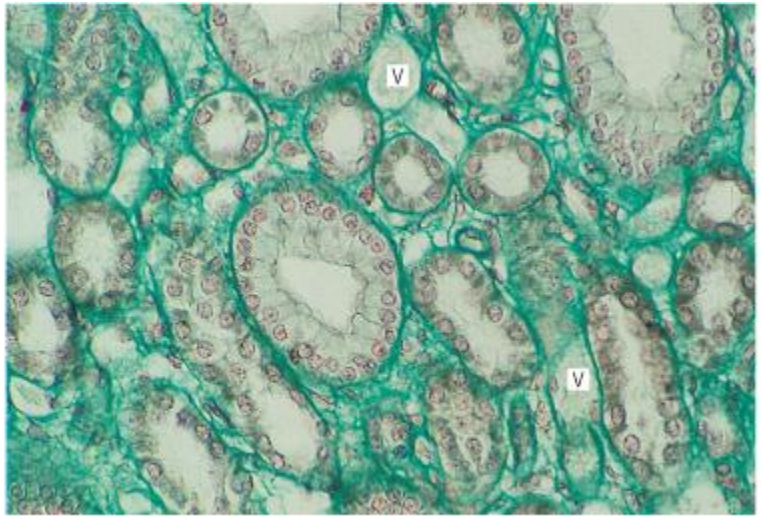


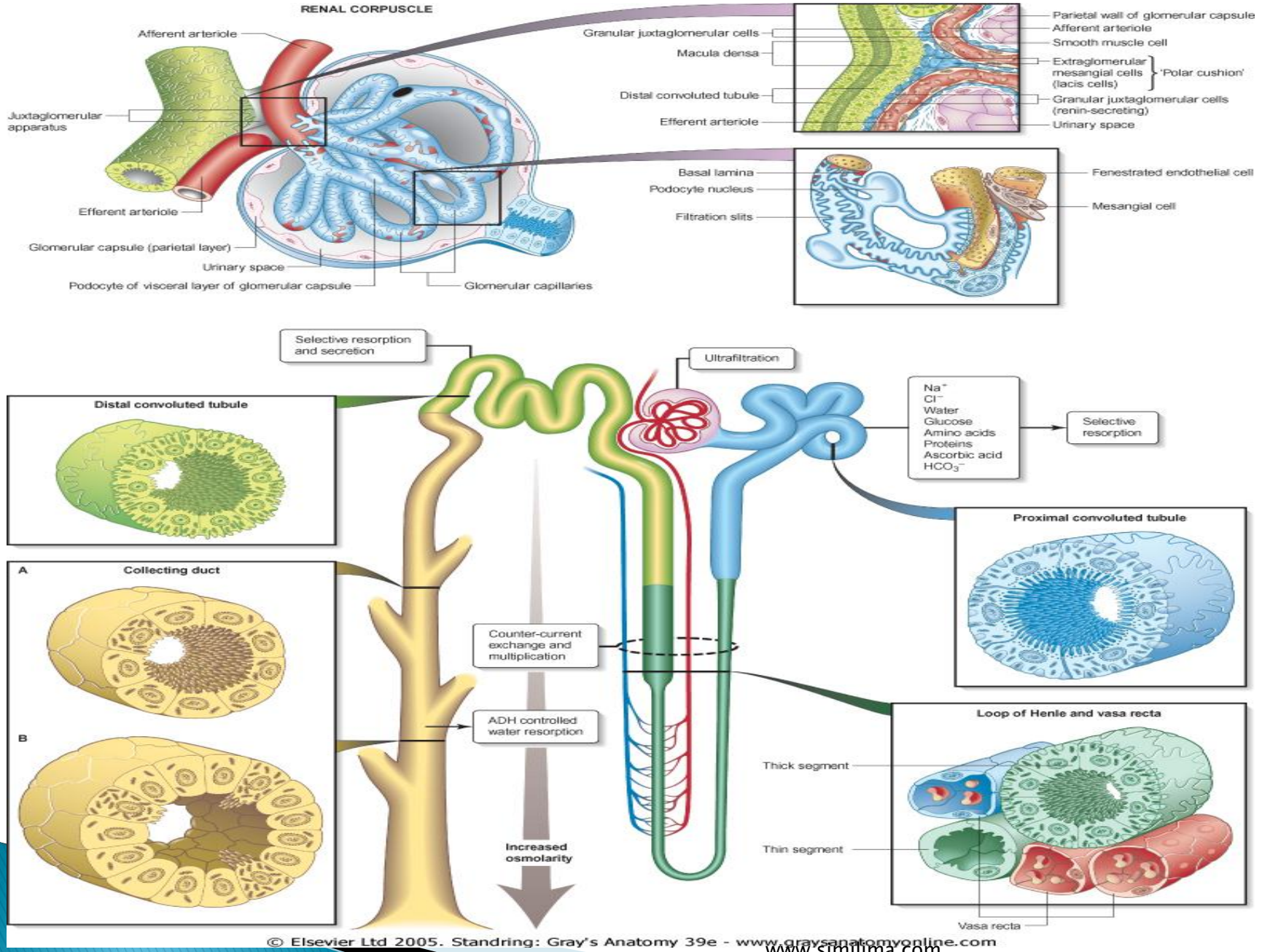

Proximal tubule
Podocytes
Capillary loops
Bowman's space
Bowman's capsule
Afferent arteriole
Efferent arteriole
A
Slit pores
Epithelium
Basement membrane

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.

The human **proximal convoluted tubule** is about 15 mm long and 55 um 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 1×0.7 um microvilli.




RENAL CORPUSCLE
Afferent arteriole
Juxtaglomerular apparatus
Efferent arteriole
Glomerular capsule (parietal layer)
Urinary space
Podocyte of visceral layer of glomerular capsule
Glomerular capillaries
Granular juxtaglomerular cells
Macula densa
Distal convoluted tubule
Efferent arteriole
Parietal wall of glomerular capsule
Afferent arteriole
Smooth muscle cell
Extraglomerular mesangial cells (lacis cells)
'Polar cushion'
Granular juxtaglomerular cells (renin-secreting)
Urinary space
Basal lamina
Podocyte nucleus
Filtration slits
Fenestrated endothelial cell
Mesangial cell
Selective resorption and secretion
Ultrafiltration
Distal convoluted tubule
Na+
Cl−
Water
Glucose
Amino acids
Proteins
Ascorbic acid
HCO3−
Selective resorption
Proximal convoluted tubule
A
Collecting duct
B
Counter-current exchange and multiplication
ADH controlled water resorption
Increased osmolarity
Loop of Henle and vasa recta
Thick segment
Thin segment
Vasa recta
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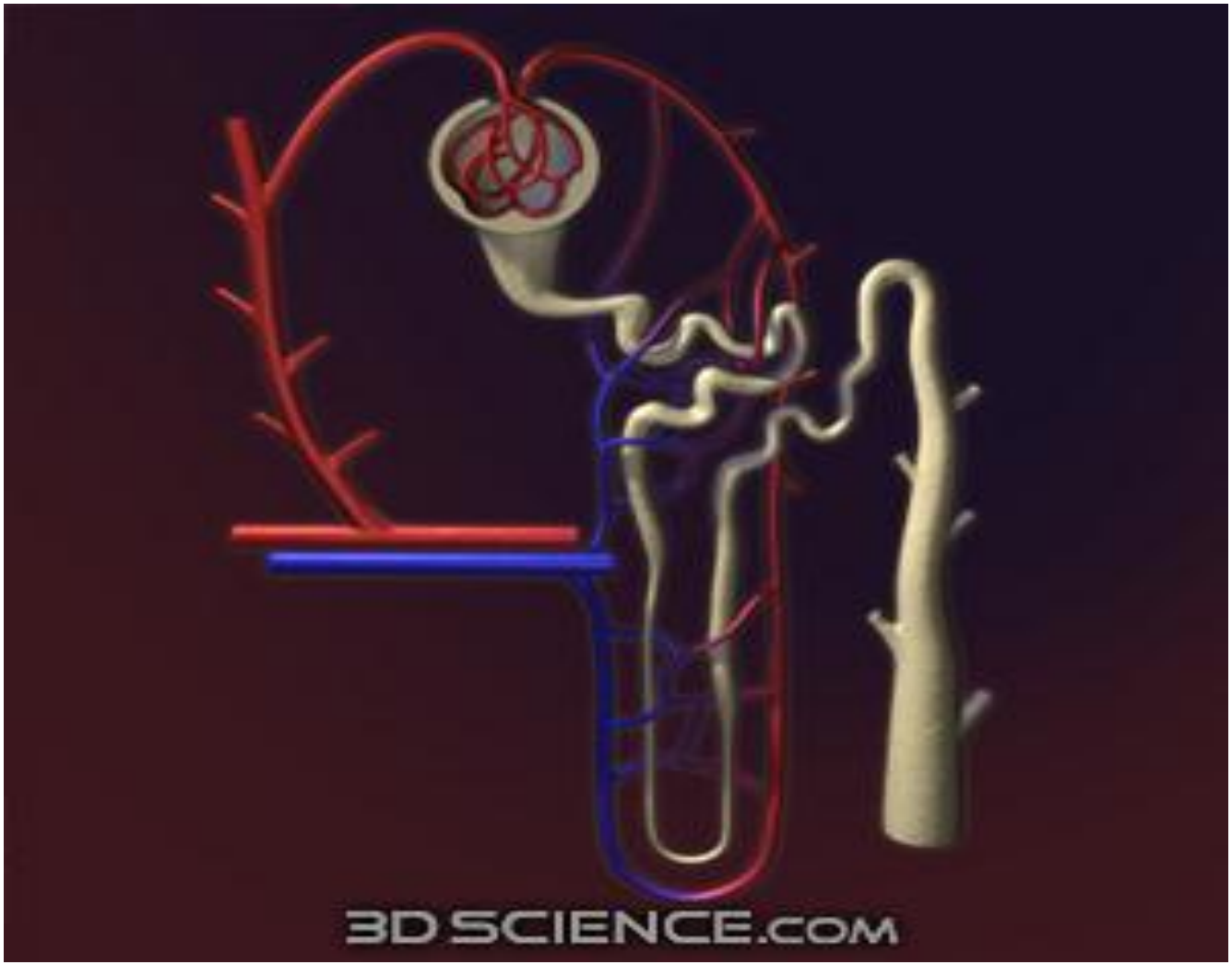
The convoluted portion of the proximal tubule **(pars convoluta)** drains into the straight portion **(pars recta)**, which forms the first part of the **loop of Henle** . The proximal tubule terminates in the thin segment of the **descending limb of the loop of Henle**, which has an epithelium made up of **attenuated, flat cells.** 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.

The total length of the thin segment of the loop varies from 2 to 14 mm. It ends in the thick segment of the ascending limb, which 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.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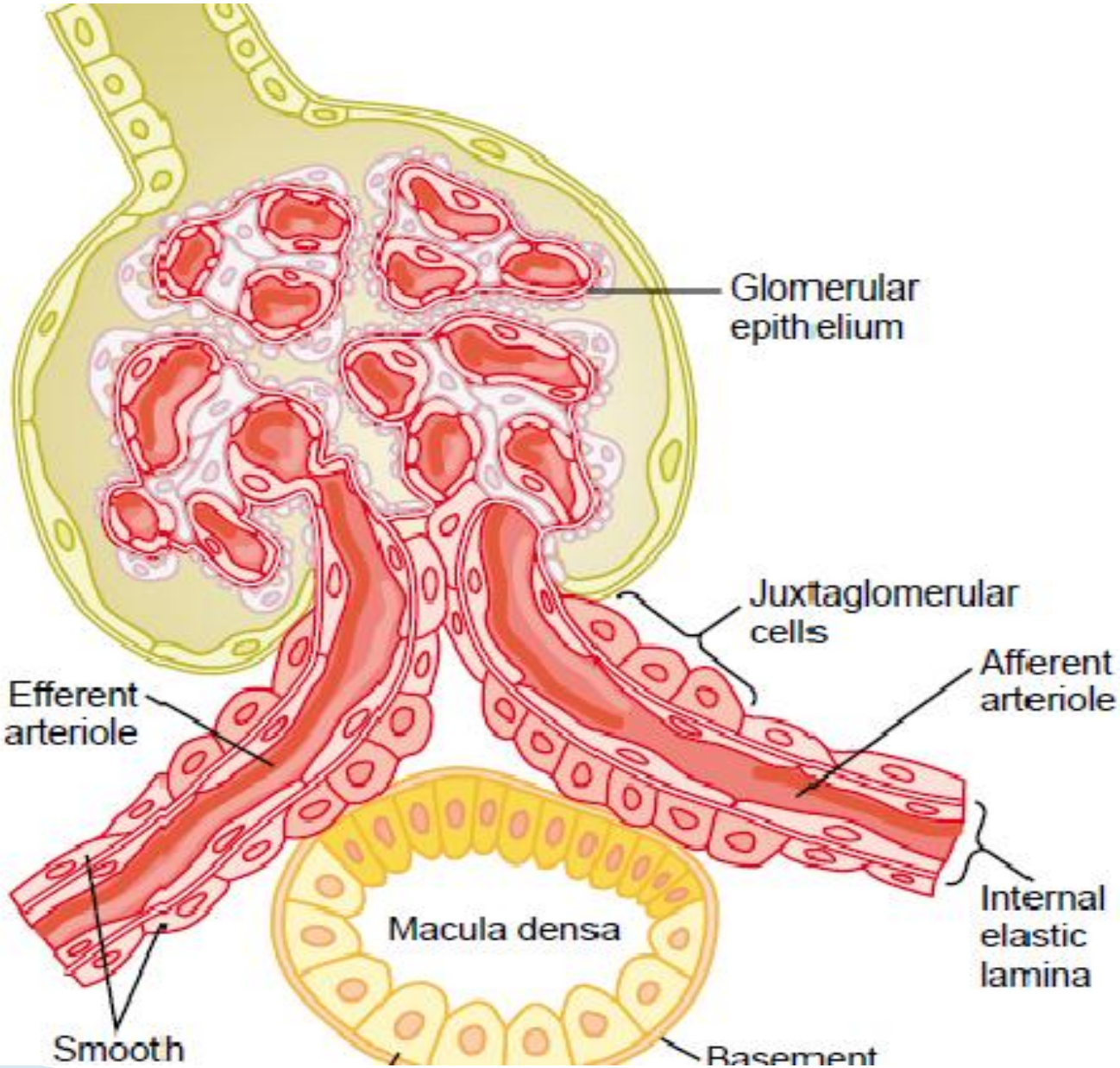
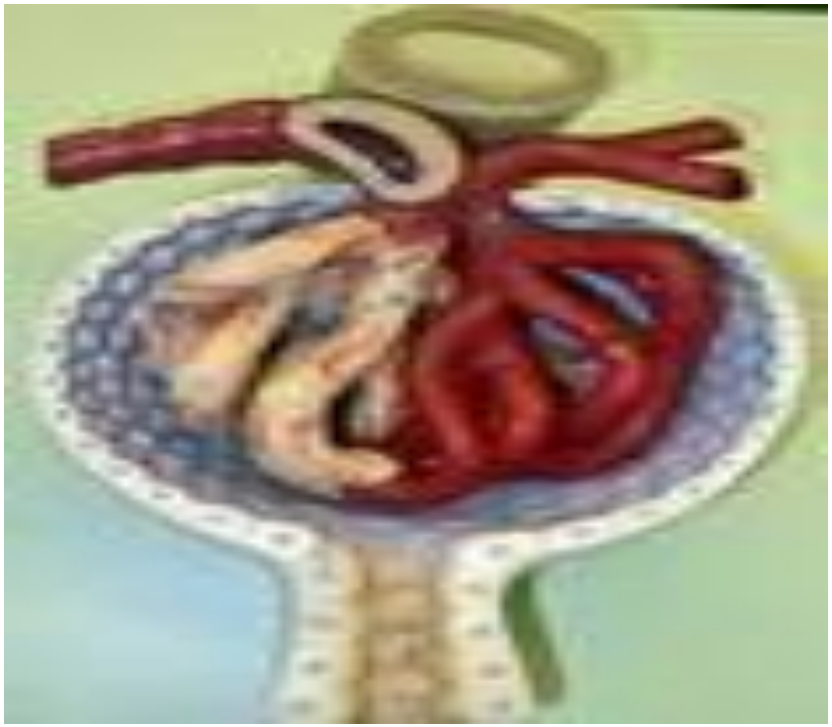
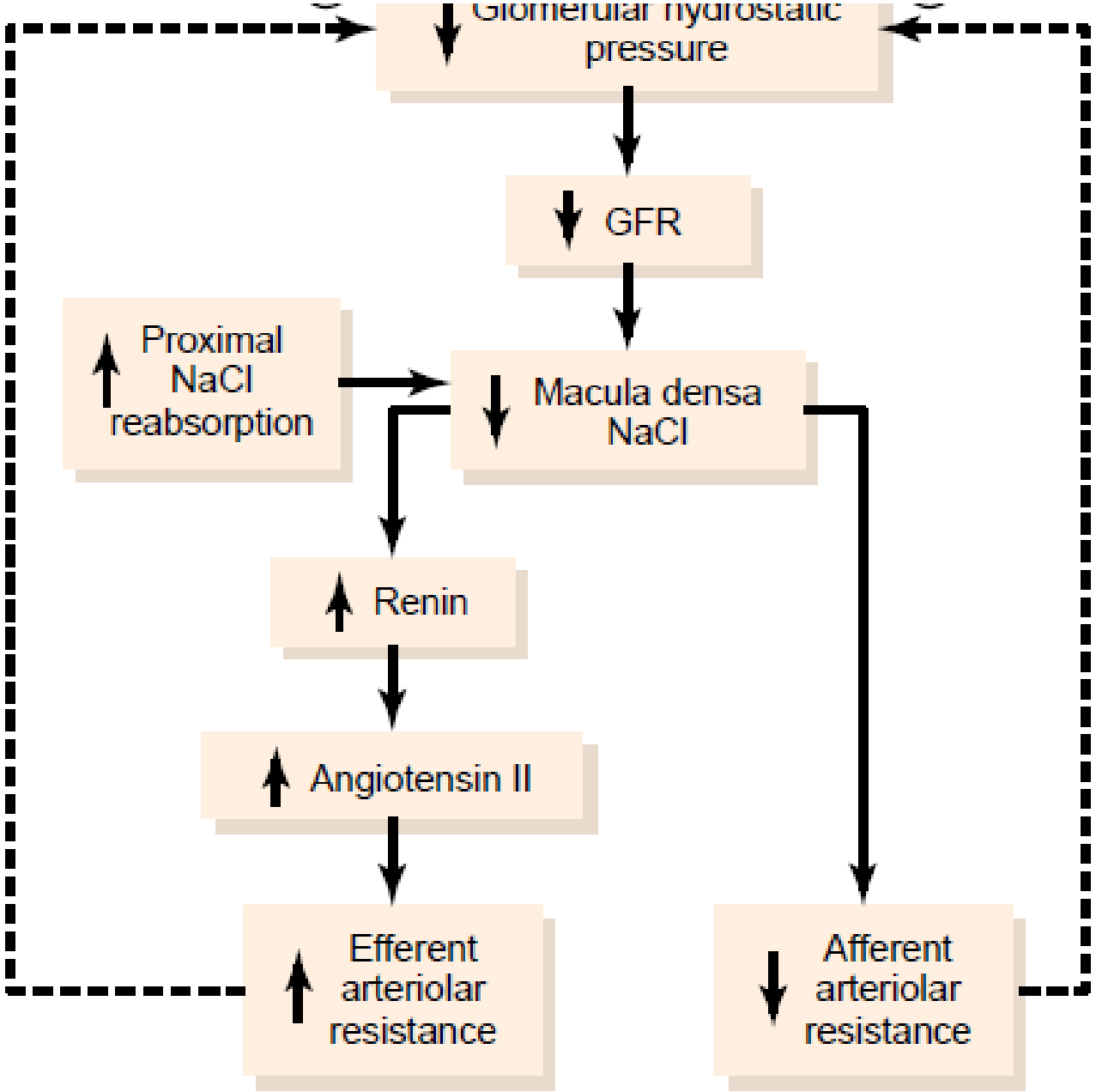
The thick ascending limb of the loop of Henle reaches the glomerulus of the nephron from which the tubule arose and passes close to its afferent arteriole and efferent arteriole. The walls of the afferent arterioles contain the renin-secreting juxtaglomerular cells. At this point, the tubular epithelium is modified histologically to form the **macula densa.**


Glomerular epithelium
Juxtaglomerular cells
Afferent arteriole
Efferent arteriole
Internal elastic lamina
Macula densa
Smooth
Basement

The juxtaglomerular cells, the macula densa, and the lacis cells near them are known collectively as the **juxtaglomerular apparatus**.



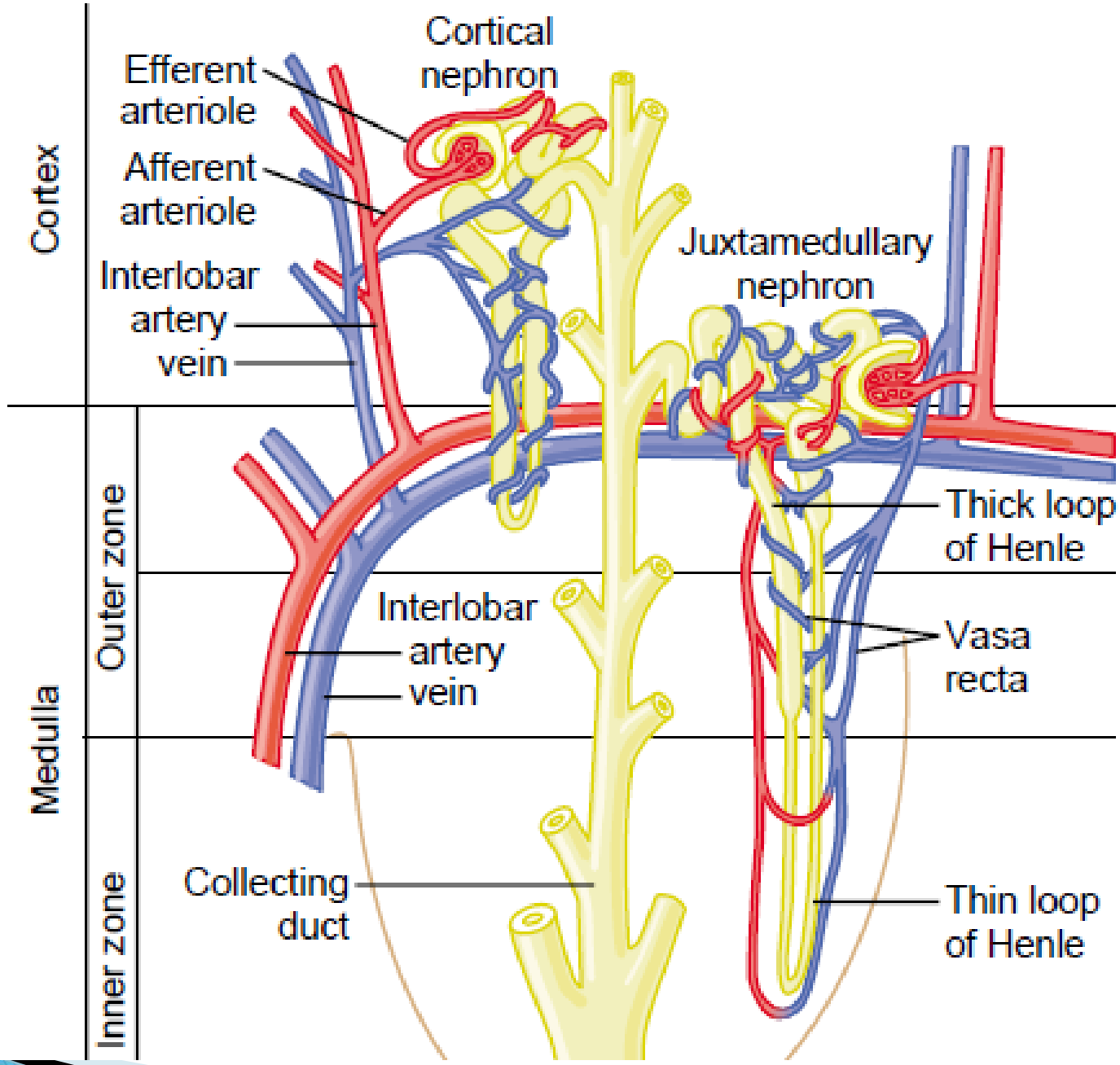

Glomerular hydrostatic pressure
GFR
Proximal NaCl reabsorption
Macula densa NaCl
Renin
Angiotensin II
Efferent arteriolar resistance
Afferent arteriolar resistance

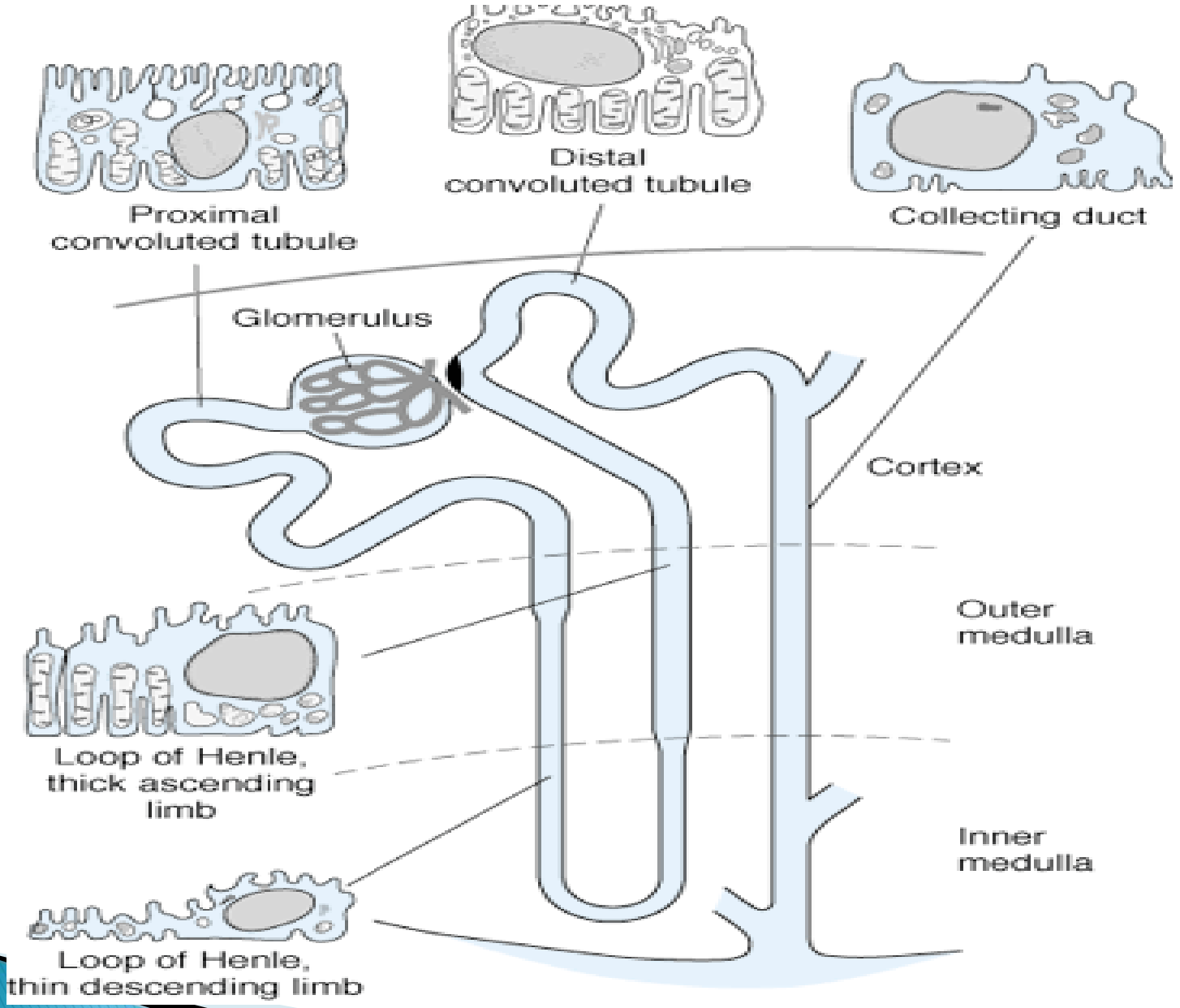
The **distal convoluted tubule** is about 5 mm long. Its epithelium is lower than that of the proximal tubule, and although there are a few microvilli, there is no distinct brush border. The distal tubules coalesce to form **collecting ducts** that are about 20 mm long and pass through the renal cortex and medulla to empty into the pelvis of the kidney at the apexes of the medullary pyramids. 5 to 65 mm.

The epithelium of the collecting ducts is made up of **principal cells (P cells)** and **intercalated cells (I cells).** The P cells, which predominate, are relatively tall and have few organelles.

They are involved in Na^+ reabsorption and vasopressin-stimulated water reabsorption. The I cells, which are present in smaller numbers and are also found in the distal tubules, have more microvilli, cytoplasmic vesicles, and mitochondria. They are concerned with acid secretion and HCO_3^- transport.

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


Cortical nephron
Efferent arteriole
Afferent arteriole
Interlobar artery
vein
Juxtamedullary nephron
Cortex
Medulla
Outer zone
Inner zone
Thick loop of Henle
Interlobar artery
vein
Vasa recta
Collecting duct
Thin loop of Henle


Distal convoluted tubule
Proximal convoluted tubule
Collecting duct
Glomerulus
Cortex
Outer medulla
Loop of Henle, thick ascending limb
Inner medulla
Loop of Henle, thin descending limb

Urine Formation

Results from Glomerular Filtration, Tubular Reabsorption and Tubular Secretion

In the kidneys, a fluid that resembles plasma is filtered through the glomerular capillaries into the renal tubules **(glomerular filtration).** Most substances in the plasma, except for proteins, are freely filtered, so that their concentration in the glomerular filtrate in Bowman's capsule is almost the same as in the plasma. 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.

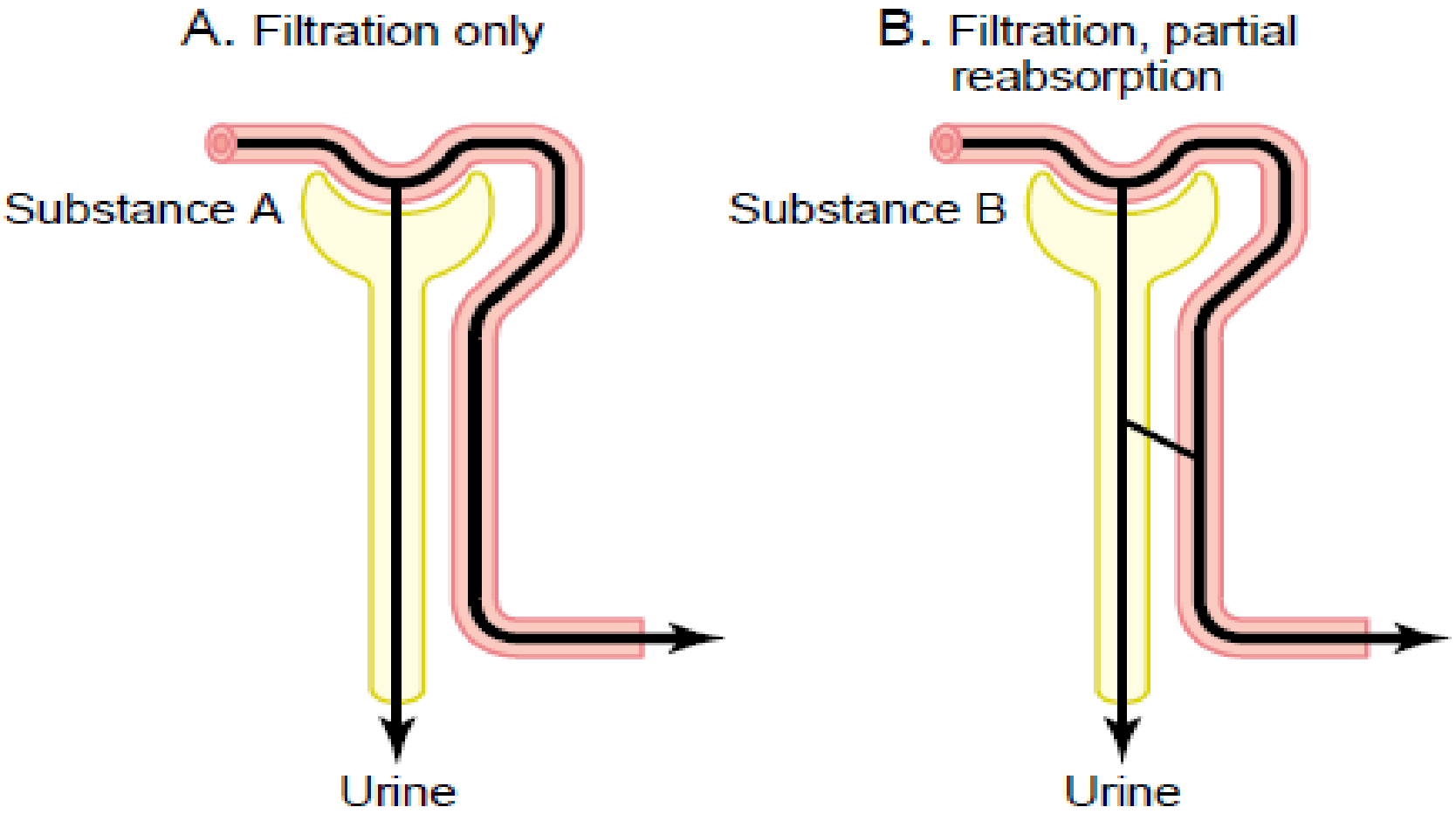
. From the renal pelvis, the urine passes to the bladder and is expelled to the exterior by the process of urination, or **micturition.**

Expressed mathematically,Urinary excretion rate = Filtration rate- Reabsorption rate + Secretion rate

The substance shown in panel A is **freely filtered by the glomerular capillaries but is neither reabsorbed nor secreted.**

Therefore, its excretion rate is equal to the rate at which it was filtered. Certain waste products in the body, such as creatinine,urea,uricacid,and urates, are handled by the kidneys in this manner, allowing excretion of essentially all that is filtered.

In panel B, the **substance is freely filtered but is also partly reabsorbed from the tubules back into the blood.** Therefore, the rate of urinary excretion is less than the rate of filtration at the glomerular capillaries.In this case, the excretion rate is calculated as the filtration rate minus the reabsorption rate.This is typical for many of the electrolytes of the body.

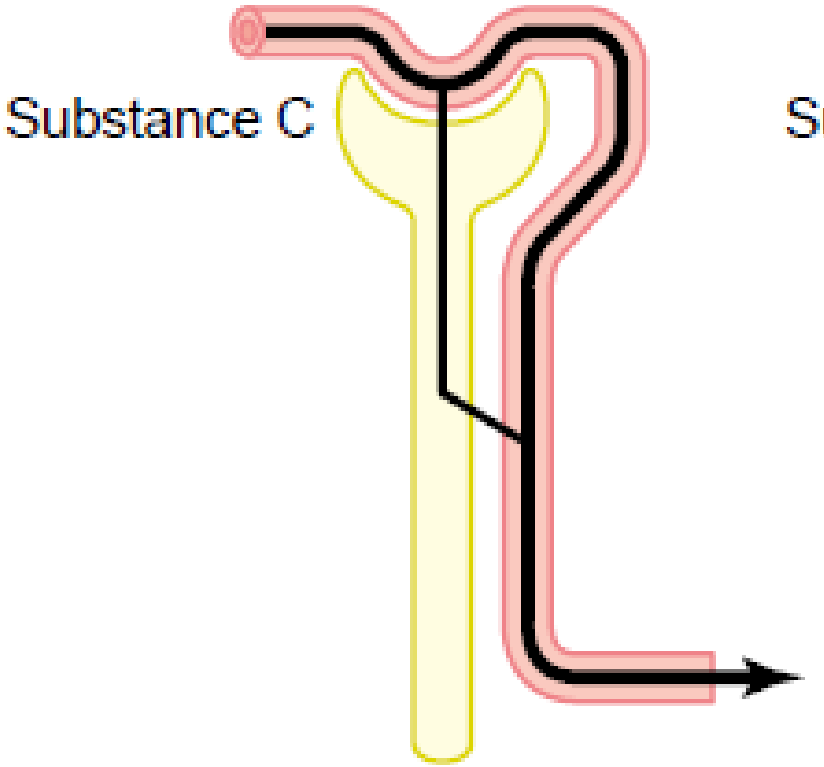

A. Filtration only
Substance A
Urine
B. Filtration, partial reabsorption
Substance B
Urine

In panel C, the substance is **freely filtered at the glomerular capillaries but is not excreted into the urine because all the filtered substance is reabsorbed from the tubules back into the blood.**

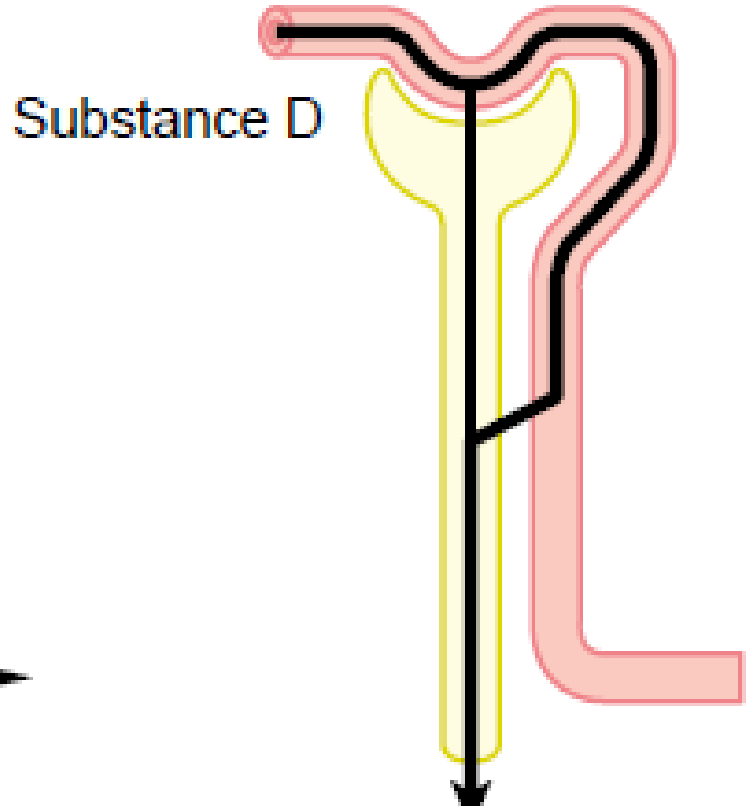
This pattern occurs for some of the nutritional substances in the blood, such as **amino acids and glucose,** allowing them to be conserved in the body fluids.

The substance in panel D **is freely filtered at the glomerular capillaries and is not reabsorbed, but additional quantities of this substance are secreted from the peritubular capillary blood into the renal tubules.**

C. Filtration, complete reabsorption



D. Filtration, secretion



This pattern often occurs for organic acids and bases, permitting them to be rapidly cleared from the blood and excreted in large amounts in the urine.The excretion rate in this case is calculated as filtration rate plus tubular secretion rate.

Glomerular Filtration—The First Step in Urine Formation
Composition of the Glomerular Filtrate

Urine formation begins with filtration of large amounts of fluid through the glomerular capillaries into Bowman's capsule. Like most capillaries, the glomerular capillaries are relatively impermeable to proteins, so that the filtered fluid (called the glomerular filtrate) is essentially protein-free and devoid of cellular elements, including red blood cells.

The concentrations of other constituents of the glomerular filtrate, including most salts and organicmolecules, are similar to the concentrations in the plasma. Exceptions to this generalization include a few low-molecular-weight substances, such as calcium and fatty acids, that are not freely filtered because they are partially bound to the plasma proteins. Almost one half of the plasma calcium and most of the plasma fatty acids are bound to proteins, and these bound portions are not filtered through the glomerular capillaries.

GLOMERULAR FILTRATION

Measuring GFR

The **glomerular filtration rate (GFR)** can be measured in intact animals and humans by measuring the excretion and plasma level of a substance that is freely filtered through the glomeruli and neither secreted nor reabsorbed by the tubule.

Therefore, if the substance is designated by the letter X, the GFR is equal to the concentration of X in urine (U_X) times the urine flow per unit of time (V.) divided by the arterial plasma level of X (P_X)

$$U_X V./P_X.$$

This value is called the clearance of X (C_X).

.

Substances Used to Measure GFR

In addition to the requirement that it be freely filtered and neither reabsorbed nor secreted in the tubules, a substance suitable for measuring the GFR should be nontoxic and not metabolized by the body. **Inulin, a polymer of fructose with a molecular weight of 5200** that is found in dahlia tubers, meets these criteria in humans and most animals and is extensively used to measure GFR. Radioisotopes such as ^{51}Cr-EDTA are also used, but inulin remains the standard substance. In practice, a loading dose of inulin is administered intravenously, followed by a sustaining infusion to keep the arterial plasma level constant. After the inulin has equilibrated with body fluids, an accurately timed urine specimen is collected and a plasma sample obtained halfway through the collection. Plasma and urinary inulin concentrations are determined and the clearance calculated.

•Control of GFR

The factors governing filtration across the glomerular capillaries are ,

- **the size of the capillary bed**

- **the permeability of the capillaries**

- **the hydrostatic and osmotic pressure gradients across the capillary wall.**

- **the capillary filtration coefficient (Kf)**

the product of the permeability and filtering surface area of the capillaries.

The glomerular capillaries have a much higher rate of filtration than most other capillaries because of a high glomerular hydrostatic pressure and a large Kf.

Normal GFR

The GFR in an average-sized normal man is approximately 125 mL/min. 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. A rate of 125 mL/min is 7.5 L/h, or 180 L/d, whereas the normal urine volume is about 1 L/d. Thus, 99% or more of the filtrate is normally reabsorbed.

Filtration Fraction

The ratio of the GFR to the renal plasma flow (RPF), the **filtration fraction,** is normally 0.16-0.20. The GFR varies less than the RPF. When there is a fall in systemic blood pressure, the GFR falls less than the RPF because of efferent arteriolar constriction, and consequently the filtration fraction rises.

Filtration fraction = GFR/Renal plasma flow

Reabsorption and Secretion by the Renal Tubules

unlike glomerular filtration, which is relatively nonselective (that is,essentially all solutes in the plasma are filtered except the plasma proteins or substances bound to them)

tubular reabsorption is highly selective.

Tubular Reabsorption Includes Passive and Active Mechanisms

For a substance to be reabsorbed, it must first be transported(1) across the tubular epithelial membranesinto the renal interstitial fluid and then (2) 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,water and solutes can be transported either through the cell membranes themselves (*transcellular route*) or through the junctional spaces between the cells (*paracellular route*).

Then, 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.

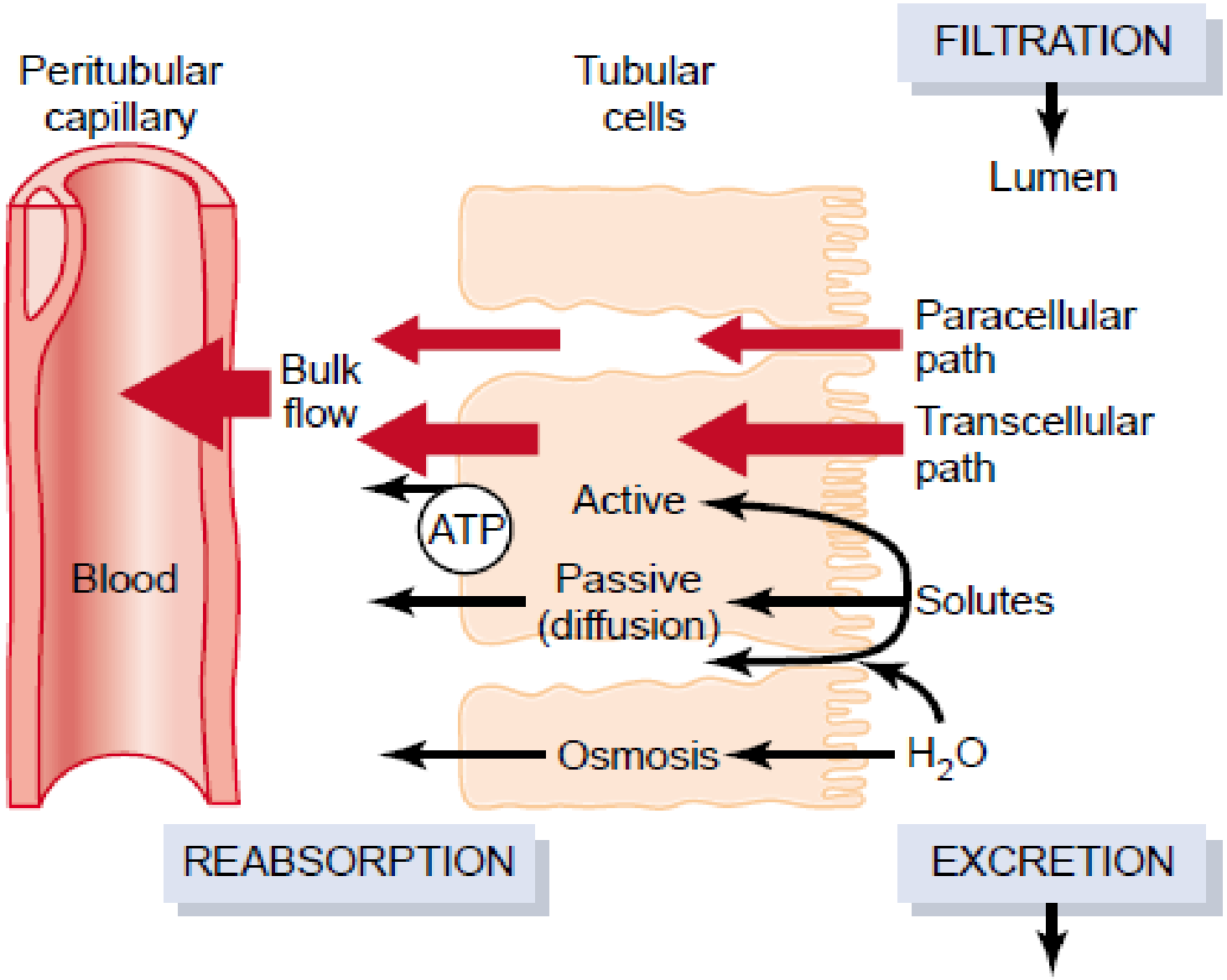
Active Transport

Primary Active Transport Through the Tubular Membrane Is Linked to Hydrolysis of ATP

. ***The special importance of primary active transport is that it can move solutes against an electrochemical gradient.***

The energy for this active transport comes from the hydrolysis of ATP byway of membrane-bound ATPase; the ATPase is also a component of the carrier mechanism that binds and moves solutes across the cell membranes.The primaryactive transporters that are known include *sodium potassium ATPasehydrogenATPase*,*hydrogenpotassiumATPase*, and *calcium ATPase*.

A good example of a primary active transport system is the reabsorption of sodium ions across the proximal tubular membrane,


FILTRATION
Peritubular capillary
Tubular cells
Lumen
Paracellular path
Bulk flow
Transcellular path
ATP
Active
Blood
Passive (diffusion)
Solutes
Osmosis
H_2O
REABSORPTION
EXCRETION

Secondary Active Reabsorption Through the Tubular Membrane.

In secondary active transport, two or more substances interact with a specific membrane protein (a carrier molecule) and are transported together across the membrane. As one of the substances (for instance, sodium) diffuses down its electrochemical gradient,the energy released is used to drive another substanc**. Reabsorption of glucose by the renal tubule is an example of secondary active transport.** (for instance, glucose) against its electrochemical gradient. Thus, secondary active transport does not require energy directly from ATP or from other high energy phosphate sources. Rather, the direct source of the energy is that liberated by the simultaneous facilitated diffusion of another transported substance down its own electrochemical gradient.

Although solutes can be reabsorbed by active and/or passive mechanisms by the tubule, **water is always reabsorbed by a passive(non active) 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).

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 interstitial fluid.

Because pinocytosis requires energy, it is considered a form of active transport.

Secondary Active Secretion into the Tubules.

Some substances are secreted into the tubules by secondary active transport. This often involves *counter-transport* of the substance with sodium ions. In counter transport,the energy liberated from the downhill movement of one of the substances (for example, sodium ions) enables uphill movement of a second substance in the opposite direction

.

Transport Maximum for Substances That Are Actively Reabsorbed.

For most substances that are actively reabsorbed or secreted, there is a limit to the rate at which the solute can be transported, often referred to as the *transport maximum*

Mechanisms of Tubular Reabsorption & Secretion

Small proteins and some peptide hormones are reabsorbed in the proximal tubules by endocytosis. Other substances are secreted or reabsorbed in the tubules by passive diffusion between cells and through cells by facilitated diffusion down chemical or electrical gradients or active transport against such gradients . Movement is by way of ion channels, exchangers, cotransporters, and pumps. Many of these have now been cloned, and their regulation is being studied. Mutations of individual genes for many of them cause specific syndromes such as Dent's disease, Bartter's syndrome, and Liddle's syndrome, and a large number of mutations have been described.

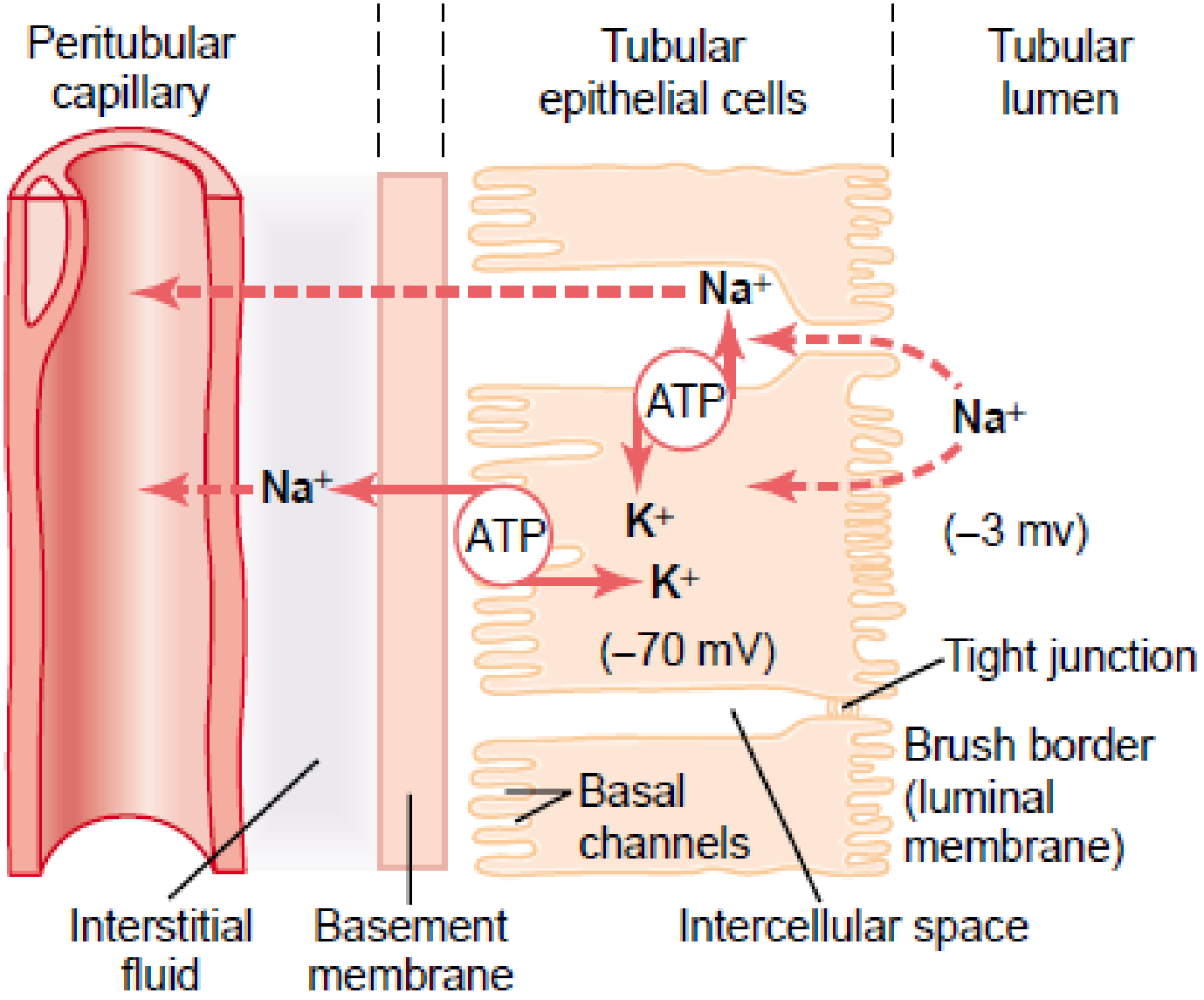
It should also be noted that the tubular epithelium, like that of the small intestine and gallbladder, is a **leaky epithelium** in that the tight junctions between cells permit the passage of some water and electrolytes. The degree to which leakage by this **paracellular pathway** contributes to the net flux of fluid and solute into and out of the tubules is controversial since it is difficult to measure, but current evidence seems to suggest that it is a significant factor.

One indication of this is that paracellin-1, a protein localized to tight junctions, is related to Mg^{2+} reabsorption, and a loss-of-function mutation of its gene causes severe Mg^{2+} and Ca^{2+} loss in the urine..

Na^+ Reabsorption

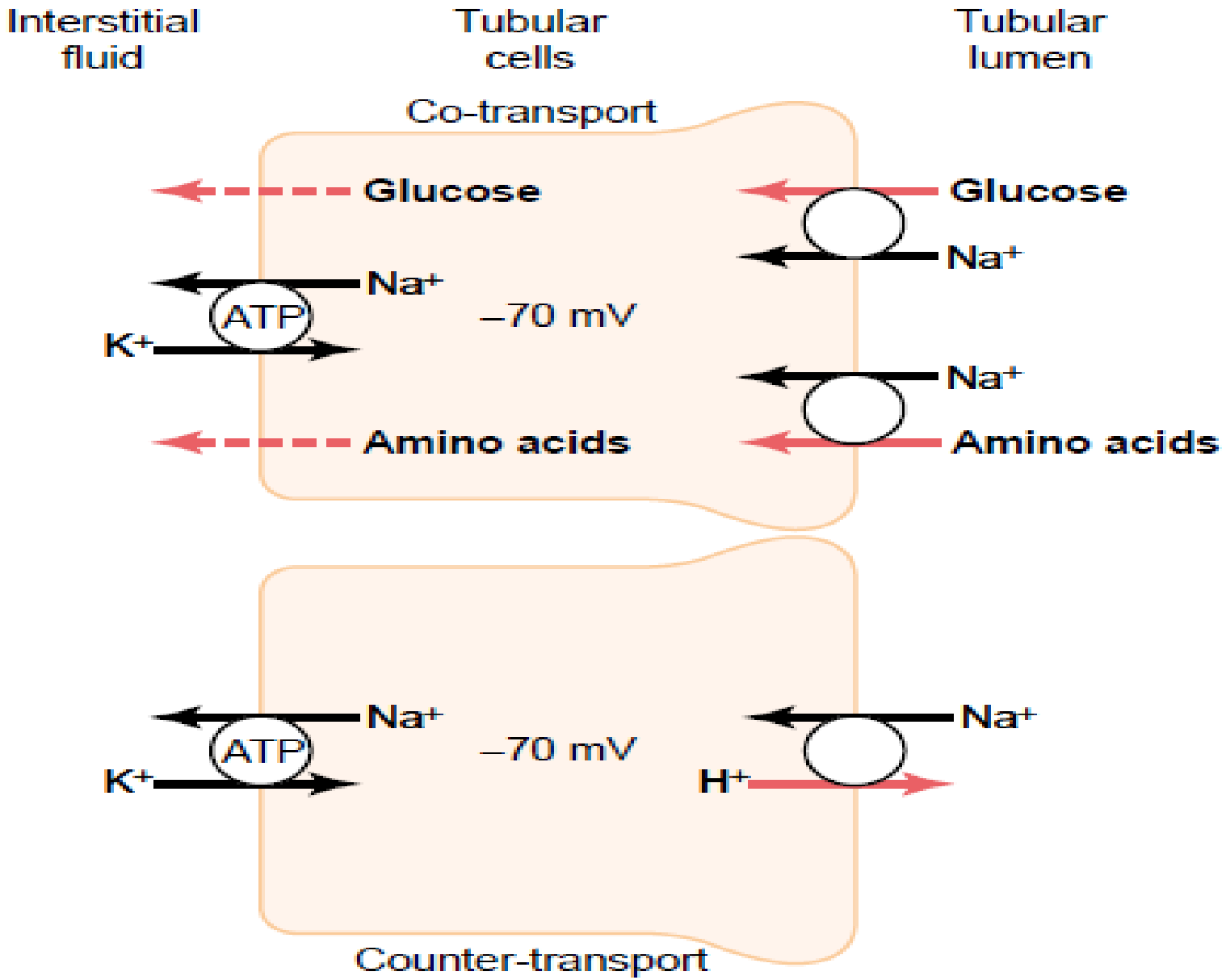
In the proximal tubules, the thick portion of the ascending limb of the loop of Henle, the distal tubules, and the collecting ducts, Na^+ moves by co transport or exchange from the tubular lumen into the tubular epithelial cells down its concentration and electrical gradients and is actively pumped from these cells into the interstitial space. Thus, Na^+ is actively transported out of all parts of the renal tubule except the thin portions of the loop of Henle.

Na^+ is pumped into the interstitium by Na^+–K^+ ATPase.. It extrudes three Na^+ in exchange for two K^+ that are pumped into the cell.


Peritubular capillary
Tubular epithelial cells
Tubular lumen
Na+
ATP
Na+
Na+
ATP
K+
(–3 mv)
K+
(–70 mV)
Tight junction
Brush border (luminal membrane)
Basal channels
Interstitial fluid
Basement membrane
Intercellular space

. Much of the Na^+ is actively transported into the extensions of the interstitial space, the **lateral intercellular spaces** .

Proximal tubular reabsorbate is slightly hypertonic, and water moves passively along the osmotic gradient created by its absorption into tubular epithelial cells.


Interstitial fluid
Tubular cells
Tubular lumen
Co-transport
Glucose
Glucose
Na+
Na+
ATP
K+
−70 mV
Na+
Amino acids
Amino acids
Na+
ATP
K+
−70 mV
Na+
H+
Counter-transport

The rate at which solutes and water move into the capillaries from the lateral intercellular spaces and the rest of the interstitium is determined by the Starling forces determining movement across the walls of all capillaries, **ie, the hydrostatic and osmotic pressures in the interstitium and the capillaries** .

Na^+ and H_2O leak back to the tubular lumen via the intercellular junctions, especially when the lateral intercellular spaces are distended.

Reabsorption of Chloride, Urea, and Other Solutes by Passive Diffusion

When sodium is reabsorbed through the tubular epithelial cell, negative ions such as chloride are transported along with sodium because of electrical potentials.

That is, transport of positively charged sodium ions out of the lumen leaves the inside of the lumen negatively charged, compared with the interstitial fluid. This causes chloride ions to diffuse *passively* through the *paracellular pathway*. Additional reabsorption of chloride ions occurs because of a chloride concentration gradient that develops when water is reabsorbed from the tubule by osmosis, thereby concentrating the chloride ions in the tubular lumen

Thus, the active reabsorption of sodium is closely coupled to the passive reabsorption of chloride by way of an electrical potential and a chloride concentration gradient.

Chloride ions can also be reabsorbed by secondary active transport.The most important of the secondary active transport processes for chloride reabsorption involves co-transport of chloride with sodium across the luminal membrane.

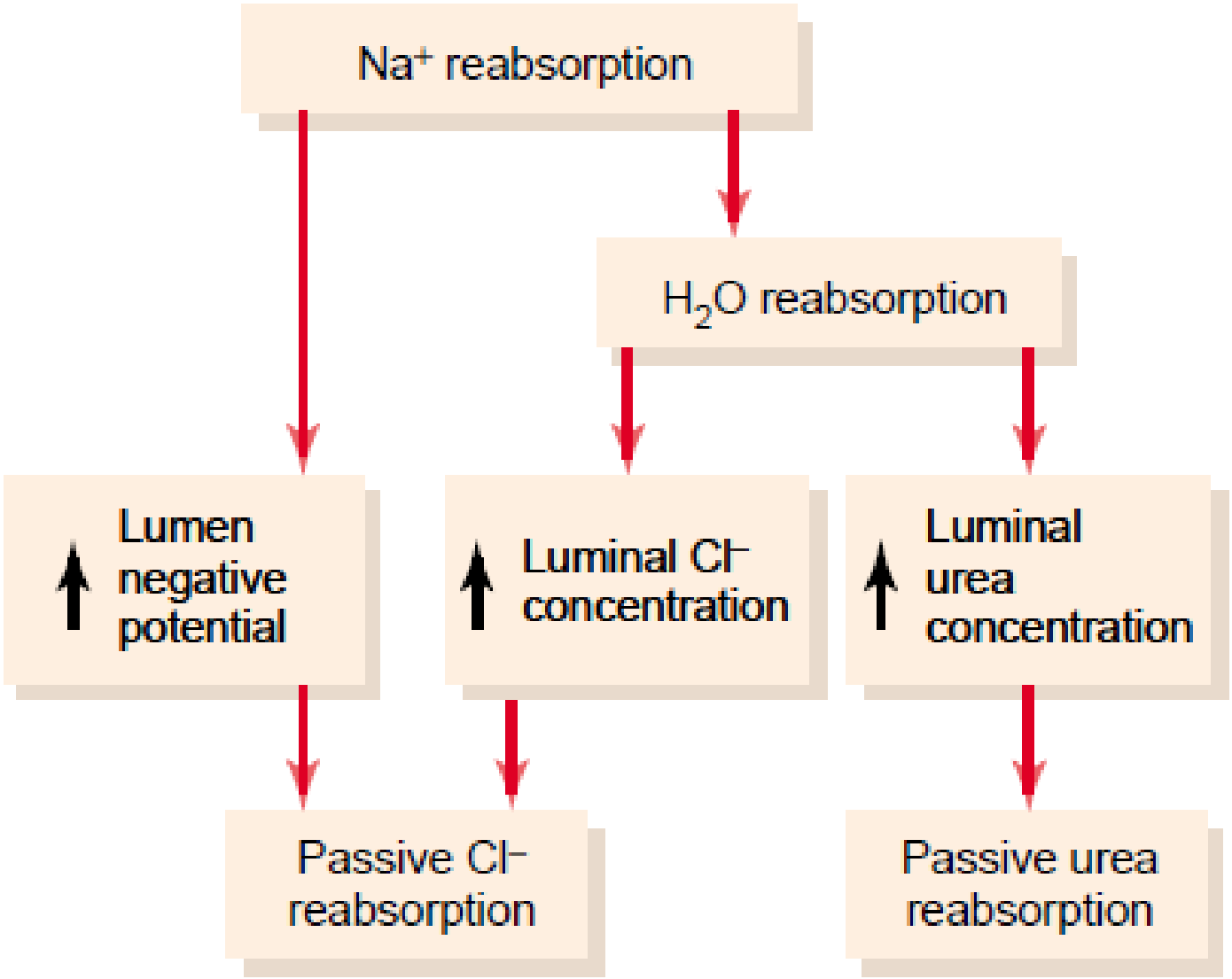
Some Cl^- is reabsorbed with Na^+ and K^+ in the thick ascending limb of the loop of Henle . In addition, two members of a family of Cl^- channels have been identified in the kidney. The family is characterized by 12 transmembrane domains, and members of it are also found in muscle and other tissues.

Mutations in the gene for one of the renal channels is associated with Ca^{2+}–containing kidney stones and hypercalciuria (Dent's disease), but how tubular transport of Ca^{2+} and Cl^- are linked is still unsettled.

Urea is also passively reabsorbed from the tubule, but to a much lesser extent than chloride ions. As water is reabsorbed from the tubules (by osmosis coupled to sodium reabsorption), urea concentration in the tubular lumen increases . This creates a concentration gradient favoring the reabsorption of urea. However, urea does not permeate the tubule as readily as water. In some parts of the nephron, especially the inner medullary collecting duct, passive urea reabsorption is facilitated by specific *urea transporters*.

Yet only about one half of the urea that is filtered by the glomerular capillaries is reabsorbed from the tubules. The remainder of the urea passes into the urine, allowing the kidneys to excrete large amounts of this waste product of metabolism.

Another waste product of metabolism, creatinine, is an even larger molecule than urea and is essentially impermeant to the tubular membrane. Therefore, almost none of the creatinine that is filtered is reabsorbed, so that virtually all the creatinine filtered by the glomerulus is excreted in the urine.


Na+ reabsorption
H2O reabsorption
↑ Lumen negative potential
↑ Luminal Cl− concentration
↑ Luminal urea concentration
Passive Cl− reabsorption
Passive urea reabsorption

Glucose Reabsorption

Glucose, amino acids, and bicarbonate are reabsorbed along with Na^+ in the early portion of the proximal tubule . Farther along the tubule, Na^+ is reabsorbed with Cl^-. Glucose is typical of substances removed from the urine by secondary active transport. It is filtered at a rate of approximately 100 mg/min (80 mg/dL of plasma $\times$ 125 mL/min). Essentially all of the glucose is reabsorbed, and no more than a few milligrams appear in the urine per 24 hours. The amount reabsorbed is proportionate to the amount filtered and hence to the plasma glucose level (P_G) times the GFR up to the transport maximum (Tm_G); but when the Tm_G is exceeded, the amount of glucose in the urine rises . The Tm_G is about 375 mg/min in men and 300 mg/min in women.

The **renal threshold** for glucose is the plasma level at which the glucose first appears in the urine in more than the normal minute amounts. One would predict that the renal threshold would be about 300 mg/dL—ie, 375 mg/min (Tm_G) divided by 125 mL/min (GFR). However, the actual renal threshold is about 200 mg/dL of arterial plasma, which corresponds to a venous level of about 180 mg/dL..

Additional Examples of Secondary Active Transport

A variety of other substances are transported by secondary active transport via symports, with the energy provided by active transport of Na^+ out of the renal tubular cells. These substances include some amino acids, lactate, inorganic phosphate (Pi), H^+, and Cl^-.

Like glucose reabsorption, amino acid reabsorption is most marked in the early portion of the proximal convoluted tubule. Absorption in this location resembles absorption in the intestine . The main carriers in the luminal membrane cotransport Na^+, whereas the carriers in the basolateral membranes are not Na^+-dependent. Na^+ is pumped out of the cells by Na^+-K^+ ATPase and the amino acids leave by passive or facilitated diffusion to the interstitial fluid.

Other Substances Secreted by the Tubules

Derivatives of hippuric acid in addition to PAH, phenol red and other sulfonphthalein dyes, penicillin, and a variety of iodinated dyes are actively secreted into the tubular fluid. Substances that are normally produced in the body and secreted by the tubules include various ethereal sulfates, steroid and other glucuronides, and 5-hydroxyindoleacetic acid, the principal metabolite of serotonin .

Tubuloglomerular Feedback & Glomerulotubular Balance

Signals from the renal tubules feed back to affect glomerular filtration. As the rate of flow through the ascending limb of the loop of Henle and first part of the distal tubule increases, glomerular filtration in the same nephron decreases, and, conversely, a decrease in flow increases the GFR . This process, which is called **tubuloglomerular feedback,** tends to maintain the constancy of the load delivered to the distal tubule. The sensor for the response appears to be the macula densa, and GFR is adjusted by constriction or dilation of the afferent arteriole. Constriction may be mediated by thromboxane A_2.

Conversely, an increase in GFR causes an increase in the reabsorption of solutes, and consequently of water, primarily in the proximal tubule, so that in general the percentage of the solute reabsorbed is held constant. This process is called **glomerulotubular balance,** and it is particularly prominent for Na^+. The change in Na^+ reabsorption occurs within seconds after a change in filtration, so it seems unlikely that an extrarenal humoral factor is involved. One factor is the oncotic pressure in the peritubular capillaries. When the GFR is high, there is a relatively large increase in the oncotic pressure of the plasma by the time it reaches the efferent arterioles and their capillary branches. This increases the reabsorption of Na^+ from the tubule.

WATER EXCRETION

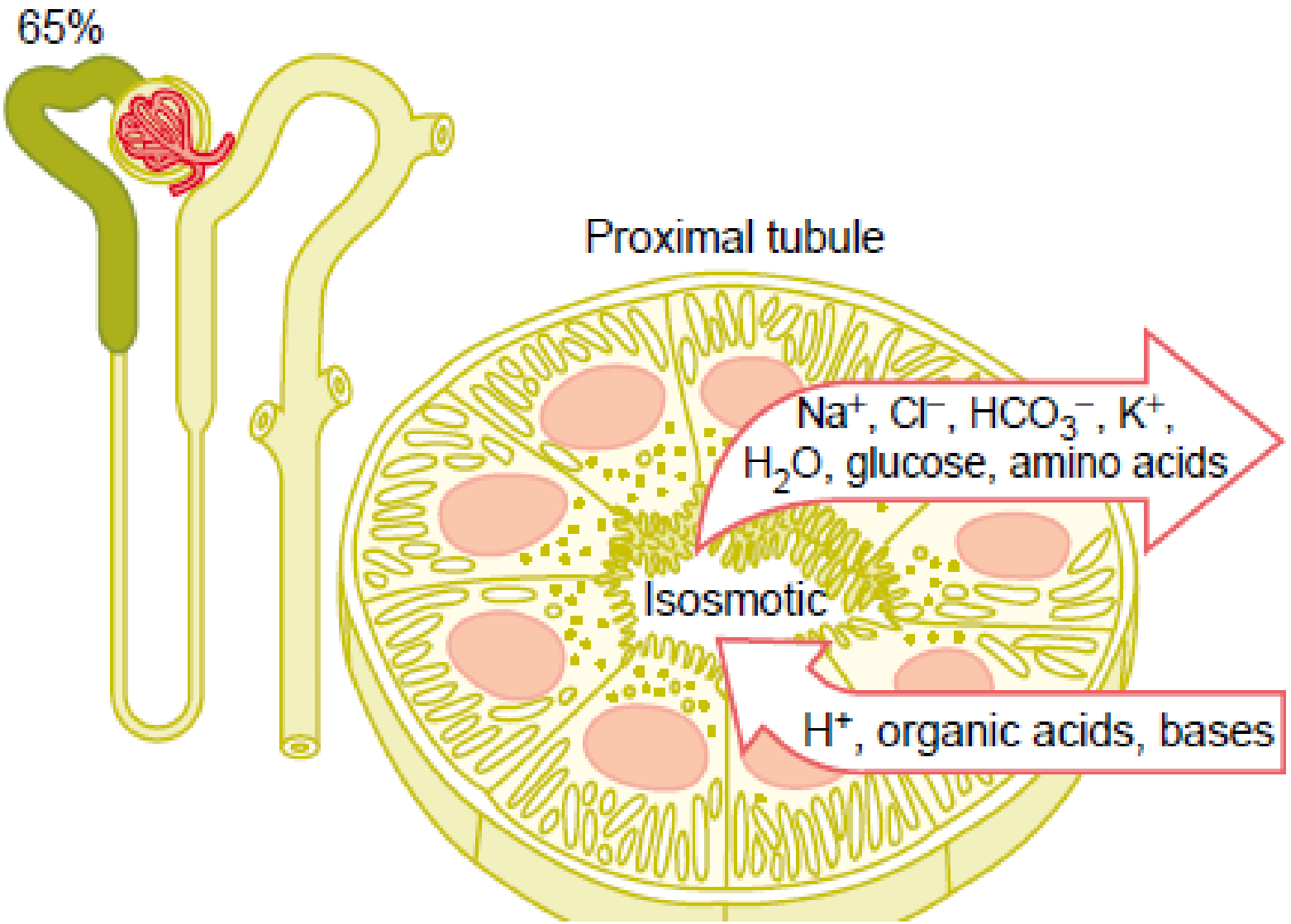
Normally, 180 L of fluid is filtered through the glomeruli each day, while the average daily urine volume is about 1 L.These figures demonstrate two important facts: first, that at least 87% of the filtered water is reabsorbed, even when the urine volume is 23 L; and second, that the reabsorption of the remainder of the filtered water can be varied without affecting total solute excretion. Therefore, when the urine is concentrated, water is retained in excess of solute; and when it is dilute, water is lost from the body in excess of solute. Both facts have great importance in the body economy and the regulation of the osmolality of the body fluids. A key regulator of water output is vasopressin acting on the collecting ducts.

Aquaporins

Research on mice, rats, and humans indicates that rapid diffusion of water across cell membranes depends on water channels made up of proteins called **aquaporins.** Four aquaporins—aquaporin-1, aquaporin-2, aquaporin-5, and aquaporin-9—have been characterized in humans, and additional aquaporins have been identified in rats. Most are found in the kidneys, though aquaporin-9 is found in human leukocytes, liver, lung, and spleen; and aquaporin-5 is found in human lacrimal glands. The key roles played by aquaporin-1 and aquaporin-2 in water excretion are discussed below.

Proximal Tubule

Many substances are actively transported out of the fluid in the proximal tubule, but fluid obtained by micropuncture remains essentially isosmotic to the end of the proximal tubule . Therefore, in the proximal tubule, water moves passively out of the tubule along the osmotic gradients set up by active transport of solutes, and isotonicity is maintained. Since the ratio of the concentration in tubular fluid to the concentration in plasma (TF/P) of the nonreabsorbable substance inulin is 2.5–3.3 at the end of the proximal tubule, it follows that 60–70% of the filtered solute and 60–70% of the filtered water have been removed by the time the filtrate reaches this point .


65%
Proximal tubule
Na^+, Cl^-, HCO_3^-, K^+,
H_2O, glucose, amino acids
Isosmotic
H^+, organic acids, bases

Aquaporin-1 is localized in the proximal tubules. When it is knocked out in mice, proximal tubular water permeability is reduced 80%, and their plasma osmolality increases to 500 mosm/kg when the mice are subjected to dehydration even though their other aquaporins are intact. In humans with mutations that eliminate aquaporin-1 activity, the defect in water metabolism is not as severe, though their response to dehydration is defective.

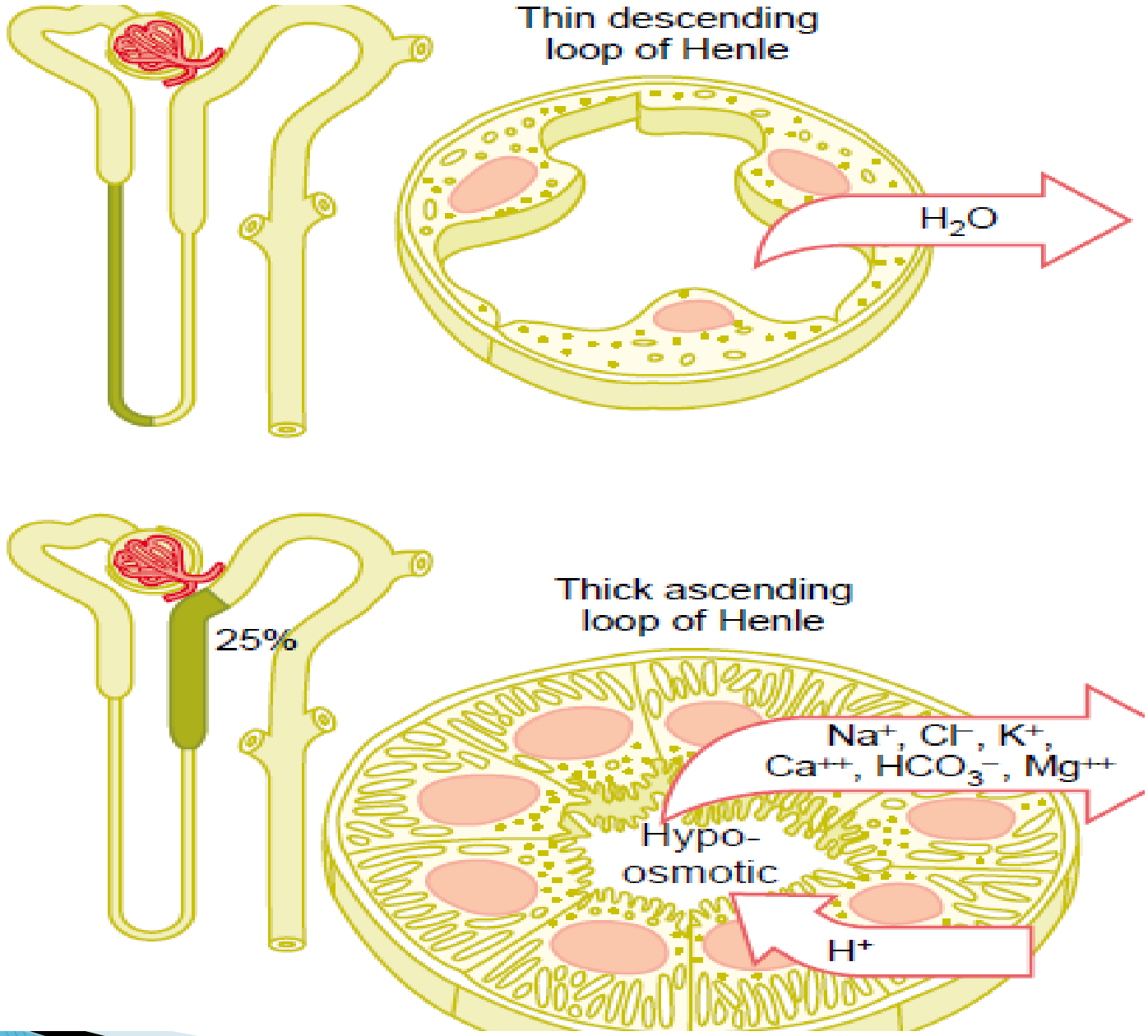
Loop of Henle

As noted above, the loops of Henle of the juxta-medullary nephrons dip deeply into the medullary pyramids before draining into the distal convoluted tubules in the cortex, and all of the collecting ducts descend back through the medullary pyramids to drain at the tips of the pyramids into the renal pelvis. There is a graded increase in the osmolality of the interstitium of the pyramids, the osmolality at the tips of the papillae normally being about 1200 mosm/kg of H_2O, approximately four times that of plasma. **The descending limb of the loop of Henle is permeable to water, but the ascending limb is impermeable**

. Na^+, K^+, and Cl^- are cotransported out of the thick segment of the ascending limb . Therefore, the fluid in the descending limb of the loop of Henle becomes hypertonic as water moves into the hypertonic interstitium. In the ascending limb it becomes more dilute, and when it reaches the top it is hypotonic to plasma because of the movement of Na^+ and Cl^- out of the tubular lumen. In passing through the loop of Henle, another 15% of the filtered water is removed, so approximately 20% of the filtered water enters the distal tubule, and the TF/P of inulin at this point is about 5.

In the thick ascending limb, a carrier cotransports one Na^+, one K^+, and 2 Cl^- from the tubular lumen into the tubular cells. This is another example of secondary active transport; the Na^+ is actively transported from the cells into the interstitium by Na^+–K^+ ATPase in the basolateral membranes of the cells, keeping the intracellular Na^+ low.

The K^+ diffuses back into the tubular lumen and back into the interstitium via ROMK and other K^+ channels. The Cl^- diffuses into the interstitium via ClC-Kb channels . This K^+ recycles across the luminal and the basolateral membrane, while there is no transport of Na^+ and Cl^- into the interstitium.


Thin descending
loop of Henle
H_2O
25%
Thick ascending
loop of Henle
Na^+, Cl^-, K^+,
Ca^{++}, HCO_3^-, Mg^{++}
Hypo-
osmotic
H^+

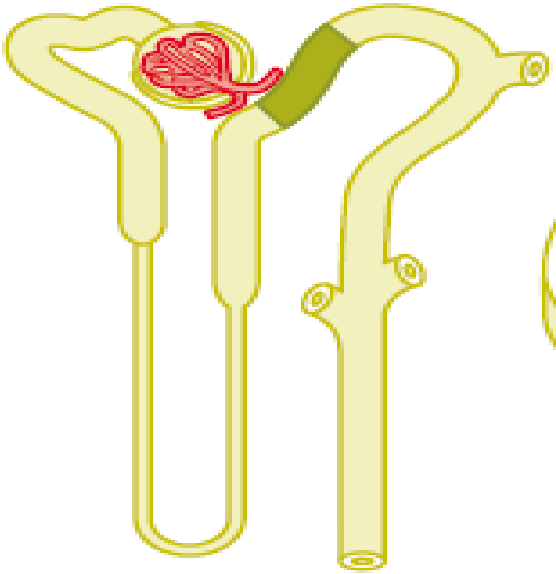
Bartter's Syndrome

Bartter's syndrome is a rare but interesting condition that is due to defective transport in the thick ascending limb. It is characterized by chronic Na^+ loss in the urine, with resultant hypovolemia causing stimulation of renin and aldosterone secretion without hypertension, plus hyperkalemia and alkalosis. The condition can be caused by loss-of-function mutations in the gene for any of four key proteins: the Na^+-K^+-$2Cl^-$ cotransporter, the ROMK K^+ channel, the ClC-Kb Cl^- channel, or **barttin,** a recently described integral membrane protein that is necessary for the normal function of ClC-Kb Cl^- channels.

The stria vascularis in the inner ear is responsible for maintaining the high K^+ concentration in the scala media that is essential for normal hearing . It contains both ClC-Kb and ClC-Ka Cl^- channels. Bartter's syndrome associated with mutated ClC Kb channels is not associated with deafness because the Clc-Ka channels can carry the load. However, both types of Cl^- channels are barttin-dependent, so patients with Bartter's syndrome due to mutated barttin are also deaf.

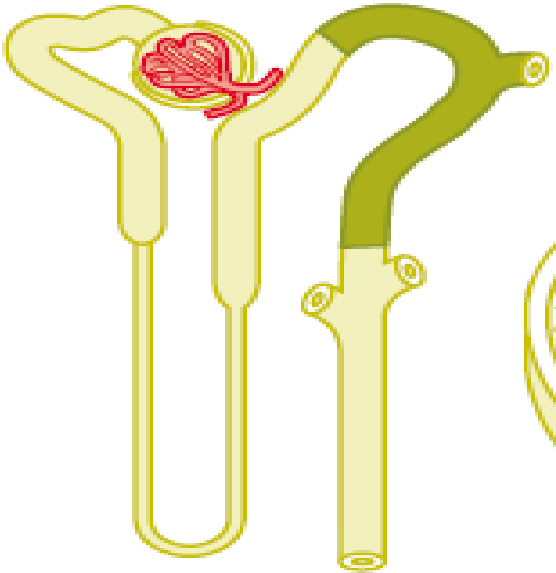
Distal Tubule

The distal tubule, particularly its first part, is in effect an extension of the thick segment of the ascending limb. It is relatively impermeable to water, and continued removal of the solute in excess of solvent further dilutes the tubular fluid. About 5% of the filtered water is removed in this segment.



Early distal tubule

Na^+, Cl^-, Ca^{++}, Mg^{++}



Late distal tubule and collecting tubule

Principal cells

Na^+, Cl^-

K^+

(+ADH) H_2O

H^+

Intercalated cells

K^+

HCO_3^-

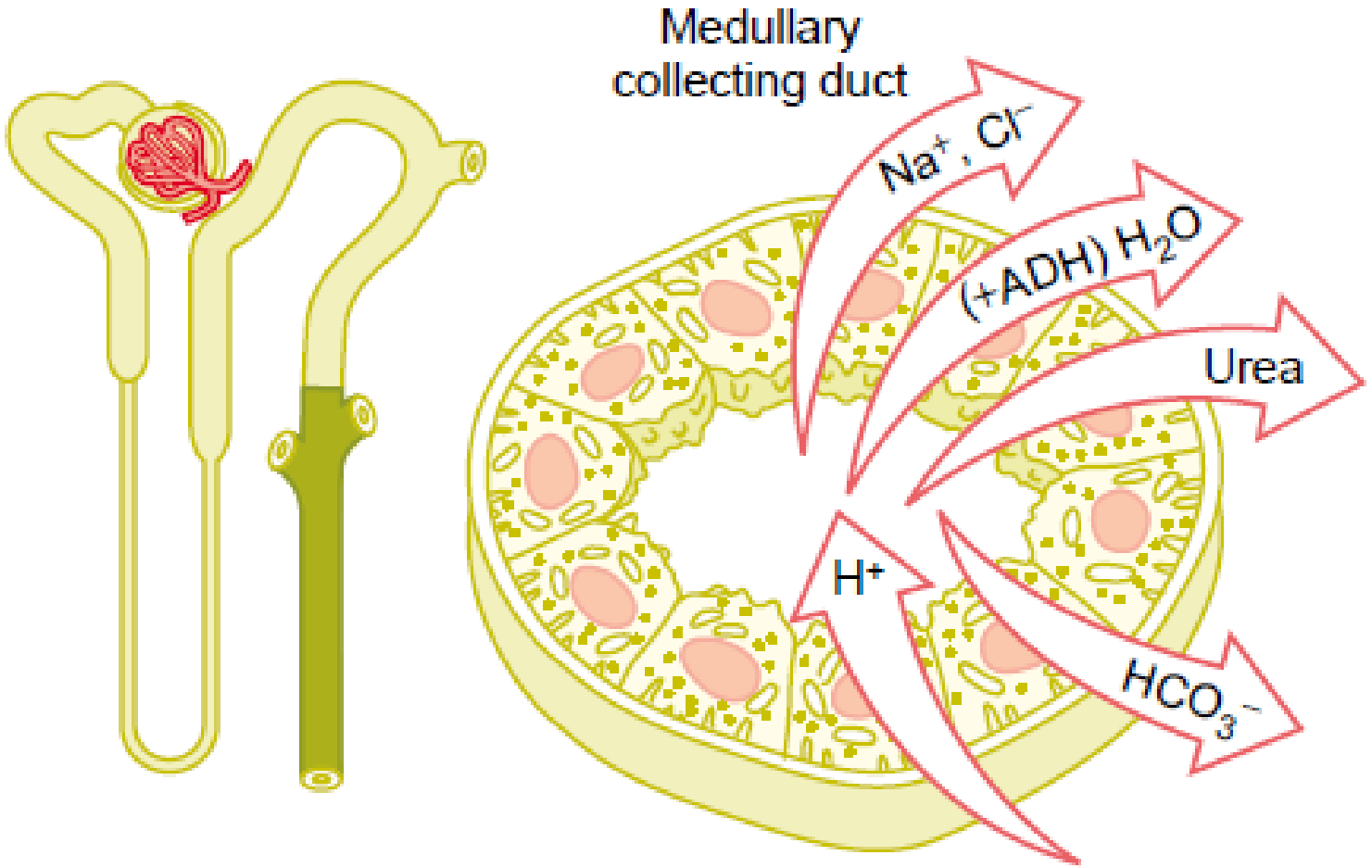
Collecting Ducts

The collecting ducts have two portions: a cortical portion and a medullary portion. The changes in osmolality and volume in the collecting ducts depend on the amount of vasopressin acting on the ducts. This antidiuretic hormone from the posterior pituitary gland increases the permeability of the collecting ducts to water. The key to the action of vasopressin on the collecting ducts is aquaporin-2.

Unlike the other aquaporins, this aquaporin is stored in vesicles in the cytoplasm of principal cells. Vasopressin causes rapid insertion of these vesicles into the apical membrane of cells. The effect is mediated via the vasopressin V_2 receptor, cyclic AMP, protein kinase A, and a molecular motor, one of the dyneins .

In the presence of enough vasopressin to produce maximal antidiuresis, water moves out of the hypotonic fluid entering the cortical collecting ducts into the interstitium of the cortex, and the tubular fluid becomes isotonic. In this fashion, as much as 10% of the filtered water is removed. The isotonic fluid then enters the medullary collecting ducts.

An additional 4.7% or more of the filtrate is reabsorbed into the hypertonic interstitium of the medulla, producing a concentrated urine . In humans, the osmolality of urine may reach 1400 mosm/kg of H_2O, almost five times the osmolality of plasma, with a total of 99.7% of the filtered water being reabsorbed. In other species, the ability to concentrate urine is even greater.


Medullary
collecting duct
Na^+, Cl^-
(+ADH) H_2O
Urea
H^+
HCO_3^-

The causes of diabetes insipidus, the condition caused by vasopressin deficiency or failure to respond to the hormone. In nephrogenic diabetes insipidus, the collecting ducts fail to respond to vasopressin. Two forms of this disease have been described. In one, the gene for the V_2 receptor is mutated, making the receptor unresponsive. The V_2 receptor gene is on the X chromosome, and the mode of inheritance is sex-linked recessive. In the other form, the autosomal gene for aquaporin-2 is mutated.

Countercurrent multiplier mechanism

- The countercurrent multiplier mechanism is responsible for producing a high osmolality in the extratubular interstitial tissue of the renal medulla.
- Water passes freely from the tubular lumen into the adjacent medullary interstitium along the descending limb of the loop of Henle. This part of the tubule is less permeable to solutes.
- In the thick segment of the ascending limb, sodium and chloride ions are actively transported from the tubule lumen to interstitial spaces, whilst the tubular epithelium remains impermeable to water.

- The increased interstitial osmolality causes water to be withdrawn from the descending part of the loop, thus concentrating the filtrate. Tubular fluid flows in a countercurrent on its descent into and ascent out of the medulla: it is augmented by new isotonic fluid entering the loop and depleted by hypotonic fluid leaving the loop, as solutes are actively resorbed.

- In this way the osmotic gradient within the interstitium is multiplied from the corticomedullary boundary to the medullary pyramids, where it reaches an equilibrium of four to five times the osmolality of plasma.

- Urea contributes 50% of the medullary osmotic strength, mainly contributed passively by the medullary part of the collecting ducts.

These are generally highly permeable to urea , and permeability is enhanced by antidiuretic hormone (ADH, vasopressin).

Although the tonicity of the tubular fluid changes during its passage through the steep osmotic gradient within the medulla, the osmotic gradient between ascending and descending limbs at each level never exceeds 200 mOsm/kg, a force which can be sustained by the cells of the tubular wall.

Countercurrent exchange mechanism

- Rapid removal of ions from the renal medulla by the circulation of blood is minimized by another looped countercurrent system. This is the countercurrent exchange mechanism, in which arterioles entering the medulla pass for long distances parallel to the venules leaving it, before ending in capillary beds around tubules.
- This close apposition of oppositely flowing blood allows the direct diffusion of ions from outflowing to inflowing blood, so that the vasa recta conserve the high osmotic pressure in the medulla.

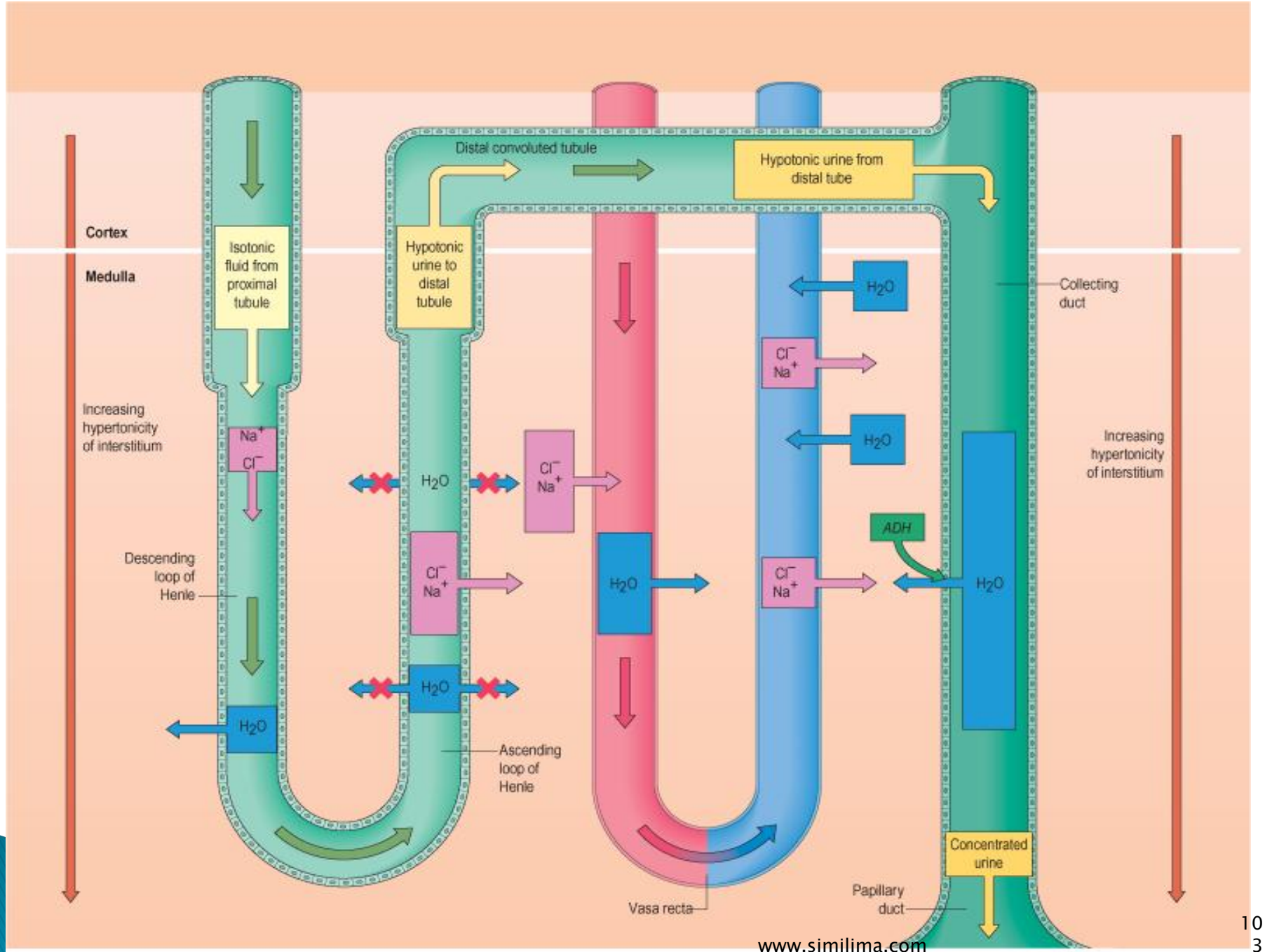
Concentration of urine

- Because sodium and chloride ions are selectively resorbed by the cells of the ascending limbs and distal tubules under aldosterone control, the filtrate at the distal end of the convoluted tubules is hypotonic.
- As it reaches the collecting ducts, fluid descends again through the medulla and thus re-enters a region of high osmotic pressure. The cells lining the collecting ducts are variably permeable to water, under the influence of neurohypophyseal ADH.

- Water follows an osmotic gradient into the adjacent extratubular spaces, so that the tonicity of the filtrate gradually rises along collecting ducts, until at the tip of the renal pyramids it is above that of blood. As much as 95% of water in the original glomerular filtrate is thus resorbed into blood.

- This complex system is highly flexible and the balance between the rate of filtration and absorption can be varied to meet current physiological demands.

- Control of hydrogen and ammonium ion concentrations is essential to the regulation of acids and bases in the blood; secretion of various ions occurs at several sites.
- Over 91% of ingested potassium is excreted in urine, largely through secretion by cells of the distal tubule and collecting duct.



ACIDIFICATION OF THE URINE & BICARBONATE EXCRETION

H^+ Secretion

The cells of the proximal and distal tubules, like the cells of the gastric glands, secrete hydrogen ions . Acidification also occurs in the collecting ducts. The reaction that is primarily responsible for H^+ secretion in the proximal tubules is Na^+-H^+ exchange. This is an example of secondary active transport; extrusion of Na^+ from the cells into the interstitium by Na^+-K^+ ATPase lowers intracellular Na^+, and this causes Na^+ to enter the cell from the tubular lumen, with coupled extrusion of H^+. The H^+ comes from intracellular dissociation of H_2CO_3, and the HCO_3^- that is formed diffuses into the interstitial fluid. Thus, for each H^+ ion secreted, one Na^+ ion and one HCO_3^- ion enter the interstitial fluid.

Fate of H^+ in the Urine.

However, three important reactions in the tubular fluid remove free H^+, permitting more acid to be secreted . These are the reactions with HCO_3^- to form CO_2 and H_2O, with HPO_4^{2-} to form $H_2PO_4^-$, and with NH_3 to form NH_4^+.

pH Changes Along the Nephrons

There is a moderate drop in pH in the proximal tubular fluid, but, as noted above, most of the secreted H^+ has little effect on luminal pH because of the formation of CO_2 and H_2O from H_2CO_3. In contrast, the distal tubule has less capacity to secrete H^+, but secretion in this segment has a greater effect on urinary pH.

Aldosterone Increases Sodium Reabsorption and Increases Potassium Secretion.

Aldosterone, secreted by the zona glomerulosa cells of the adrenal cortex, is an important regulator of sodium reabsorption and potassium secretion by the renal tubules. ***The primary site of aldosterone action is on the principal cells of the cortical collecting tubule*.** The mechanism by which aldosterone increases sodium reabsorption while at the same time increasing potassium secretion is by stimulating the sodium-potassium ATPase pump on the basolateral side of the cortical collecting tubule membrane. Aldosterone also increases the sodium permeability of the luminal side of the membrane.

In Liddle's syndrome, mutations in the genes that code for the β subunit and less commonly the γ subunit of the ENaCs cause them to become constitutively active in the kidney. This leads to Na^+ retention and hypertension.

In the absence of aldosterone, as occurs with adrenal destruction or malfunction **(*Addison's disease*),** there is marked loss of sodium from the body and accumulation of potassium. Conversely, excess aldosterone secretion, as occurs in patients with adrenal tumors **(*Conn's syndrome*)** is associated with sodium retention and potassium depletion., aldosterone is even more important as a regulator of potassium concentration than it is for sodium concentration.

Angiotensin II Increases Sodium and Water Reabsorption

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Angiotensin II is perhaps the body's most powerful sodium-retaining hormone.

The increased formation of angiotensin II helps to return blood pressure and extracellular volume toward normal by increasing sodium and water reabsorption from the renal tubules through three main effects:

1Angiotensin II stimulates aldosterone secretion, which in turn increases sodium reabsorption.

2. *Angiotensin II constricts the efferent arterioles*, which has two effects on peritubular capillary dynamics that raise sodium and water

3. *Angiotensin II directly stimulates sodium reabsorption in the proximal tubules*, *the loops of Henle*, *the distal tubules*, *and the collecting tubules*.

Hormones That Regulate Tubular Reabsorption

Aldosterone

Collecting tubule and duct
NaCl, H2O reabsorption, K+ secretion

Angiotensin II

Proximal tubule, thick ascending loop of Henle/distal tubule, collecting tubule
NaCl, H2O reabsorption, H+ secretion

Antidiuretic hormone

Distal tubule/collecting tubule and duct
H2Oreabsorption

Atrial natriuretic peptide

Distal tubule/collecting tubule and duct
NaCl reabsorption

Parathyroid hormone

Proximal tubule, thick ascending loop of henlee/distal
PO4 reabsorption, Ca++ reabsorption

REGULATION OF K^+ EXCRETION

Much of the filtered K^+ is removed from the tubular fluid by active reabsorption in the proximal tubules , and K^+ is then secreted into the fluid by the distal tubular cells. The rate of K^+ secretion is proportionate to the rate of flow of the tubular fluid through the distal portions of the nephron, because with rapid flow there is less opportunity for the tubular K^+ concentration to rise to a value that stops further secretion. In the distal tubules, Na^+ is generally reabsorbed and K^+ is secreted. There is no rigid one-for-one exchange, and much of the movement of K^+ is passive.. Since Na^+ is also reabsorbed in association with H^+ secretion, there is competition for the Na^+ in the tubular fluid. K^+ excretion is decreased when the amount of Na^+ reaching the distal tubule is small, and it is also decreased when H^+ secretion is increased. When total body K^+ is high, H^+ secretion is inhibited, apparently because of intracellular alkalosis; K^+ secretion and excretion are therefore facilitated. Conversely, the cells are acidic in K^+ depletion, and K^+ secretion declines.

Hypokalemia is common and can be severe. In addition to its occurrence when there is excessive loss in the urine, it is occasionally seen in patients with excess loss in diarrheic stools, in patients in whom K^+ is shifted into cells by insulin or β-adrenergic agonists, and in patients with a prolonged low intake of K^+. **Hyperkalemia** is a more dangerous condition because of its effects on the heart , but it rarely occurs unless renal function is depressed.

THANK U