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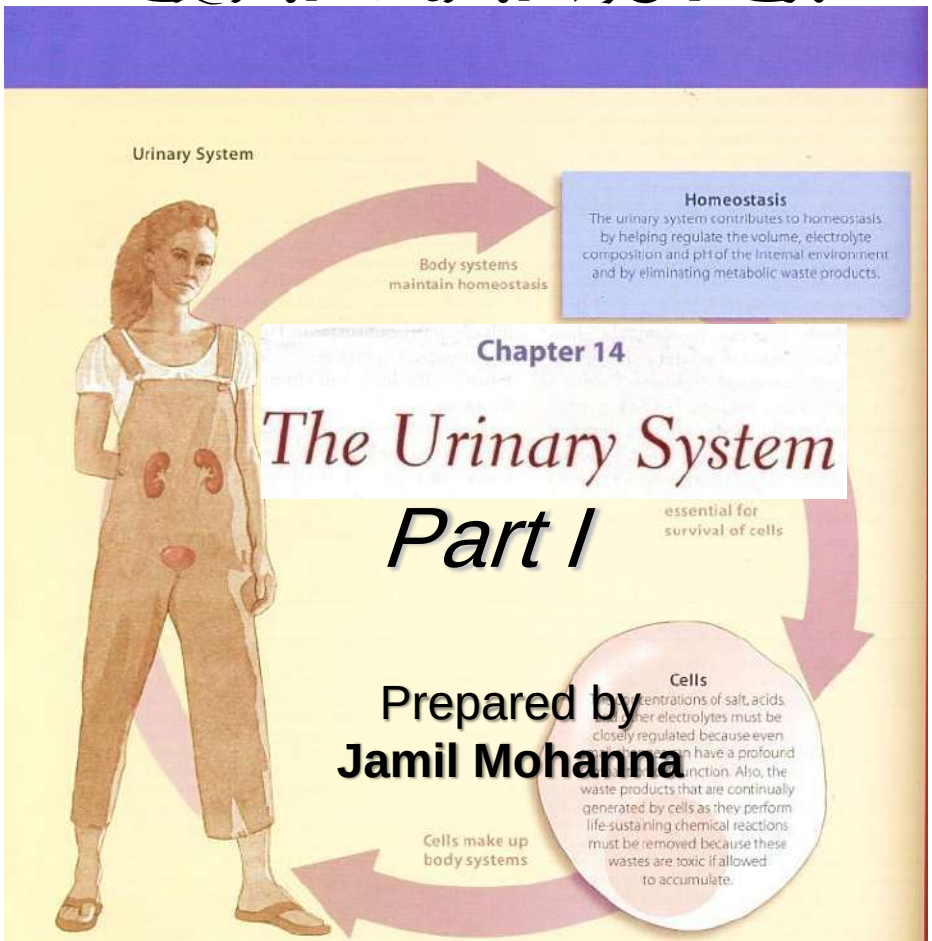


Chapter 14

The Urinary System

Part I

Prepared by

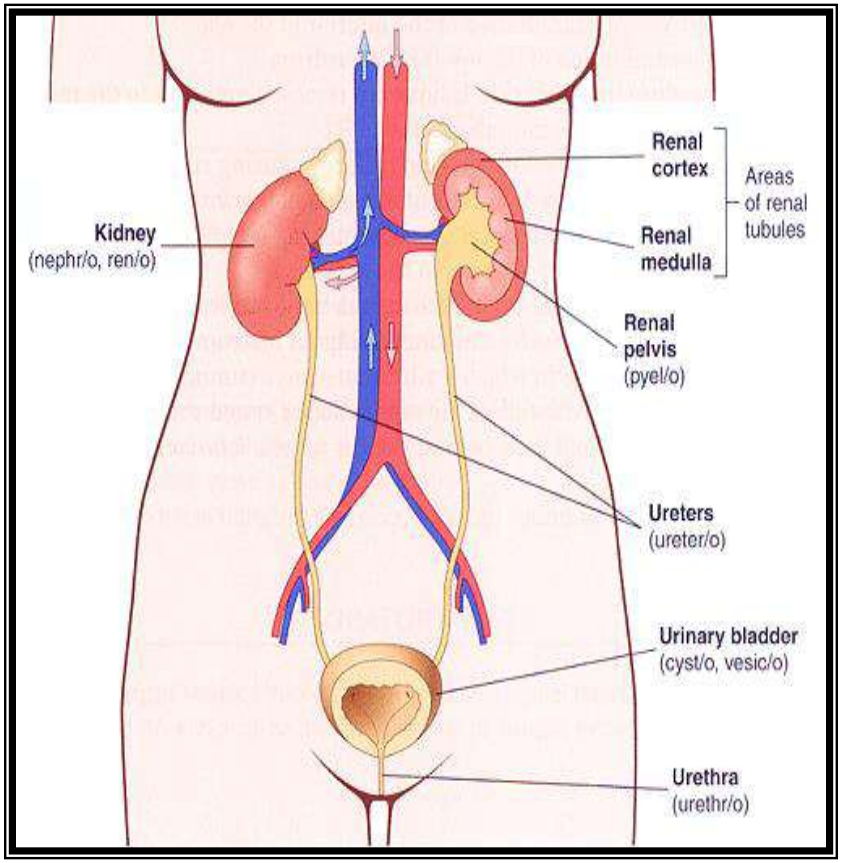
Jamil Mohanna

The survival and proper functioning of cells depend on the maintenance of stable concentrations of salt, acids, and other electrolytes in the internal fluid environment. Cell survival also depends on continual removal of the toxic metabolic wastes that cells produce as they perform life-sustaining chemical reactions. The kidneys play a major role in maintaining homeostasis by regulating the concentration of many plasma constituents, especially electrolytes and water, and by eliminating all metabolic wastes (except CO_2, which is removed by the lungs). As plasma repeatedly filters through the kidneys, they retain constituents of value for the body and eliminate undesirable or excess materials in urine. Of special importance is the kidneys' ability to regulate the volume and osmolarity (solute concentration) of the internal fluid environment by controlling salt and water balance. Also crucial is their ability to help regulate pH by controlling elimination of acid and base in urine.

Introduction

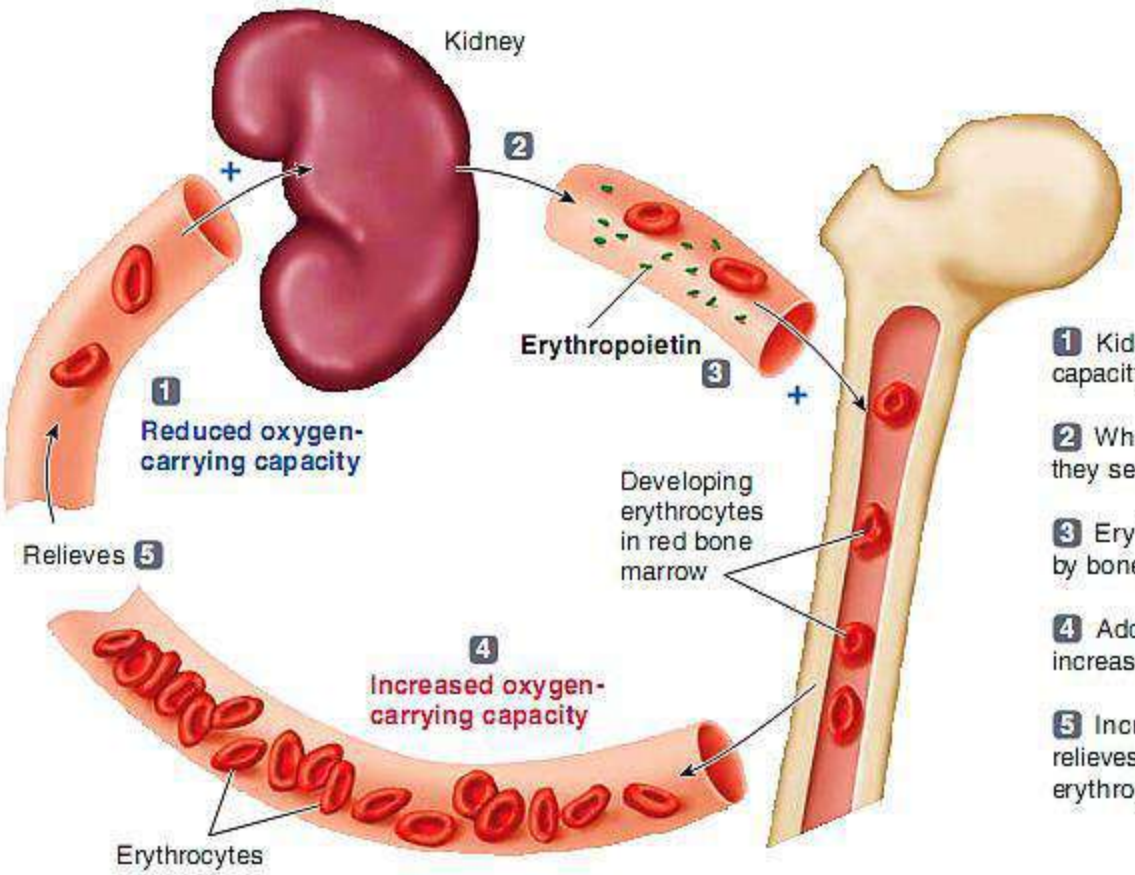
The kidneys perform a variety of functions aimed at maintaining homeostasis

- The kidneys are primarily responsible for maintaining the stability of ECF volume, electrolyte composition, and osmolarity.
- The kidneys not only adjust for wide variations in ingestion of H_2O, salt, and other electrolytes, but also adjust urinary output of these ECF constituents to compensate for abnormal losses through heavy sweating, vomiting, diarrhea, or hemorrhage. The kidneys can compensate more efficiently for excesses than for deficits.
- The kidneys are the primary route for eliminating potentially toxic metabolic wastes and foreign compounds from the body, they must excrete around 500 ml of waste-filled urine per day.



Overview of kidney functions

1. Maintaining H_2O balance in the body.
2. Maintaining the proper osmolarity of body fluids.
3. Regulating the quantity and concentration of most ECF ions, even minor fluctuations e.g. changes in the ECF concentration of K^+ can potentially lead to fatal cardiac dysfunction.
4. Maintaining proper plasma volume.
5. Helping maintain the proper acid-base balance by adjusting urinary output of H^+ and HCO_3^- .
6. Excreting the end products such as urea, uric acid, and creatinine, these wastes are toxic especially to the brain.
7. Excreting drugs, food additives, pesticides, and other exogenous nonnutritive materials that have entered the body.
8. Producing erythropoietin.
9. Producing renin, an enzymatic hormone that triggers a chain reaction important in salt conservation by the kidneys.
10. Converting vitamin D into its active form.



1 Kidneys detect reduced O_2-carrying capacity of blood.

2 When less O_2 is delivered to the kidneys, they secrete erythropoietin into blood.

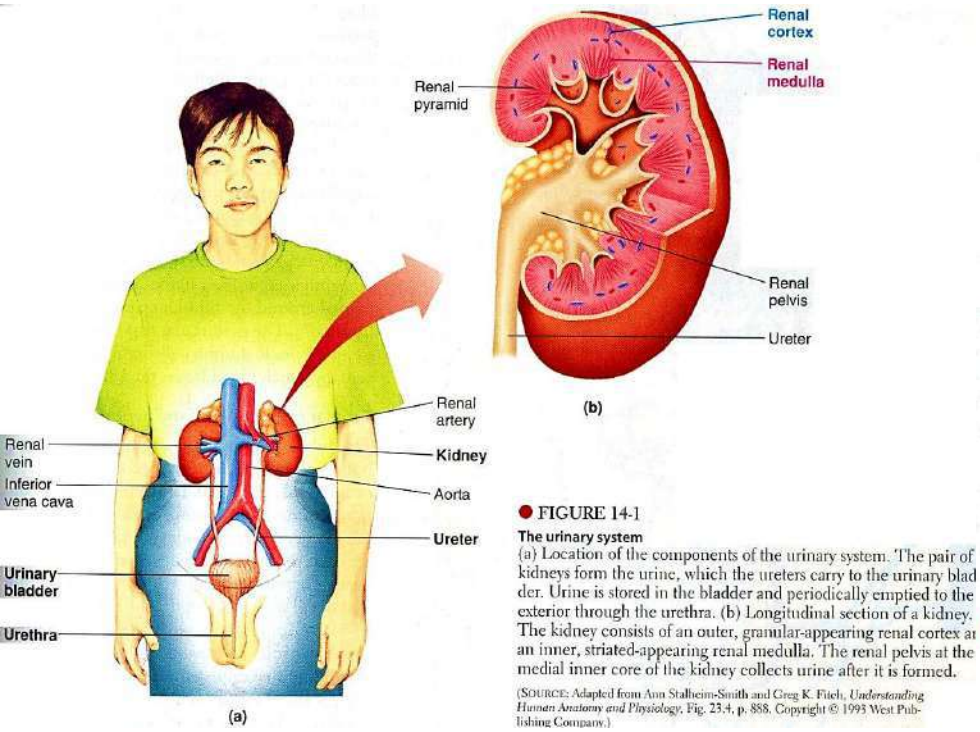
3 Erythropoietin stimulates erythropoiesis by bone marrow.

4 Additional circulating erythrocytes increase O_2-carrying capacity of blood.

5 Increased O_2-carrying capacity relieves initial stimulus that triggered erythropoietin secretion.

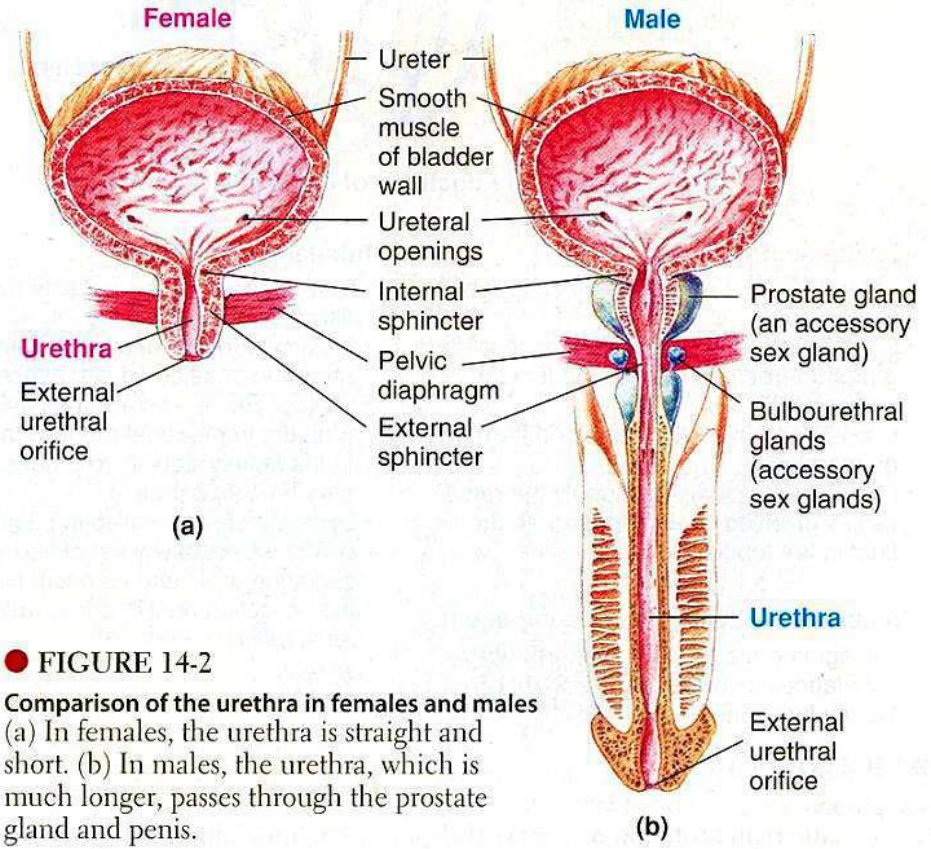
● **FIGURE 11-4 Control of erythropoiesis.**

The kidneys form the urine; the remainder of the urinary system carries the urine to the outside



● FIGURE 14-1
The urinary system
(a) Location of the components of the urinary system. The pair of kidneys form the urine, which the ureters carry to the urinary bladder. Urine is stored in the bladder and periodically emptied to the exterior through the urethra. (b) Longitudinal section of a kidney. The kidney consists of an outer, granular-appearing renal cortex and an inner, striated-appearing renal medulla. The renal pelvis at the medial inner core of the kidney collects urine after it is formed.

(SOURCE: Adapted from Ann Stalheim-Smith and Greg K. Fitch, *Understanding Human Anatomy and Physiology*, Fig. 23.4, p. 888. Copyright © 1993 West Publishing Company.)



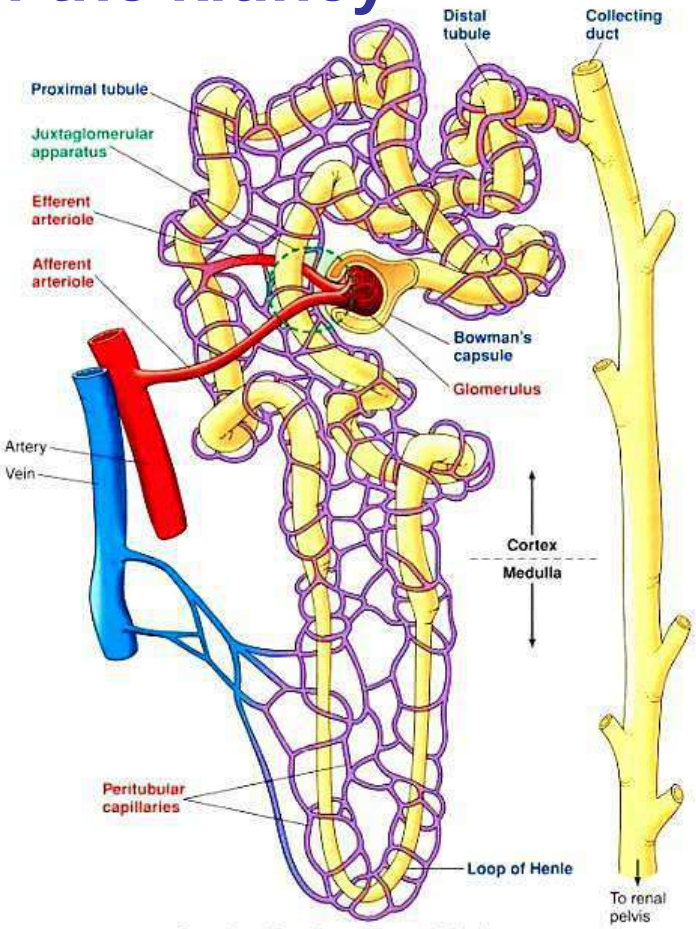
● FIGURE 14-2
Comparison of the urethra in females and males
(a) In females, the urethra is straight and short. (b) In males, the urethra, which is much longer, passes through the prostate gland and penis.

The nephron is the functional unit of the kidney

- Each kidney is composed of about 1 million microscopic functional units, **nephrons**, which are bound together by connective tissue.
- The arrangement of nephrons within the kidneys gives rise to an outer region, the **renal cortex** which appears granular, and an inner region the **renal medulla** made up of striated triangles, the **renal pyramids**.
- Each nephron consists of a ***vascular component*** and a ***tubular component***.

N.B. (1) The efferent arterioles are the only arterioles in the body that drain from capillaries.

(2) the ascending limb returns to the glomerular region of its own nephron, where it passes through the fork formed by the afferent and efferent arterioles, **juxtaglomerular apparatus**; specialized region plays an important role in regulating kidney function.



Overview of Functions of Parts of a Nephron

Vascular component
- Afferent arteriole—carries blood to the glomerulus
- Glomerulus—a tuft of capillaries that filters a protein-free plasma into the tubular component
- Efferent arteriole—carries blood from the glomerulus
- Peritubular capillaries—supply the renal tissue; involved in exchanges with the fluid in the tubular lumen

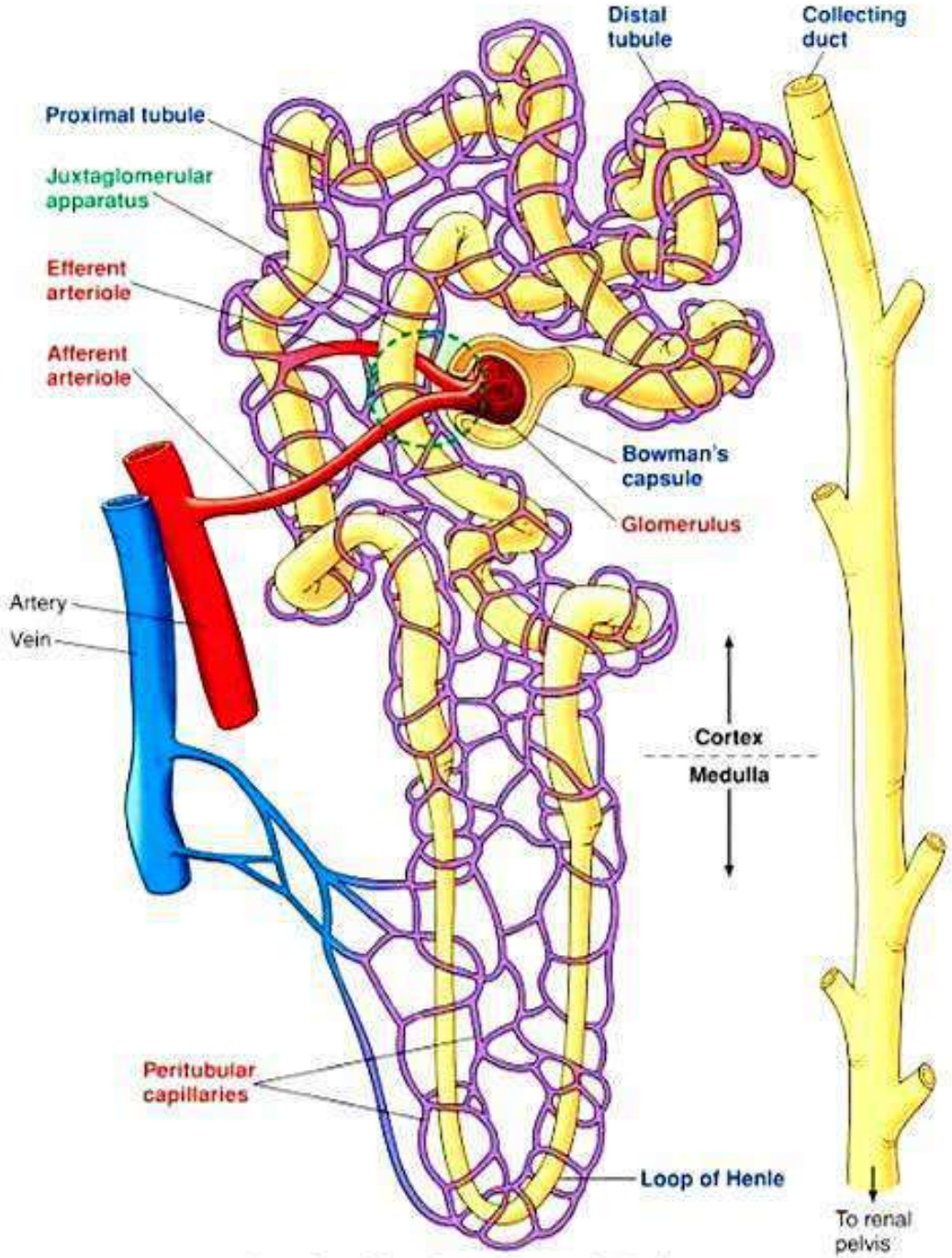
Combined vascular/tubular component
- Juxtaglomerular apparatus—produces substances involved in the control of kidney function

Tubular component
- Bowman's capsule—collects the glomerular filtrate
- Proximal tubule—uncontrolled reabsorption and secretion of selected substances occur here
- Loop of Henle—establishes an osmotic gradient in the renal medulla that is important in the kidney's ability to produce urine of varying concentration
- Distal tubule and collecting duct—variable, controlled reabsorption of Na^+ and H_2O and secretion of K^+ and H^+ occur here; fluid leaving the collecting duct is urine, which enters the renal pelvis

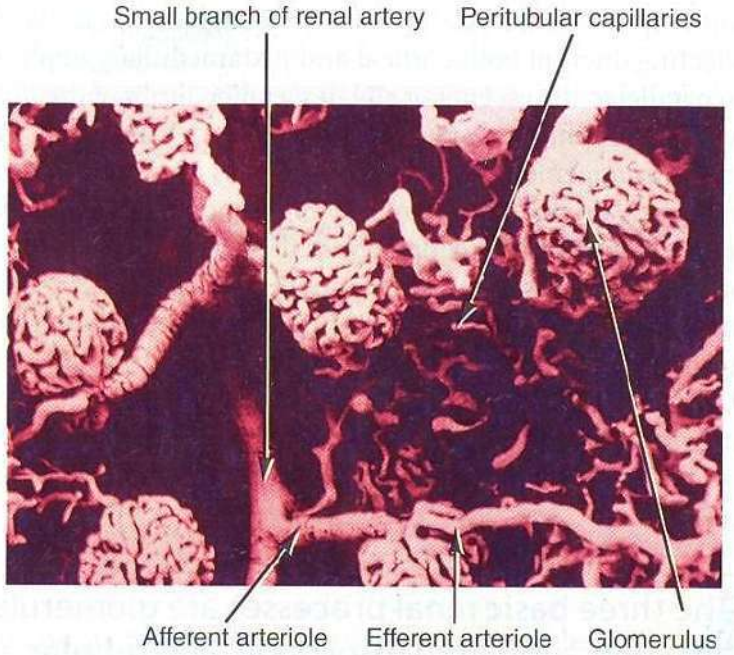
FIGURE 14-3

A nephron

A schematic representation of a cortical nephron, the most abundant type of nephron in humans.

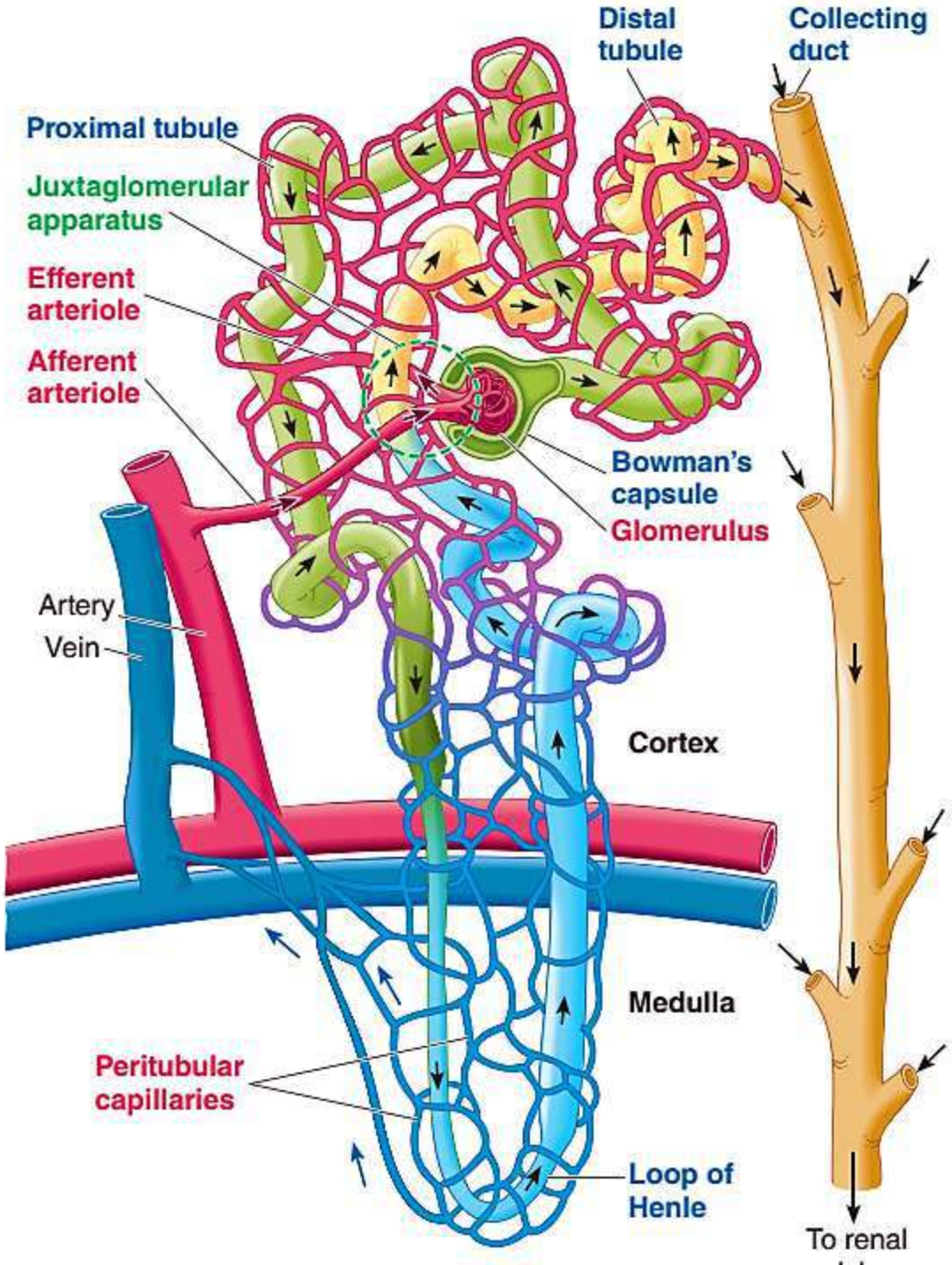


Overview of Functions of Parts of a Nephron



● FIGURE 14-4

Scanning electron micrograph of a glomerulus and associated arterioles



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Tubular component

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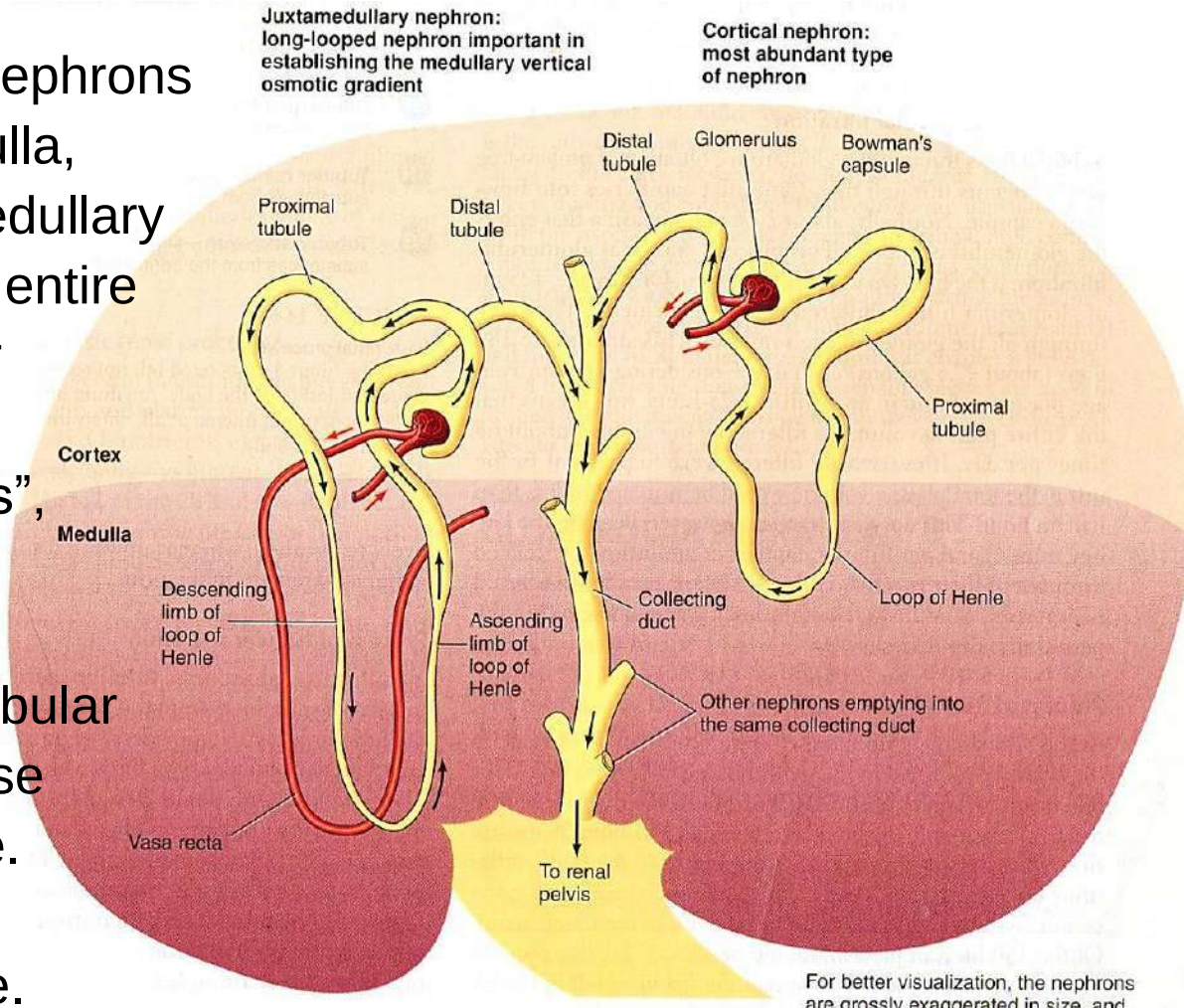
Combined vascular/tubular component

- Juxtaglomerular apparatus—produces substances involved in the control of kidney function

Cortical and juxtamedullary nephrons

- The two types of nephrons are distinguished by the location and length of some of their structures.
- The glomeruli of **cortical nephrons**, lie in the outer layer of the cortex, whereas the glomeruli of **juxtamedullary nephrons** lie in the inner layer of the cortex.
- Loops of Henle of cortical nephrons dips only slightly into the medulla, in contrast, the loop of juxtamedullary nephrons plunges through the entire depth of the medulla, and their peritubular capillaries, known as **vasa recta** "straight vessels", which run in close association with the long loops of Henle. In cortical nephrons, the peritubular capillaries entwine around these nephrons' short loops of Henle. About 80% of the nephrons in humans are of the cortical type.



The three basic renal processes are glomerular filtration, tubular reabsorption, and tubular secretion

- **Process of glomerular filtration**

Normally, about 20% of the plasma that enters the glomerulus is filtered, 125 ml/min of glomerular filtrate are formed 180 l/day, the average plasma volume in an adult is 2.75 L, this means that the entire plasma volume is filtered by the kidneys about 65 times per day.

- **Process of tubular reabsorption**

Substances of value are returned selectively to the peritubular capillary plasma,whereas unwanted substances that must be eliminated remain in the urine 178.5L of the 180L of plasma filtered per day are reabsorbed, the remaining 1.5 L eliminated as urine.

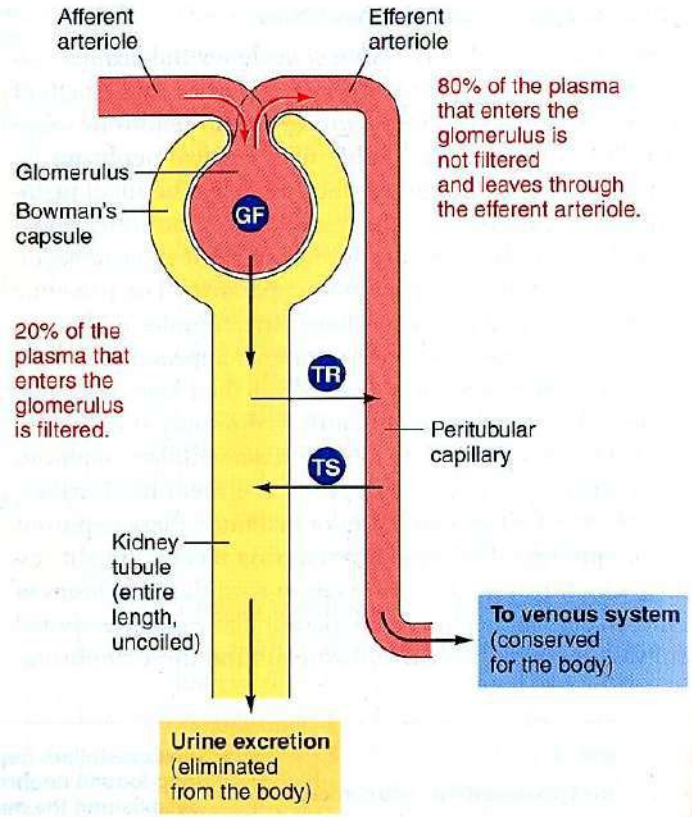


FIGURE 14-6
Basic renal processes
Anything filtered or secreted but not reabsorbed is excreted in the urine and lost from the body. Anything filtered and subsequently reabsorbed, or not filtered at all, enters the venous blood and is saved for the body.

Process of tubular secretion

- Is the selective transfer of substances from the peritubular capillary blood into the tubular lumen. Tubular secretion extracting an additional quantity of a particular substance from the 80% of unfiltered plasma .

Urine excretion

- Is the elimination of substances from the body in urine is the result of the first three processes. All plasma constituents that are filtered or secreted but are not reabsorbed remain in the tubules and pass into the renal pelvis to be excreted as urine and eliminated from the body (fig. 14-7).
- For many substances, these renal processes are subject to physiologic control.

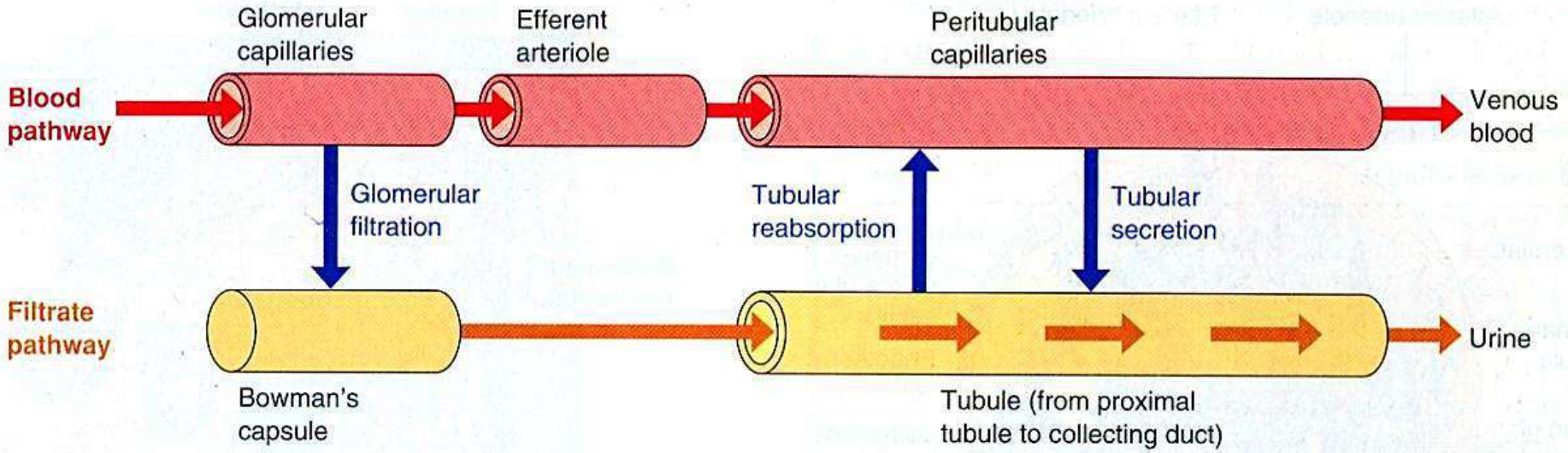


FIGURE 14-7

Pathways traveled by blood and filtrate as urine is formed in the nephron

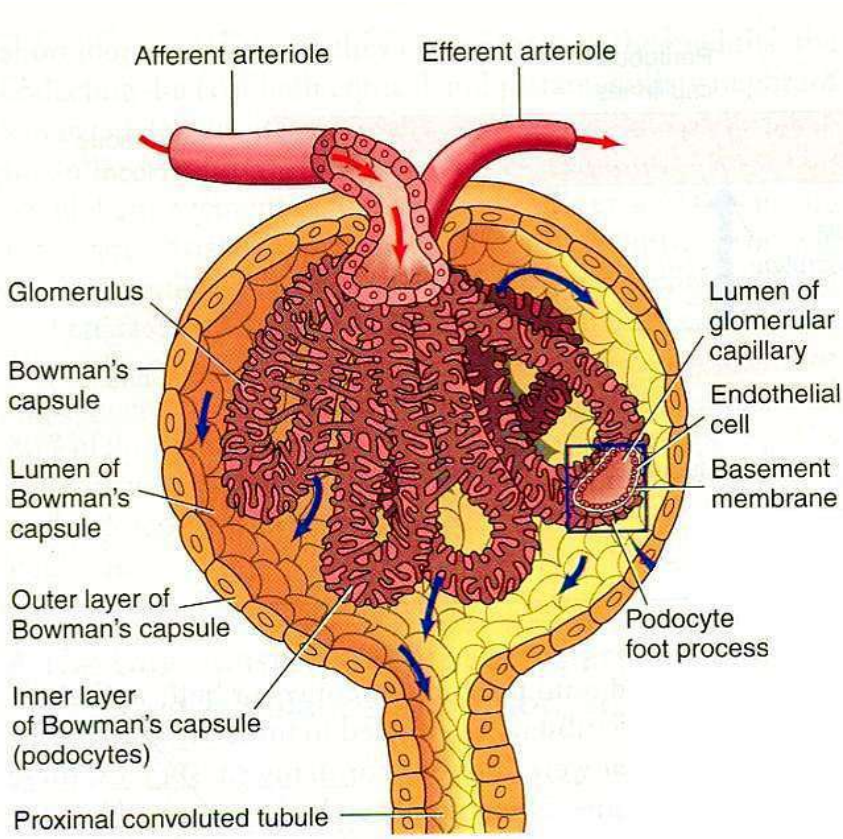
Glomerular filtration

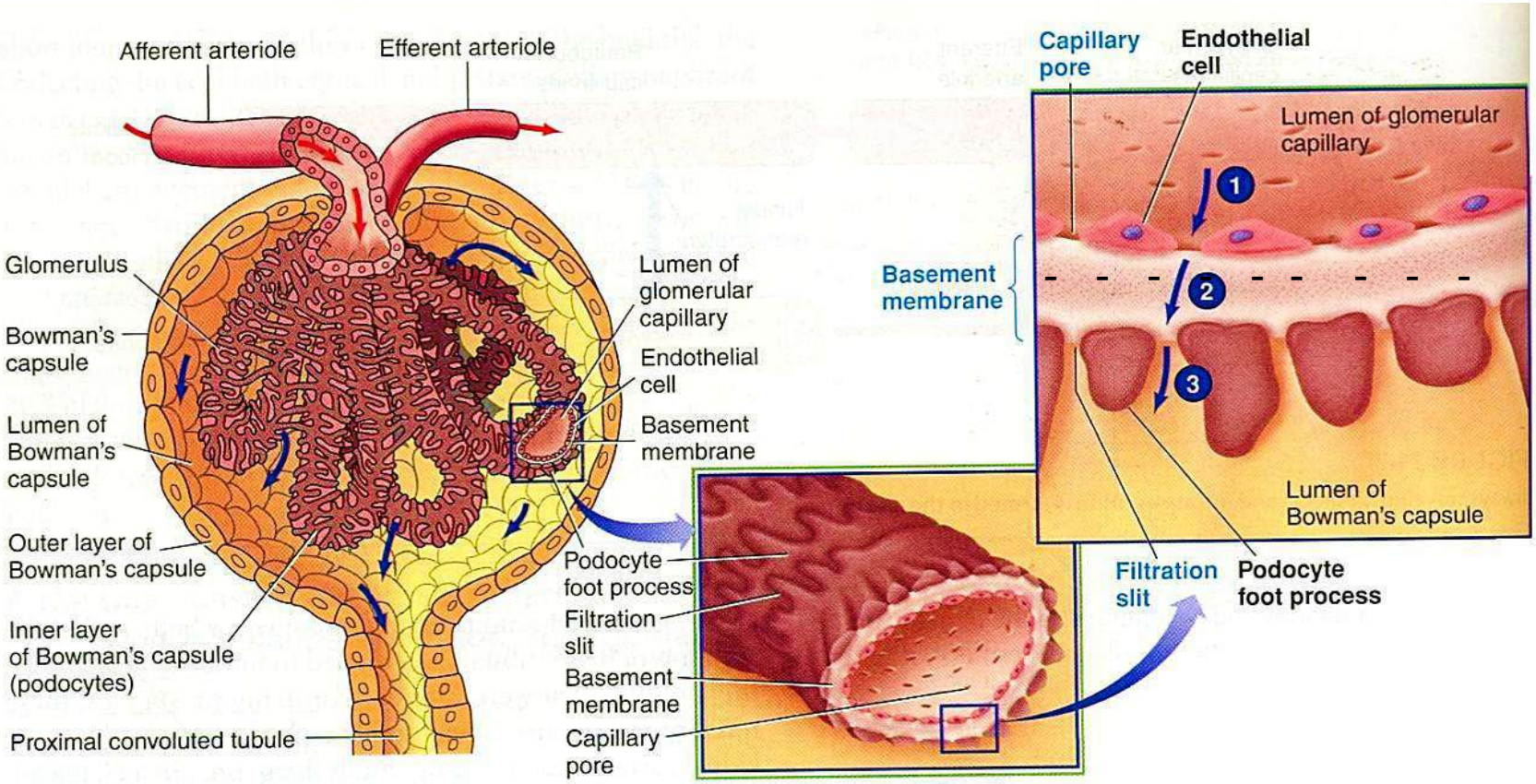
- Fluid filtered from the glomerulus into Bowman's capsule must pass through

(1) the wall of the glomerular capillaries,

(2) the basement membrane,

(3) the inner layer of Bowman's capsule, function as a fine molecular sieve.





To be filtered, a substance must pass through

1. the pores between the endothelial cells of the glomerular capillary
2. an acellular basement membrane
3. the filtration slits between the foot processes of the podocytes of the inner layer of Bowman's capsule

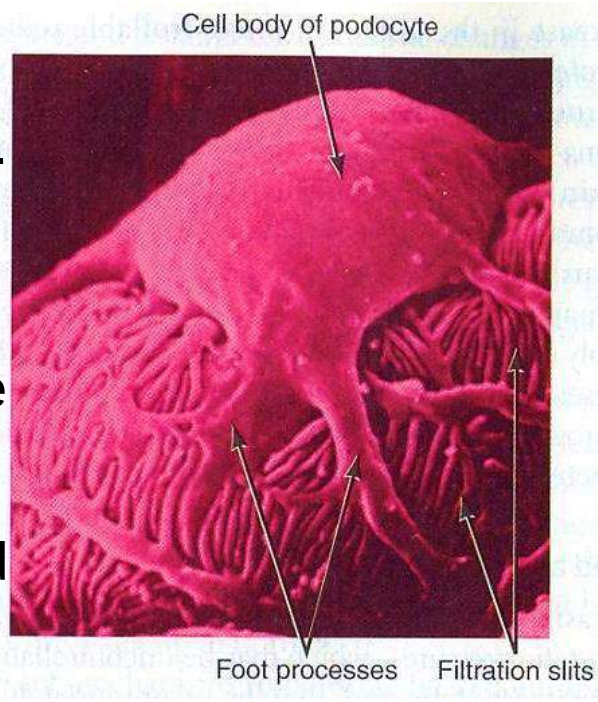
● FIGURE 14-8

Layers of the glomerular membrane

The glomerular membrane is considerably more permeable than capillaries elsewhere

The glomerular capillary, a single layer of flattened endothelial cells, over 100 times more permeable to H_2O and solutes than capillaries elsewhere in the body.

The basement membrane, an acellular gelatinous layer composed of collagen providing structural strength, and **glycoproteins** discouraging the filtration of small plasma proteins, because the glycoproteins are negatively charged, they repel albumin and other plasma proteins, with less than 1% of the albumin molecules escaping.Some renal diseases characterized by excessive albumin in the urine (albuminuria) are due to disruption of the negative charges even though the size of the pores remains constant.



Bowman's capsule, consists of **podocytes**, each bears many elongated foot processes (fig. 14-9).

The narrow slits between adjacent foot processes, **filtration slits** through which fluid exiting the glomerular capillaries can enter the lumen of Bowman's capsule. Thus the route that filtered substances take across the glomerular membrane is completely extracellular – first through capillary pores, then through the acellular basement membrane and finally through capsular filtration slits (fig. 14-8).

The glomerular capillary blood pressure is the major force that induces glomerular filtration

- To accomplish glomerular filtration, a force must drive a portion of the plasma in the glomerulus through the openings.
- No active transport mechanisms are involved. Passive physical forces similar to those acting across capillaries elsewhere are responsible for glomerular filtration, except for two important differences: (1) the glomerular capillaries are much more permeable than capillaries elsewhere, so more fluid is filtered for a given filtration pressure, (2) the balance of forces across the glomerular membrane.

➢ **Forces involved in glomerular filtration**

- Three physical forces are involved in glomerular filtration (table 14-1).

▲ TABLE 14-1
Forces Involved in Glomerular Filtration

Force	Effect	Magnitude (mm Hg)
Glomerular Capillary Blood Pressure	Favors filtration	55
Plasma-Colloid Osmotic Pressure	Opposes filtration	30
Bowman's Capsule Hydrostatic Pressure	Opposes filtration	15
Net Filtration Pressure (Difference Between Force Favoring Filtration and Forces Opposing Filtration)	Favors filtration	10

55 − (30 + 15) = 10

Forces involved in glomerular filtration

- Three physical forces are involved in glomerular filtration:

1- The glomerular capillary blood pressure, depends on contraction of the heart and the resistance to blood flow offered by the afferent and efferent arterioles, average 55 mm Hg, is higher than capillary blood pressure elsewhere. The reason is the larger diameter of the afferent arteriole compared to the efferent arteriole, and the high resistance offered by the efferent arterioles tends to push fluid out of the glomerulus producing glomerular filtration.

2- Plasma-colloid osmotic pressure, is caused by the unequal distribution of plasma proteins across the glomerular membrane. The resultant tendency for H2O to move by osmosis down its own concentration gradient from Bowman's capsule into the glomerulus opposes glomerular filtration, average 30 mm Hg.

3- Bowman's capsule hydrostatic pressure, the pressure exerted by the fluid in this initial part of the tubule, bout 15 mm Hg.

Glomerular filtration rate

- The forces acting across the glomerular membrane are not in balance. The net difference favoring filtration is referred to as the **net filtration pressure**. The actual rate of filtration, the **glomerular filtration rate (GFR)**, depends not only on the net filtration pressure but also on surface area and permeable the glomerular membrane collectively referred to as the **filtration coefficient (K_f)**

GFR = K_f x net filtration pressure

- **Changes in the GFR occur primarily as a result of changes in glomerular capillary blood pressure**
- The net filtration pressure responsible for inducing glomerular filtration is simply due to an imbalance of opposing physical forces, and they are not subject to regulation and under normal conditions do not vary substantially, however, they can change pathologically.
- An uncontrollable reduction in plasma protein concentration might occur, for example, in severely burned patients. *Conversely*, such as in cases of *dehydrating diarrhea*, the GFR is reduced.
- Bowman's capsule hydrostatic pressure can become uncontrollably elevated, and filtration can decrease, in the presence of a urinary tract obstruction.

Controlled adjustments in the GFR

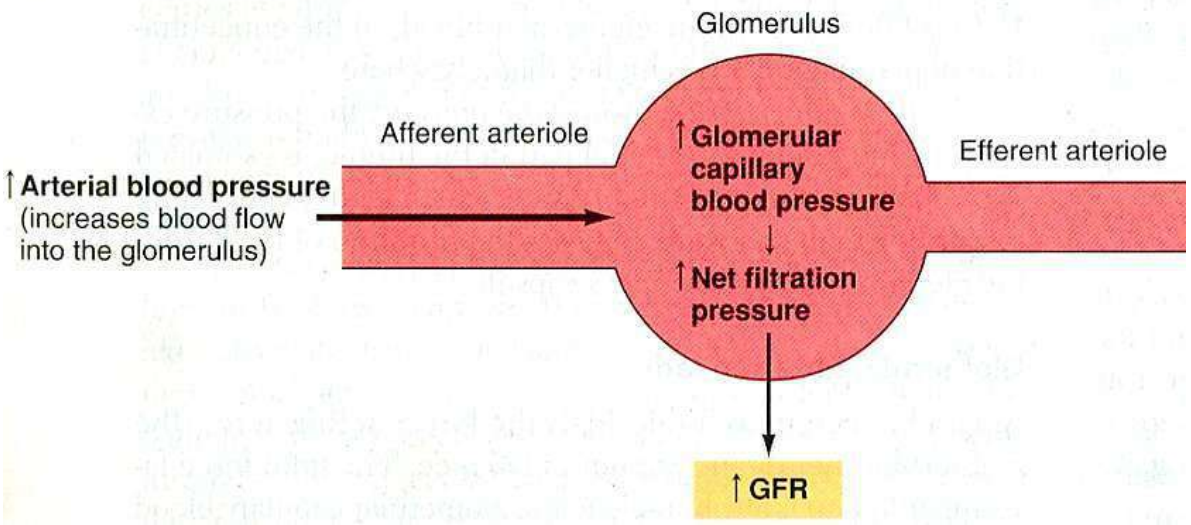
- Glomerular capillary blood pressure can be controlled to adjust the GFR to suit the body's needs, as the glomerular capillary blood pressure goes up, the net filtration pressure increases and the GFR increases correspondingly. The magnitude of the glomerular capillary blood pressure depends on the rate of blood flow which is determined largely by the magnitude of the mean systemic arterial blood pressure and the resistance offered by the nephron's arterioles.
- Two major control mechanisms regulate the GFR :

(1) Autoregulation; which is aimed at preventing spontaneous changes in GFR,

(2) Extrinsic sympathetic control; which is aimed at long-term regulation of arterial blood pressure.

FIGURE 14-10

Direct effect of arterial blood pressure on the glomerular filtration rate (GFR)

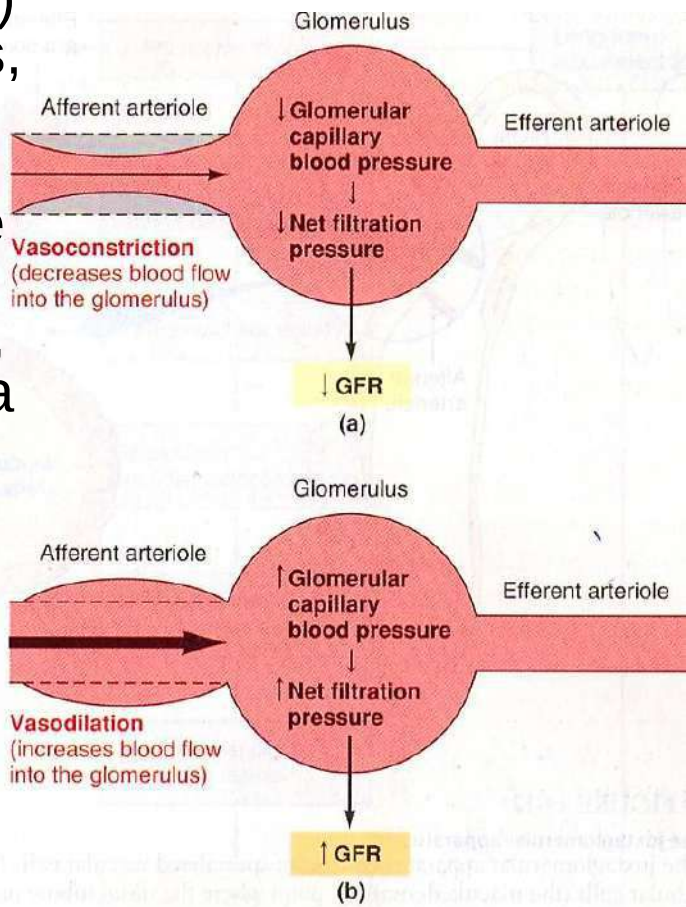


Mechanisms responsible for autoregulation

Because the arterial blood pressure is the force that drives blood into the glomerulus, if everything else remained constant (fig. 14-10) **autoregulation**. The kidneys can, within limits, maintain a constant blood flow into the glomerular capillaries (and thus a constant glomerular capillary blood pressure and stable GFR) despite changes in the driving arterial pressure, by altering afferent arteriolar caliber, e.g. if the GFR increases as a direct result of a rise in arterial pressure, the net filtration pressure and GFR can be reduced to normal by constriction of the afferent arteriole, which decreases the flow of blood into the glomerulus (fig. 14-11).

The resultant buildup of glomerular blood volume increases glomerular blood pressure, which in turn brings the GFR back up to normal. ***HOW??***

Currently, two international mechanisms are thought to contribute to autoregulation: (1) ***Myogenic mechanism,*** *(2)* ***Tubuloglomerular feedback mechanism***



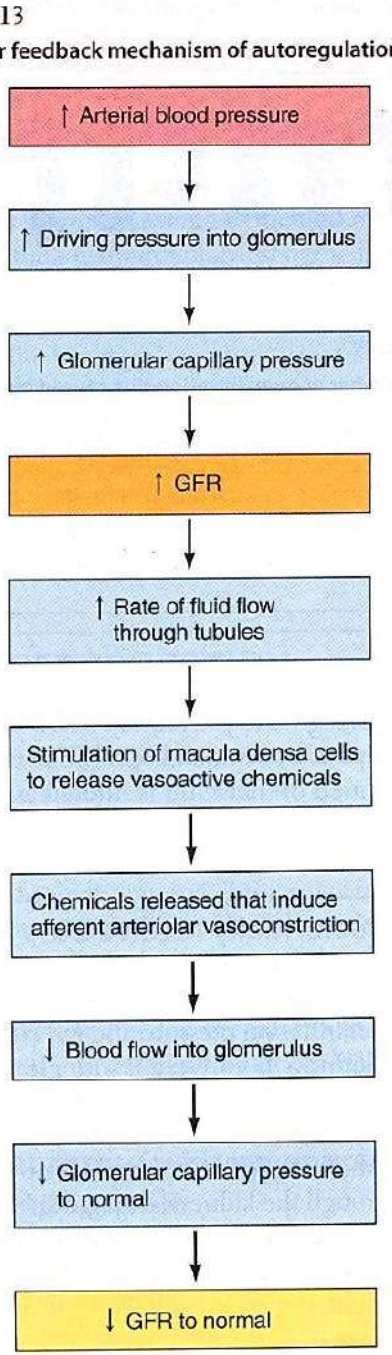
● FIGURE 14-11

Adjustments of afferent arteriole caliber to alter the GFR
(a) Arteriolar adjustment to reduce the GFR. (b) Arteriolar adjustment to increase the GFR.

(1) Myogenic mechanism, is a common property of vascular smooth muscle. Arteriolar vascular smooth muscle contacts inherently in response to the stretch accompanying increased pressure within the vessel. Conversely, inherent relaxation of an unstretched afferent arteriole when pressure within the vessel is reduced increases blood flow into the glomerulus despite the fall in arterial pressure.

(2) Tubuloglomerular feedback mechanism, involves the juxtaglomerular apparatus (fig. 14-12), **granular cells**, so called because they contain many secretary granules. The **macula densa** cells detect changes in the rate at which fluid is flowing past them through the tubule.

- If the GFR is increased secondary to an elevation in arterial pressure (fig. 14-13). Several chemical have been identified, some of which are vasoconstrictors e.g. **endothelin** and others vasodilator e.g. **bradydinin**.
- This tubuloglomerular feedback mechanism is initiated by the tubule to help each nephron regulate its own GFR.



- **Importance of autoregulation of the GFR**

- Intrinsic autoregulatory adjustments of afferent arteriolar resistance can compensate for changes in mean arterial pressure (80-180 mm Hg), thus preventing inappropriate fluctuations in GFR.
- Autoregulation is important because unintentional shifts in GFR could lead to dangerous imbalances of fluid, electrolytes and wastes. If autoregulation did not occur, the GFR would increase, and H2O and solutes would be lost needlessly, as a result of the rise in arterial pressure accompanying heavy exercise, and vice versa.
- Dramatic changes in mean arterial pressure (<80 or >180 mm Hg) directly cause the glomerular capillary pressure and, accordingly the GFR, to decrease or increase in proportion to the change in arterial pressure.

- **Importance of extrinsic sympathetic control of the GFR**

- The GFR can be ***changed on purpose*** by extrinsic-control mechanisms that override the autoregulatory responses, mediated by sympathetic nervous system input to the afferent arterioles.
- If plasma volume is decreases arterial blood pressure is detected by *baroreceptors,* which initiate neural reflexes to increase blood pressure toward normal, coordinated by the cardiovascular control center in the brain stem and are mediated primarily through increased sympathetic activity to the heart and blood vessels.
- In the long term, the plasma volume must be restored to normal. One compensation for a depleted plasma volume is reduced urine output, accomplished in part by reducing the GFR; if less fluid is filtered, less is available to be excreted.

Role of the baroreceptor reflex in extrinsic control of the GFR

- During this reflex, sympathetically induced vasoconstriction occurs in most arterioles to increase total peripheral resistance. Among the arterioles that constrict in response to the baroreceptor reflex are the afferent arterioles carrying blood to the glomeruli, less blood flows into the glomeruli than normal, lowering the glomerular capillary blood pressure (fig. 14-11).
- Other mechanisms, such as increased tubular reabsorption of H2O and salt as well as increased thirst, also contribute to long-term maintenance of blood pressure, despite a loss of plasma volume, by helping to restore plasma volume.
- Conversely, if blood pressure is elevated, sympathetic vasoconstrictor activity to the arterioles, is reflexly reduced. As more blood enters the glomeruli through the dilated afferent arterioles, glomerular capillary blood pressure rises, increasing the GFR.

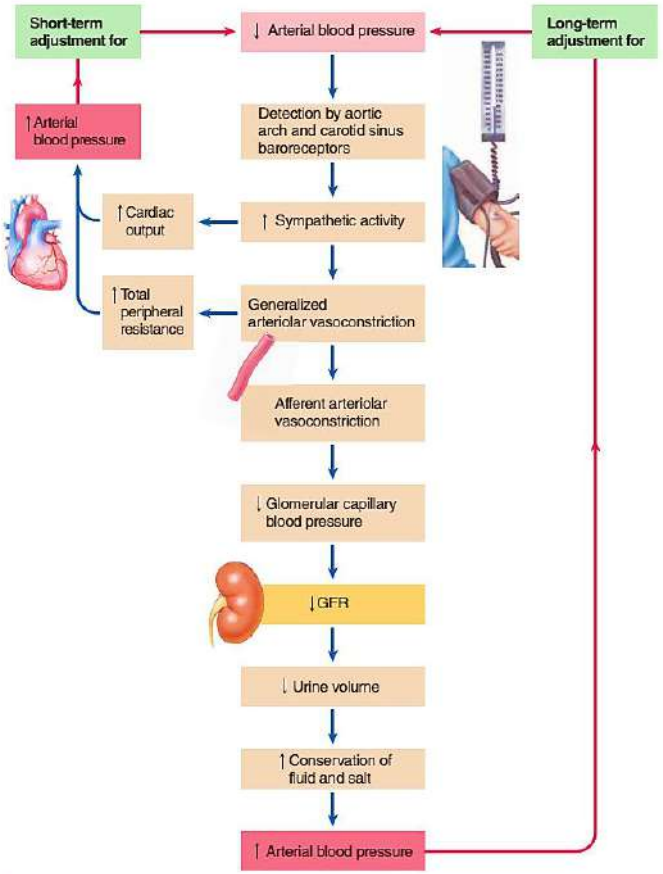
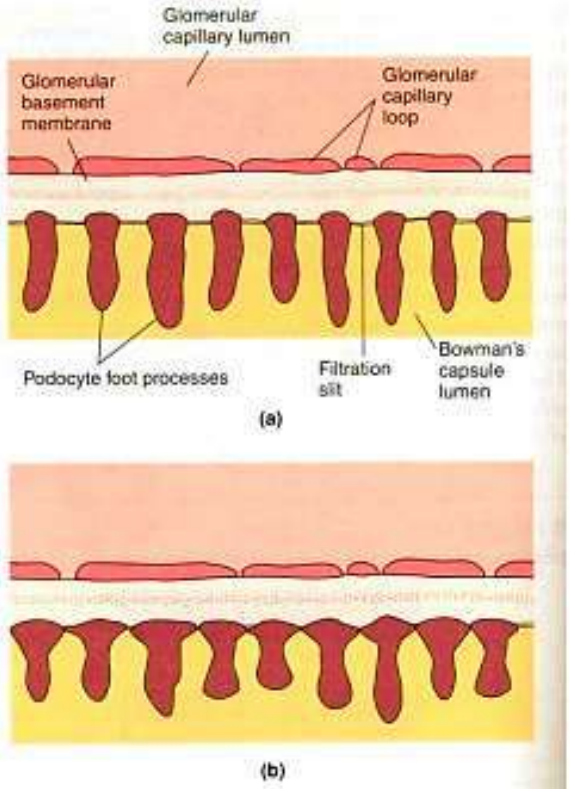


FIGURE 14-12 Baroreceptor reflex influence on the GFR in long-term regulation of arterial blood pressure.

The GFR can be influenced by changes in the filtration coefficient

We have discussed the rate of glomerular filtration, depends on the filtration coefficient (k_f) as well as on the net filtration pressure. K_f depends on the surface area and the permeability of the glomerular membrane can be modified by contractile activity within the membrane. Each tuft of glomerular capillaries is held together by **mesangial cells**, that contain contractile elements "actin-like filaments", closes off a portion of the filtrating capillaries, reducing the surface area available for filtration within the glomerular tuft, thus reduction in K_f decreases GFR. Sympathetic stimulation, in addition several hormones and local chemical mediators involved in the control of tubuloglomerular feedback or tubular reabsorption also influence mesangial cell contractile activity.

The podocytes also posses actinlike contractile filaments, whose contraction or relaxation can decrease or increase the filtration slits.



● FIGURE 14-15

Change in the number of open filtration slits caused by podocyte relaxation and contraction

(a) Podocyte relaxation narrows the bases of the foot processes, increasing the number of fully open intervening filtration slits spanning a given area. (b) Podocyte contraction flattens the foot processes and thus decreases the number of intervening filtration slits.

(Sci-ACE: Adapted from Federation Proceedings, Vol. 42, p. 3046-3052, 1983. Reprinted by permission.)

The kidneys normally receive 20% to 25% of the cardiac output

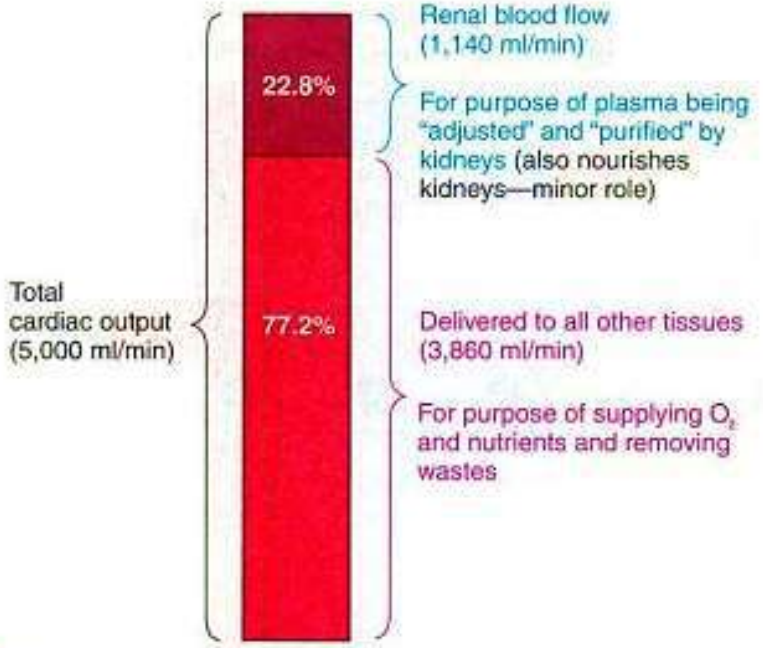


FIGURE 14-16
Percentage of the cardiac output distributed to the kidneys

- 20% of the plasma that enters the kidneys is converted into glomerular filtrate; an average of 125 ml/min, the total renal plasma flow must average about 625 ml/min.
- 20% to 25 of the blood pumped out by the heart each minute "goes to the cleaners" instead of serving its normal purpose of exchanging materials with the tissues.
- **As the full extent of various regulatory mechanisms is becoming understood, it is evident that control of glomerular filtration and control of tubular reabsorption are complexly interrelated.**

الحمد لله رب العالمين

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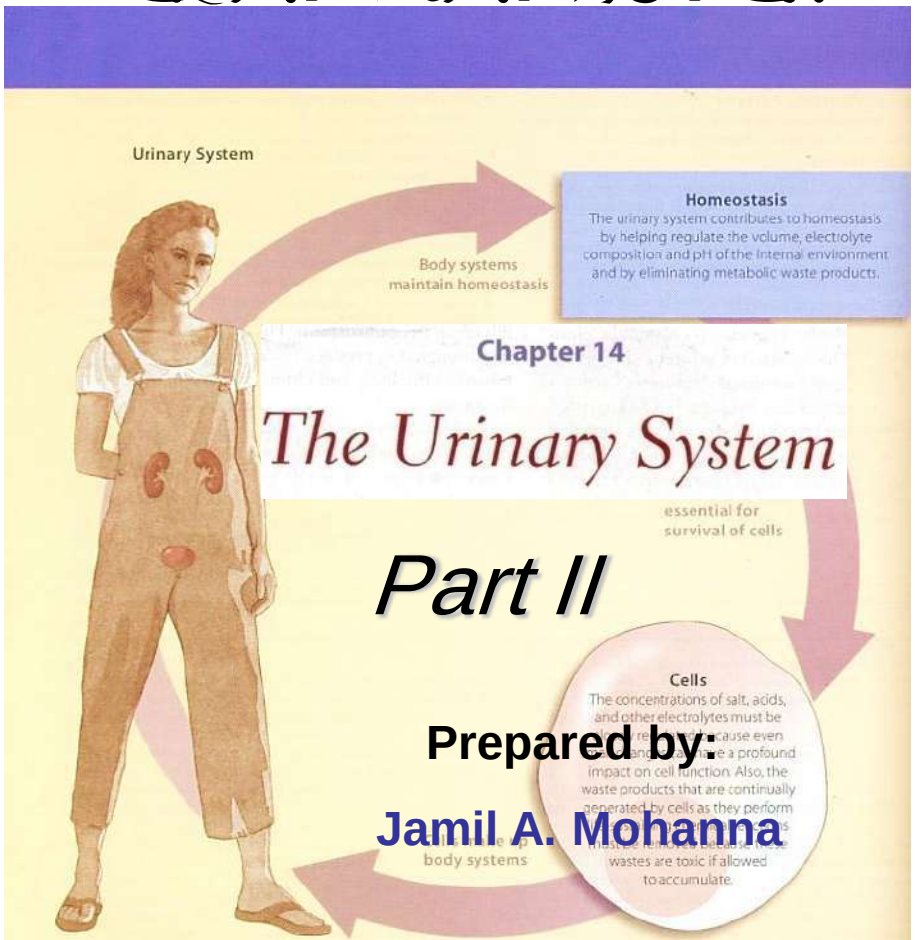


The survival and proper functioning of cells depend on the maintenance of stable concentrations of salt, acids, and other electrolytes in the internal fluid environment. Cell survival also depends on continual removal of the toxic metabolic wastes that cells produce as they perform life-sustaining chemical reactions. The kidneys play a major role in maintaining homeostasis by regulating the concentration of many plasma constituents, especially electrolytes and water, and by eliminating all metabolic wastes (except CO_2, which is removed by the lungs). As plasma repeatedly filters through the kidneys, they retain constituents of value for the body and eliminate undesirable or excess materials in urine. Of special importance is the kidneys' ability to regulate the volume and osmolarity (solute concentration) of the internal fluid environment by controlling salt and water balance. Also crucial is their ability to help regulate pH by controlling elimination of acid and base in urine.

Prepared by:

Jamil A. Mohanna

Tubular reabsorption

- After a protein-free plasma is filtered through the glomerulus, the tubules handle each substance discretely, so that even though the concentrations of all constituents in the initial glomerular filtrate are identical to their concentrations in the plasma (with the exception of plasma proteins), the concentrations of different constituents are variously altered as the filtered fluid flows through the tubular system.
- It is important that the essential material that are filtered (e.g. nutrients, electrolytes and others) be returned to the blood by the process of ***tubular reabsorption***, the discrete transfer of substances from the tubular lumen into the peritubular capillaries.

Tubular reabsorption is tremendous, highly selective, and variable

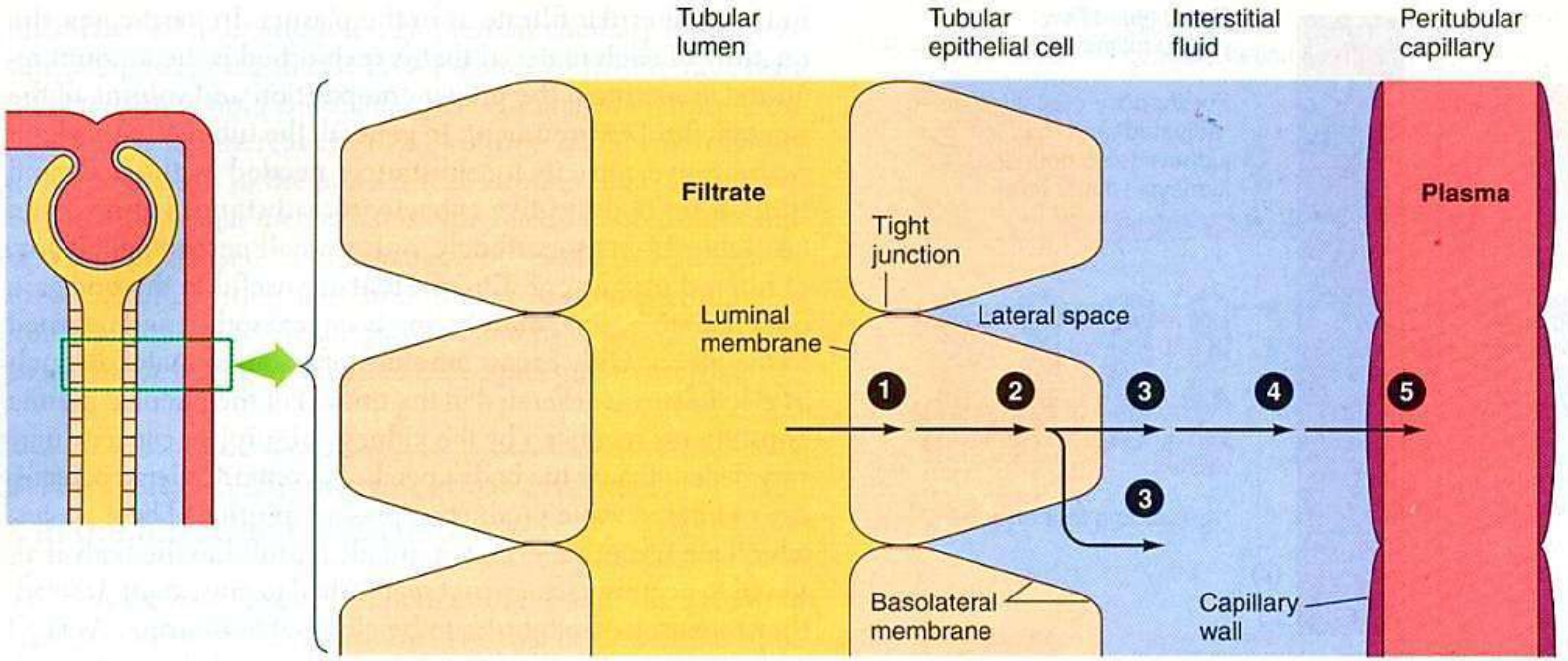
- In general, the tubules have a high reabsorptive capacity for substances of value.
- The reabsorption capacity of the tubular system is tremendous. Over 99% of the filtered plasma is returned to the blood through reabsorption. On average, 124 ml out of the 125 ml filtered per minute are reabsorbed.

▲ TABLE 14-2
Fate of Various Substances Filtered by the Kidneys

Substance	Average Percentage of Filtered Substance Reabsorbed	Average Percentage of Filtered Substance Excreted
Water	99	1
Sodium	99.5	0.5
Glucose	100	0
Urea (a waste product)	50	50
Phenol (a waste product)	0	100

Tubular reabsorption involves transepithelial transport

- The tight junctions largely prevent substances from moving *between* the cells, so materials must pass through the cells, through five distinct barriers (fig.14-17), this entire sequence of steps is known as **transepithelial transport**.



To be reabsorbed (move from the filtrate to the plasma), a substance must traverse five distinct barriers:

1. the luminal cell membrane
2. the cytosol
3. the basolateral cell membrane
4. the interstital fluid
5. the capillary wall

FIGURE 14-17

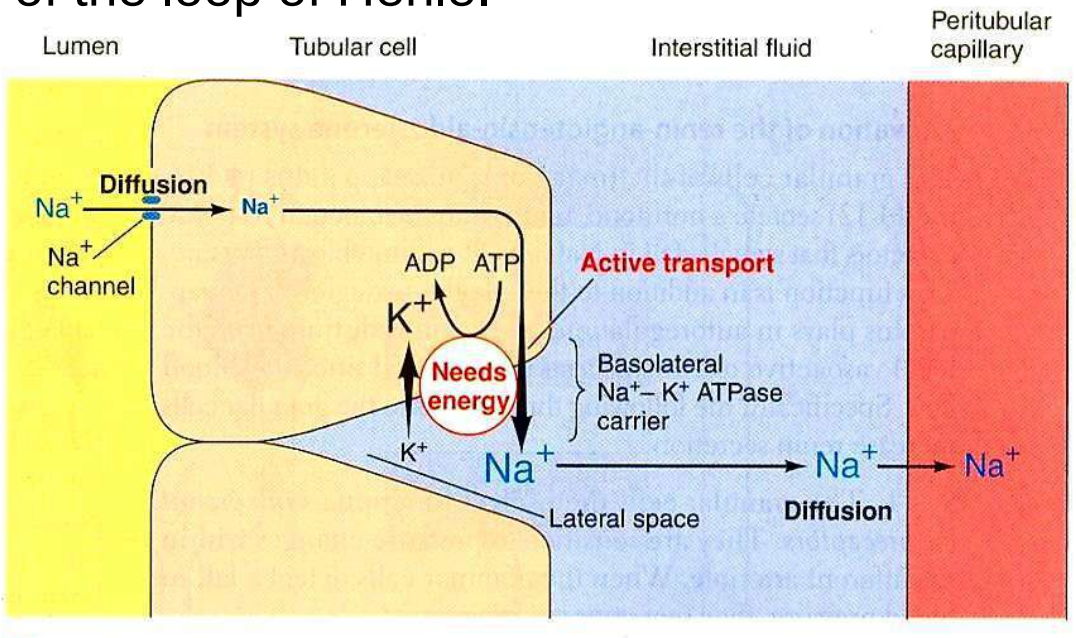
Passive versus active reabsorption

- Tubular reabsorption involves transepithelial transport from the tubular lumen into the peritubular capillary plasma. This process may be active (requiring energy) or passive (using no energy).
- In **passive reabsorption**, *all* steps in the transepithelial transport are passive. In contrast, **active reabsorption** takes place if any one of the steps requires energy, even if the four other steps are passive, occurs against an electrochemical gradient. Substances that are actively reabsorbed are of particular importance to the body, such as glucose, amino acids, and other organic nutrients, as well as Na^+ and other electrolytes such as PO_4^{3-}.

➢ **An active Na^+-K^+ ATPase pump in the basolateral membrane is essential for Na^+ reabsorption**

* Of the total energy requirement of the kidneys, 80 % is used for Na+ transport, of the Na+ filtered, 99.5 % is normally reabsorbed. 67% is reabsorbed in the proximal tubule, 25% in the loop of Henle, and 8% in the distal and collecting tubules. Sodium reabsorption plays different important roles in each of these segments.

- In the ***proximal tubule*** Na^+ reabsorption plays a pivotal role in reabsorption of glucose, amino acids, H_2O, CL^- and urea.
- In the ascending limb of the ***loop of Henle***, with CL^- reabsorption play a critical role in the kidneys' ability to produce urine of varying concentrations and volumes, depending on the body's need to conserve or eliminate H_2O.
- In the ***distal portion of the nephron*** is variable and subject to hormonal control. It is important in regulation of ECF volume and long-term control of arterial blood pressure and is also linked in part to K^+ secretion & H^+ secretion.
- Sodium is reabsorbed throughout the tubule with the exception of the descending limb of the loop of Henle.



- The pivotal event to which most reabsorptive processes are linked in some way is the active reabsorption of Na^+. An energy-dependent Na^+-K^+ ATPase carrier located in the basolateral membrane of almost all tubular cells transports Na^+ out of the cells into the lateral spaces between adjacent cells. This transport of Na^+ induces the net reabsorption of Na^+ from the tubular lumen to the peritubular capillary plasma, most of which takes place in the proximal tubules.

- The nature of the luminal Na^+ channels and/or transport carriers that permit movement of Na^+ from the lumen into the cell varies for different parts of the tubule, but always passive, e.g. in the proximal tubule, a cotransport carrier moves Na^+ and an organic nutrient such as glucose from the lumen into the cell. By contrast, in the collecting tubule there is a Na^+ channel, thus net transport of Na^+ from the tubular lumen into the blood occurs at the expense of energy.

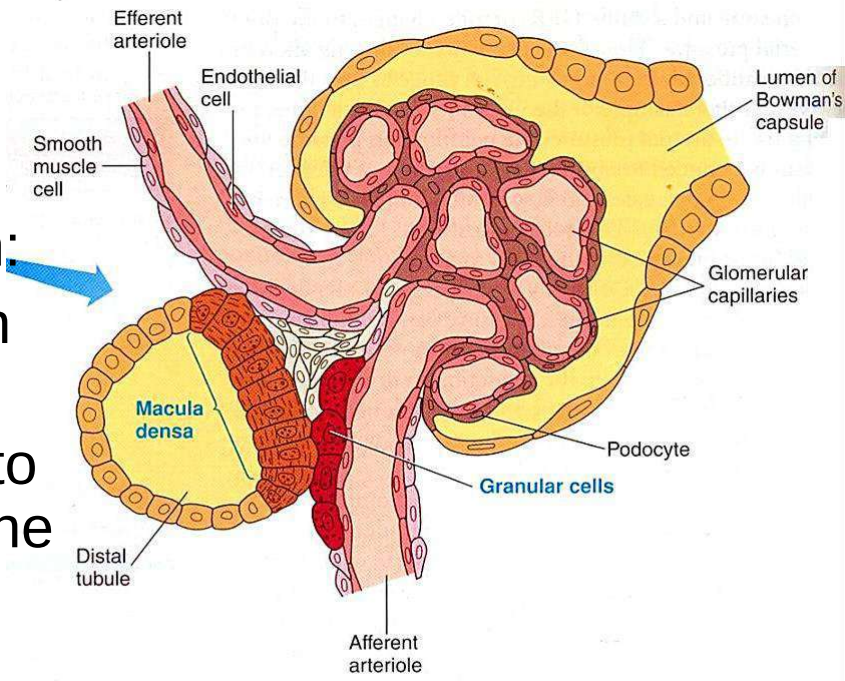
Aldosterone stimulates Na^+ reabsorption in the distal and collecting tubules

- Early in the nephron, Na^+ reabsorption occurs in constant unregulated fashion (regardless of the **Na^+ load;** total amount of Na^+ in the body fluids, not the concentration), but in the distal and collecting tubules, the reabsorption of a small percentage of the filtered Na^+ is variable and subject to hormonal control. The extent of this controlled Na^+ reabsorption depends primarily on the complex renin-angiotensin-aldosterone system.
- The Na^+ and Cl^- load in the body is reflected by the ECF volume, it has 90% of the ECF's osmotic activity. Recall that osmotic pressure can be thought of loosely as a force that attracts and holds H_2O. When the Na^+ load is above normal and the ECF's osmotic activity is therefore increase, the extra Na^+ "holds" extra H_2O, expanding the ECF volume and vice versa.
- Because plasma is a component of the ECF, a change in ECF volume is the corresponding change in blood pressure accompanying expansion (↑blood pressure) or reduction (↓blood pressure) of the plasma volume. Thus, long-term control of arterial blood pressure ultimately depends on Na^+- regulating mechanisms.

Activation of the renin-angiotensin-aldosteron system

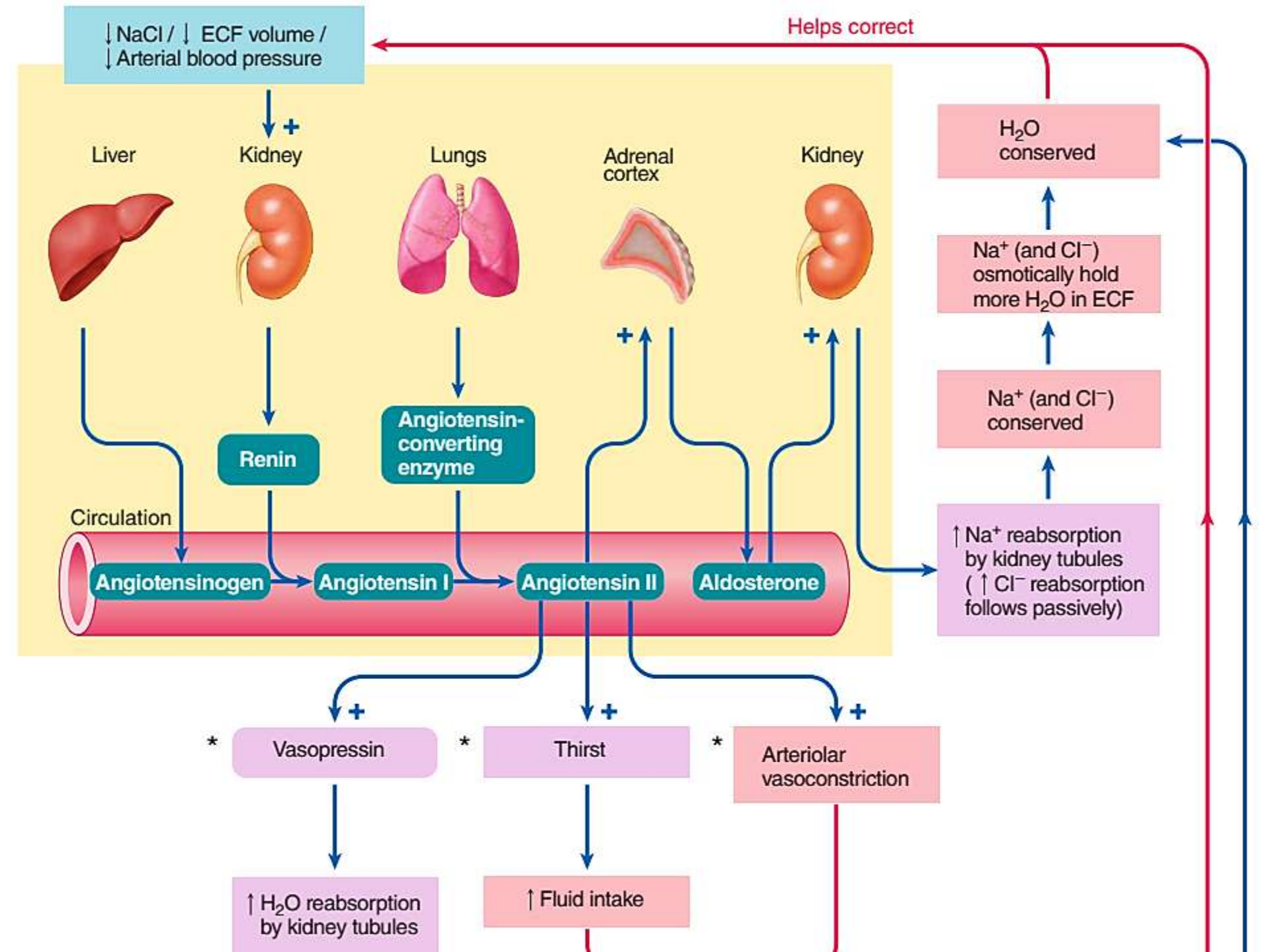
- The granular cells of the juxtaglomerular apparatus (fig. 14-12) secrete a hormone, **renin** into the blood in response to factors that signal a fall in NaCl/ECF volume/ blood pressure.
- The following three inputs to the granular cells increase renin secretion:

1. The granular cells themselves function as *intrarenal baroreceptors.*
2. The macula densa cells are sensitive to the NaCl moving past the m through the tubular lumen, then it trigger the granular cells to secrete more renin.
3. The granular cells are innervated by the sympathetic nervous system. When blood pressure falls below normal, the baroreceptor reflex increases sympathetic activity that stimulates the granular cells to secrete more renin.



ized vascular cells (the granular cells) and specialized
the distal tubule passes through the fork formed by the
on.

- Through a complex series of events, increase renin secretion brings about increases Na^+ reabsorption by the distal portion of the tubule. Chloride always passively follows Na^+ sown the electrical gradient established by sodium's active movement. The ultimate benefit of this salt retention is that it somatically promotes H_2O retention, which helps restore the plasma volume, thus being important in the long-term control of blood pressure (fig. 14-19).


↓NaCl / ↓ ECF volume / ↓Arterial blood pressure
Helps correct
Liver
Kidney
Lungs
Adrenal cortex
Kidney
+
+
+
+
Renin
Angiotensin-converting enzyme
Circulation
Angiotensinogen
Angiotensin I
Angiotensin II
Aldosterone
H_2O conserved
Na^+ (and Cl^-) osmotically hold more H_2O in ECF
Na^+ (and Cl^-) conserved
↑ Na^+ reabsorption by kidney tubules (↑ Cl^- reabsorption follows passively)
*
Vasopressin
*
Thirst
*
Arteriolar vasoconstriction
↑ H_2O reabsorption by kidney tubules
↑ Fluid intake

Function of the renin-angiotensin-aldosteron system

- *Aldosterone* increases Na^+ reabsorption by the distal and collecting tubules, by promoting the insertion of additional Na^+ channels into the luminal membranes and additional Na^+-K^+ ATPase carriers into the basolateral membranes of he distal and collecting tubular cells.
- The renin-angiotensin-aldosteron system thus promotes salt retention and a resultant H_2O retention and elevation of arterial blood pressure (-ve feedback fashion).
- In addition to **(1)** aldosterone secretion **(2)** is also a potent constrictor, thereby increasing total peripheral resistance, **(3)** it stimulates thirst and **(3)** stimulates vasopressin.
- The opposite situation exists when the Na^+ load, EDF and plasma volume, and arterial blood pressure are above normal, this nonreabsorbed Na^+ is lost in urine. An average salt consumer typically excretes about 10g/day, a heavy salt consumer excretes more, and someone who has lost considerable salt during heavy sweating excretes less urinary salt.

➢ **Role of the renin-angiotensin-aldosteron system in various diseases**

- some cases of hypertension are due to abnormal increases in renin-angiotensin-aldosterone activity, also it is responsible in part for the fluid retention and edema accompanying congestive heart failure.
- Na^+ excretion may fall to virtually zero despite continue salt ingestion and accumulation in the body, producing edema and exacerbates the congestive heart failure because the weakened heart cannot pump the additional plasma volume.

Drugs that affect Na^+ reabsorption

- Patients with congestive heart failure are placed on low-salt diets. Often they are treated with **diuretics**. Many of these drugs function by inhibiting tubular reabsorption of Na^+, so more H_2O is also lost from the body, thus helping to remove the excess ECF, as well as in treating hypertension.
- **ACE inhibitor drugs**, are also beneficial in the treatment of congestive heart failure as well as certain cases of hypertension.

➢ **Atrial natriuretic peptide inhibits Na^+ reabsorption**

- By contrast, Na^+ reabsorption is inhibited by **atrial natriuretic peptide (ANP)**, a hormone released from the cardiac atria in response to expansion of the ECF volume and a subsequent increase in blood pressure.
- The heart produces ANP, which is stored in granules in specialized atrial myocardial cells. ANP is released when muscle cells are mechanically stretched by expansion of the ECF volume (fig. 14-20).
- Importantly, derangements تعطيل of this system could logically contribute to hypertension. In fact, recent studies suggest that a deficiency of the counterbalancing natriuretic system may underlie some cases of long-term hypertension by leaving the powerful Na^+-conserving system unopposed.

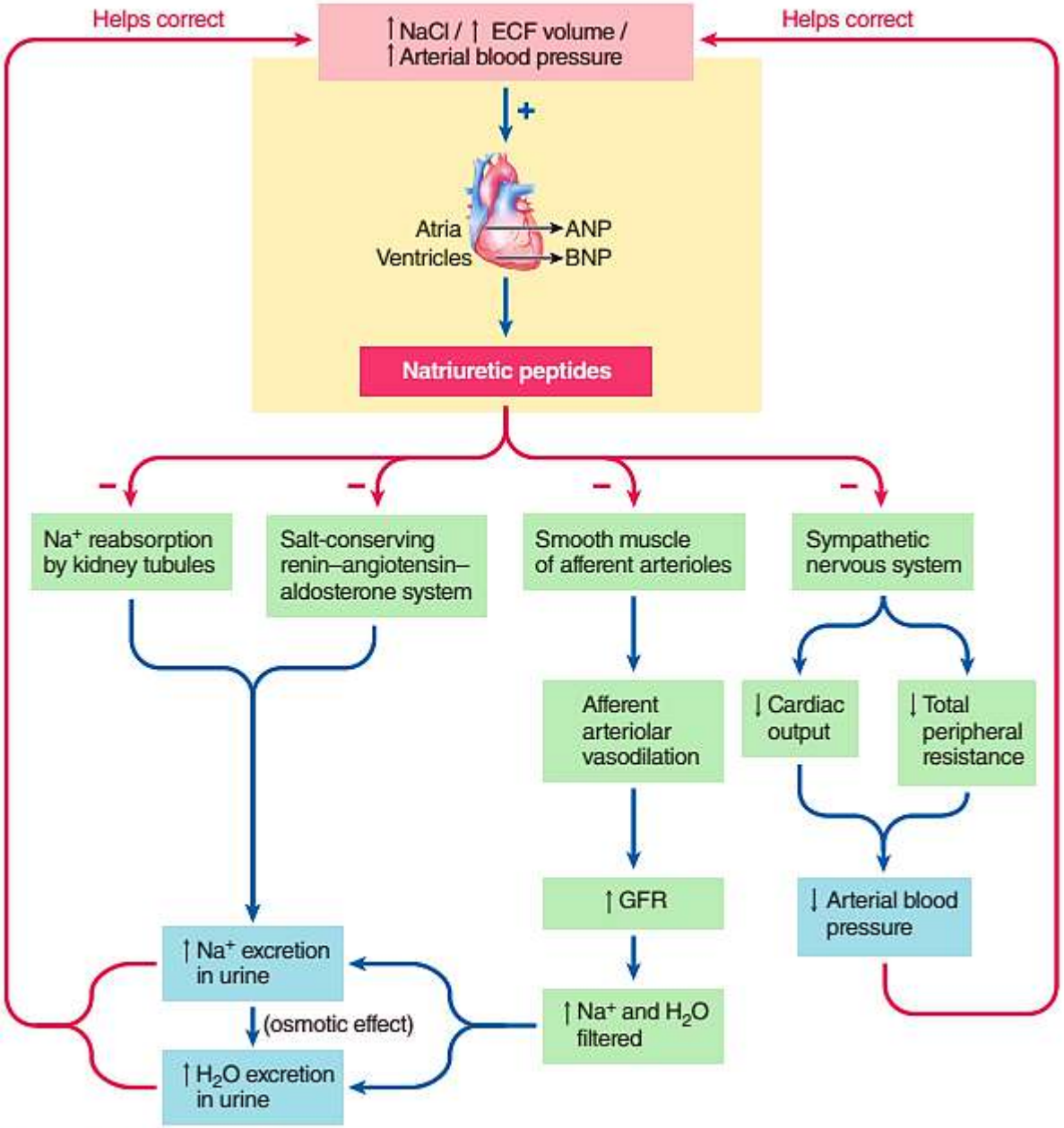


Figure 14-17 Atrial and brain natriuretic peptide. The cardiac atria secrete the hormone atrial natriuretic peptide (ANP) and the cardiac ventricles secrete brain natriuretic peptide (BNP) in response to being stretched by Na^+ retention, expansion of the ECF volume, and increase in arterial blood pressure. ANP and BNP, in turn, promote natriuretic, diuretic, and hypotensive effects to help correct the original stimuli that resulted in their release.

Glucose and amino acids are reabsorbed by Na^+-dependent secondary active transport

- In addition to driving the re-absorption of Na^+, the energy used to supply the Na^+-K^+ATPase carrier is also ultimately responsible for the reabsorption of organic nutrient molecules from the proximal tubule by secondary active transport. Specific cotransport carriers located at the luminal border of the proximal tubular cell are driven by the Na^+ concentration gradient to selectively transport glucose or an amino acid from the luminal fluid into the tubular cell, from which the nutrient eventually enters the plasma.
- In other words, the lumen-to-cell Na^+ concentration gradient maintained by the energy-consuming basolateral Na^+-K^+ pump drives this cotransport system and pulls the organic molecule against its concentration gradient without the direct expenditure of energy. Because the overall process of glucose and amino acid reabsorption depends on the use of energy, these organic molecules are considered to be actively reabsorbed, even though energy is not used directly to transport them across the membrane.
- Secondary active transport requires the presence of Na^+ in the lumen; without Na^+ the cotransport carrier is inoperable. Once transported into the tubular cells, glucose and amino acids passively diffuse down their concentration gradients across the basolateral membrane into the plasma, facilitated by a carrier that is not dependent on energy.

In general, actively reabsorbed substances exhibit a tubular maximum

- Each carrier is specific for the types of substances it can transport; for example, the glucose cotransport carrier cannot transport amino acids, or vice versa.
- Because these carriers, like the organic-nutrient cotransport carriers can become saturated, each exhibits a maximal carrier-limited transport capacity, or **Tubular maximum (T_m)**. Once the filtered load of an actively reabsorbed substance exceeds the T_m, reabsorption proceeds at a constant maximal rate, with the additional filtered quantity of the substance being excreted in urine, because Aldosterone promotes the synthesis of more active Na^+-K^+ carriers in the distal and collecting tubular cells as needed.

☞ We will compare glucose, a substance that has a T_m but *is not regulated* by the kidneys, with phosphate, a T_m-limited substance that *is regulated* by the kidneys.

Glucose is an example of an actively reabsorbed substance that is not regulated by the kidneys

- The normal plasma concentration of glucose is 100 mg of glucose/100ml of plasma, as in plasma filtered. The quantity of any substance filtered per minute, known as its **filtered load**, can be calculated as follows:

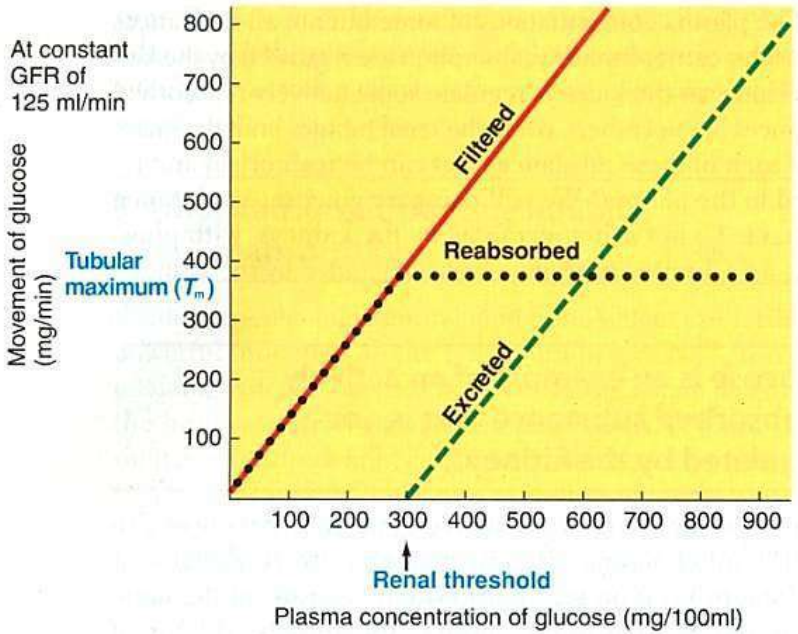
  Filtered load of Glucose = 100mg/100ml x 125ml/min = 125 mg/min

- At a constant GFR, the filtered load of glucose is directly proportional to the plasma glucose concentration (fig.14-21).

➢ **Tubular maximum for glucose**

- The T_m for glucose averages 375 mg/min, ordinarily, no glucose appears in in the urine. Not until the filtered load of glucose exceeds the T_m. Accordingly, the plasma glucose concentration must be greater than 300 mg/100 ml, **renal threshold for glucose** – more than three times the normal value- before glucose starts spilling into the urine.
- Beyond the T_m , reabsorption remains constant at its maximum rate, and any further increase in filtered load is accompanied by a directly proportional increase in amount of the substance excreted (fig.14-21).

➢ **Reason why the kidneys do not regulate glucose;** the kidneys do not regulate glucose, because they do not maintain glucose at some specific plasma concentration; instead, this concentration is normally regulated by endocrine and liver mechanisms, except when excessively high levels overwhelm the kidney's reabsorptive capacity.



Plasma concentration of substance × GFR = Amount of substance filtered

For example, 100 mg glucose/100 ml plasma × 125 ml plasma filtered/min = 125 mg glucose filtered/min

Plasma Concentration (mg/100ml)	GFR (ml/min)	Amount Filtered (mg/min)	T_m (mg/min)	Amount Reabsorbed (mg/min)	Amount Excreted (mg/min)
a. 80	125	100	375	100	0
b. 100	125	125	375	125	0
c. 200	125	250	375	250	0
d. 300	125	375	375	375	0
e. 400	125	500	375	375	125
f. 500	125	625	375	375	250

Phosphate is an example of an actively reabsorbed substance that is regulated by the kidneys

- Our diets are generally rich in PO_4^{3-} , but because the tubules can reabsorb up to the normal plasma concentration's worth of PO_4^{3-} and no more, the excess ingested PO_4^{3-} is quickly spilled into urine, restoring the plasma concentration to normal.
- ***Parathyroid hormone*** can alter the renal thresholds for PO_4^{3-} and Ca^{2+}, thus adjusting the quantity of these electrolytes conserved, depending on the body's momentary needs.
- normal plasma concentration = (2.4 – 5.4 mg/dl)

Active Na^+ reabsorption is responsible for the passive reabsorption of Cl^-, H_2O and urea

➢ Chloride reabsorption

- The negatively charged chloride ions are passively reabsorbed down the electrical gradient created by the active reabsorption of the positively charged sodium ions, passing between, not through the tubular cells. The amount of Cl^- reabsorbed is determined by the rate of active Na^+ reabsorption, instead of being directly controlled by the kidneys.

➢ Water reabsorption

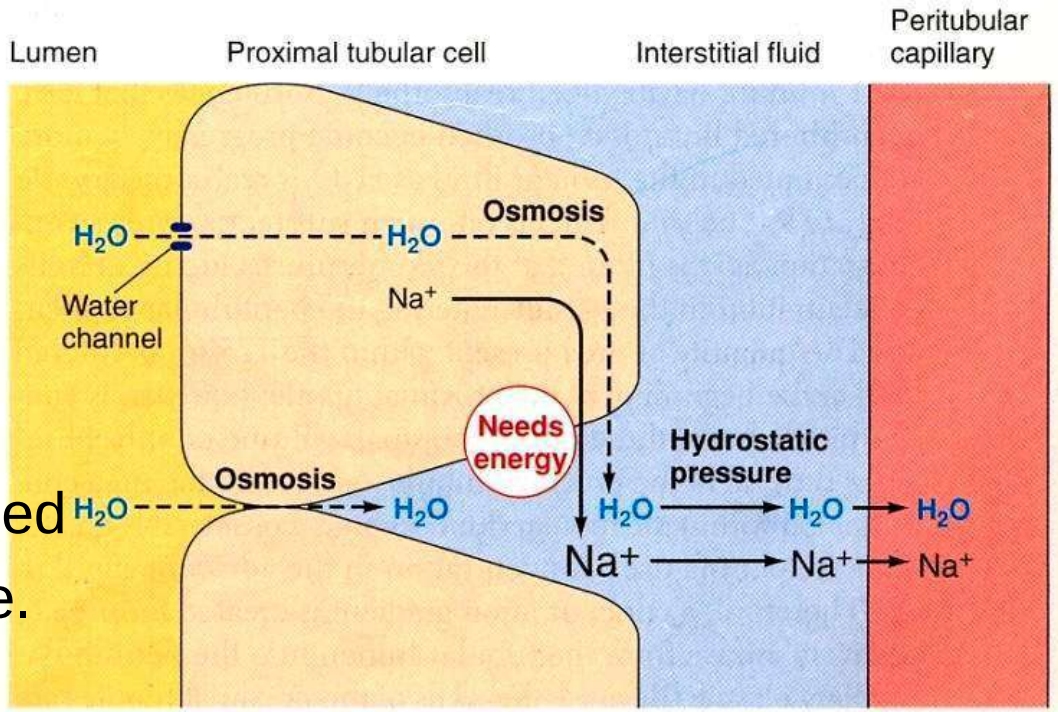
- Water is passively reabsorbed as a result of the osmotic gradient created by active Na^+ reabsorption.
- Of the H_2O filtered, 80% is obligatorily reabsorbed in the proximal tubules and loops of Henle, regardless of the H_2O load in the body. The remaining 20% are reabsorbed in the distal portions of the tubule, is subject to direct hormonal control, depending on the body's state of hydration. H_2O passes through **aquaporins**, or **water channels**. Different types of water channels in the proximal tubule are always open are regulated by the hormone ***vasopressin***.

- The main force for H_2O reabsorption in the proximal tubule is a compartment of hypertonicity in the lateral spaces that is established by the active extrusion of Na^+ by the basolateral pump (fig.14-22), either through the cells or intercellularly through “leaky” tight junctions. Also osmotically follows other solutes such as glucose .
- The return of filtered H_2O to the plasma is enhanced by the fact that the plasma-colloid osmotic pressure is greater in the peritubular capillaries than elsewhere.
- This force tends to “pull” H_2O into the peritubular capillaries, simultaneous with the “push” of the hydrostatic pressure in the lateral spaces that drives H_2O toward the capillaries. By these means, 65% of the filtered H_2O 117 L/day, is passively reabsorbed by the end of the proximal tubule.

FIGURE 14-22

Water reabsorption in the proximal tubule

The force for H_2O reabsorption is the compartment of hypertonicity in the lateral spaces established by active extrusion of Na^+ by the basolateral pump. The dashed arrows show the direction of osmotic movement of H_2O.



Urea reabsorption

- **Urea** is a waste product resulting from the breakdown of protein. The osmotically induced reabsorption of H_2O in the proximal tubule secondary to active Na^+ reabsorption produces a concentration gradient for urea that favors passive reabsorption of this nitrogenous waste (fig.14-23).
- Only about 50% of the filtered urea is passively reabsorbed by this means. The urea concentration in the plasma becomes elevated only in impaired kidney function, when much less than half of the urea is removed.
- Accordingly, clinical measurement of **blood urea nitrogen (BUN)** came into urea as a crude assessment of kidney function. Health professionals still often refer to renal failure as **uremia** "urea in the blood", indicating excess urea in the blood, even though urea retention is not this condition's major threat, but H^+ and K^+ which itself is not especially toxic.

➢ **In general, unwanted waste products are not reabsorbed**

- The other waste products,(e.g. *phenol* and *creatinine*) which are not reabsorbed, remain in urine in highly concentrated form.

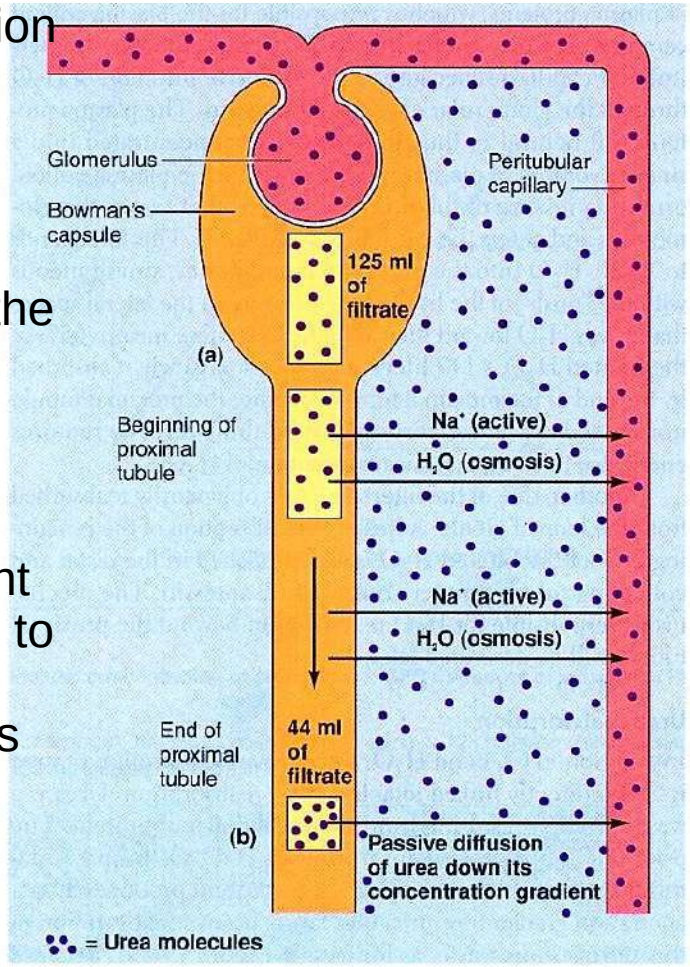


FIGURE 14-23
Passive reabsorption of urea at the end of the proximal tubule
(a) In Bowman's capsule and at the beginning of the proximal tubule, urea is at the same concentration as in the plasma and surrounding interstitial fluid. (b) By the end of the proximal tubule, 65% of the original filtrate has been reabsorbed, concentrating the filtered urea in the remaining filtrate. This establishes a concentration gradient favoring passive reabsorption of urea.

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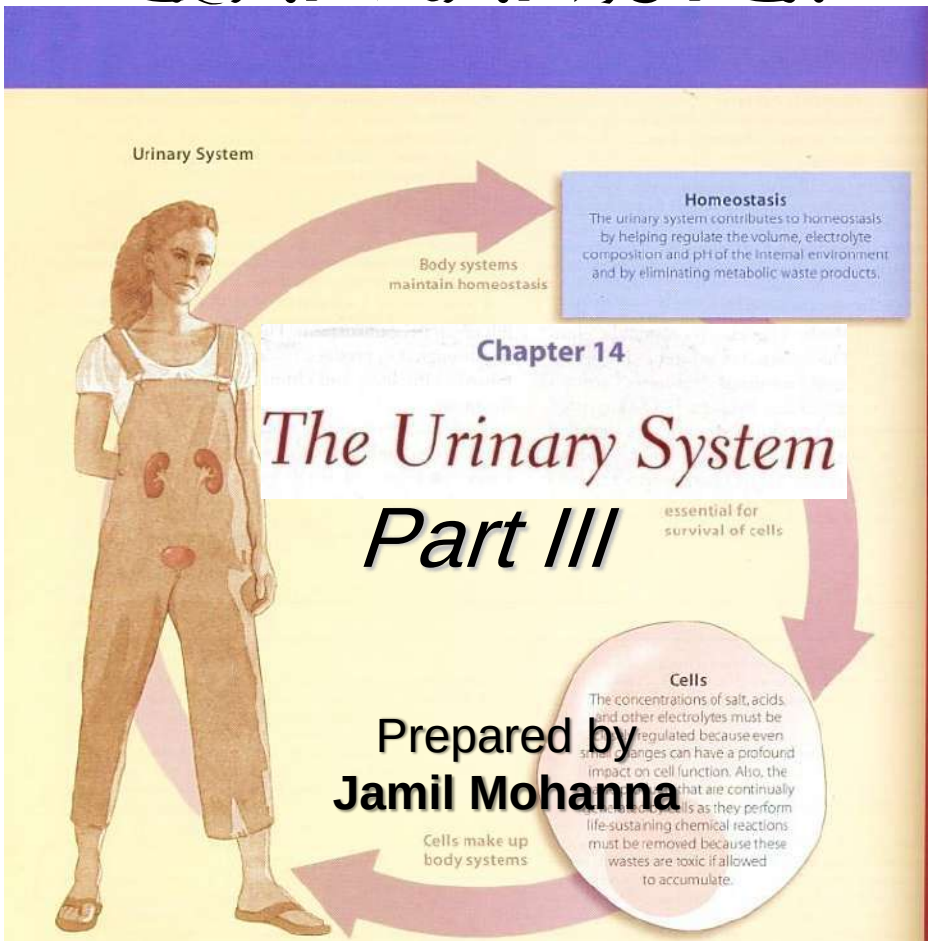


Chapter 14

The Urinary System

Part III

Prepared by

Jamil Mohanna

The survival and proper functioning of cells depend on the maintenance of stable concentrations of salt, acids, and other electrolytes in the internal fluid environment. Cell survival also depends on continual removal of the toxic metabolic wastes that cells produce as they perform life-sustaining chemical reactions. The kidneys play a major role in maintaining homeostasis by regulating the concentration of many plasma constituents, especially electrolytes and water, and by eliminating all metabolic wastes (except CO_2, which is removed by the lungs). As plasma repeatedly filters through the kidneys, they retain constituents of value for the body and eliminate undesirable or excess materials in urine. Of special importance is the kidneys' ability to regulate the volume and osmolarity (solute concentration) of the internal fluid environment by controlling salt and water balance. Also crucial is their ability to help regulate pH by controlling elimination of acid and base in urine.

Tubular Secretion

- Tubular secretion also involves transepithelial transport, in this case from the peritubular capillary plasma into the tubular lumen.
- By tubular secretion, the kidney tubules can selectively add some substances to the quantity already filtered. Secretion of substances hastens their excretion in urine.
- The most important secretary systems are for **(1)** H^+, which is important in regulation acid-base balance; **(2)** K^+, which keeps the plasma K^+ concentration at an appropriate level to maintain normal membrane excitability in muscles and nerves; and **(3)** organic anions and cations, which accomplishes more efficient elimination of foreign organic compounds form the body.

➢ **Hydrogen ion secretion is important in acid-base balance**

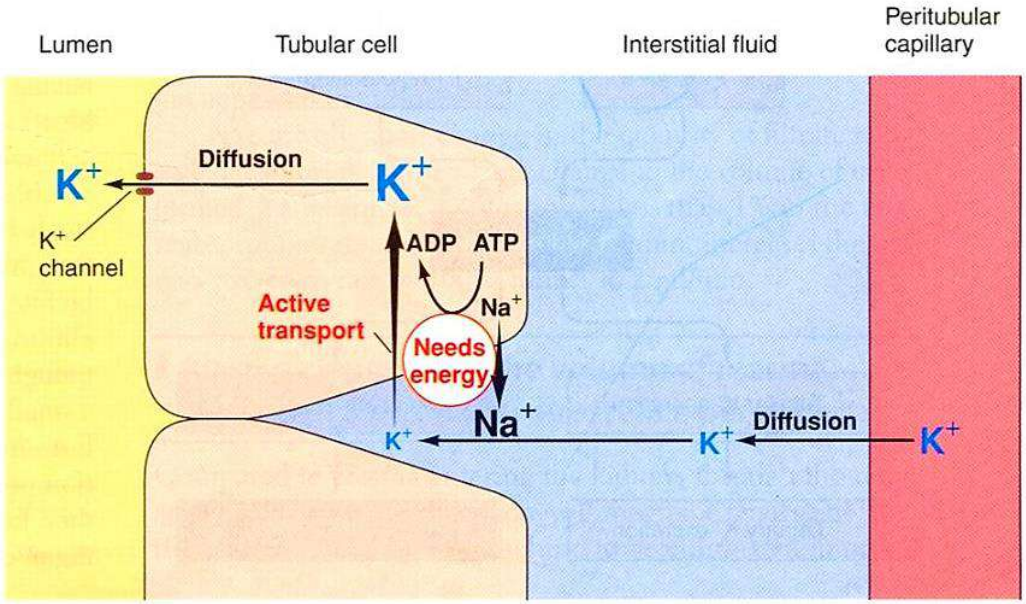
- H^+ is secreted by the proximal, distal, and collecting tubules. The extent of H^+ secretion depends on the acidity of the body fluids.

➢ **Potassium secretion is controlled by aldosterone**

- **Na^+** reabsorption early in the tubule occurs in a constant, unregulated fashion, whereas K^+ secretion later in the tubule is variable and subject to regulation. During K^+ depletion, K^+ secretion in the distal portions of the nephron is reduced to a minimum, so only the small percentage of filtered K^+ that escapes reabsorption in the proximal tubule is excreted in the urine.

Mechanism of K^+ secretion

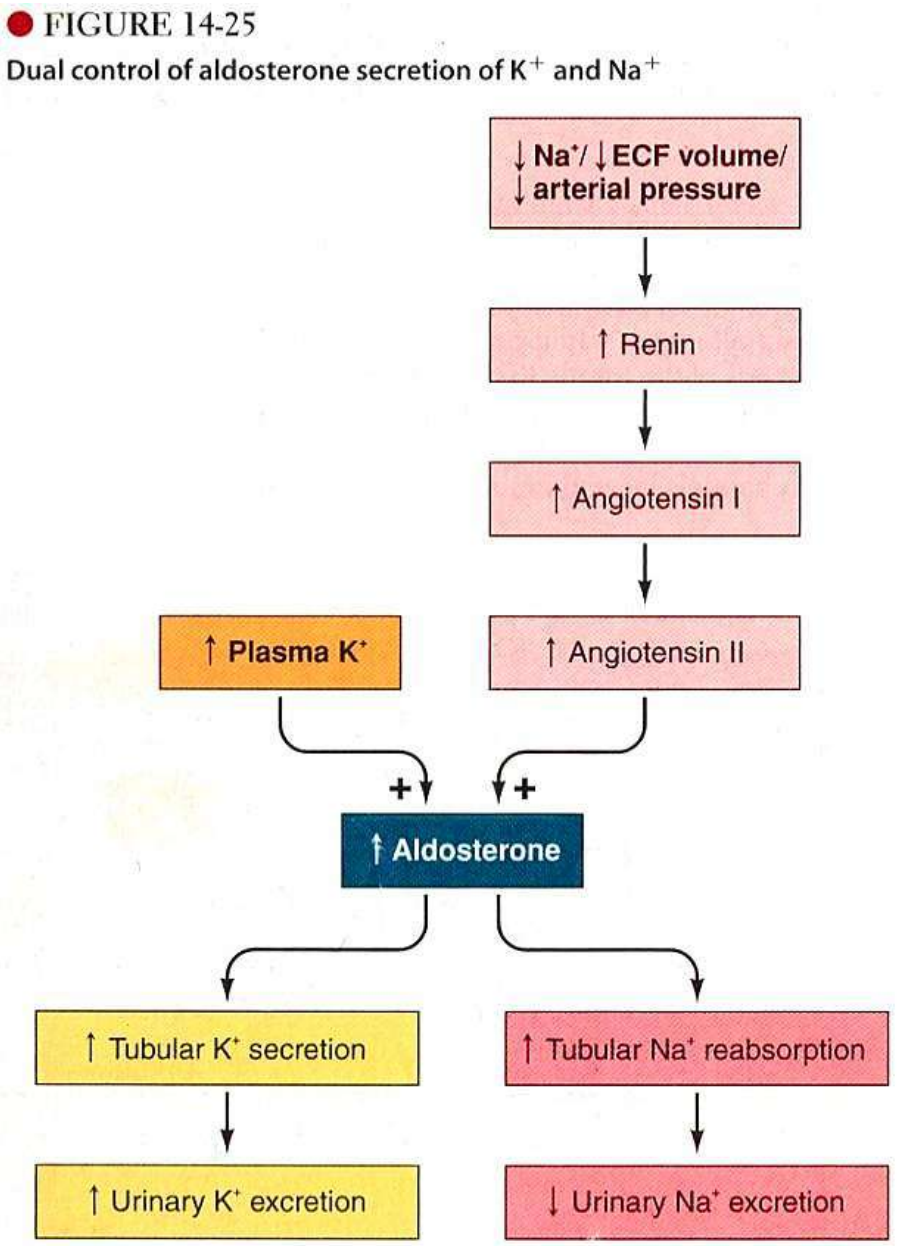
- Potassium secretion in the distal and collecting tubules is coupled to Na^+ reabsorption by means of the energy-dependent basolateral Na^+-K^- pump.



- The basolateral pump actively induces the net secretion of K^+ from the peritubular capillary plasma into the tubular lumen.
- Why isn't K^+ secreted throughout the Na^+-reabsorbing segments of the tubule instead of taking place only in the distal parts of the nephron? The answer lies in the location of the passive K^+ channels; in the distal and collecting tubules, the K^+ channels are concentrated in the luminal membrane, providing a route for K^+ pumped into the cell to exit into the lumen, thus being secreted. In *the other tubular segments*, the K^+ channels are located primarily in *the basolateral membrane* .

Control of K^+ secretion

- An elevation in plasma K^+ concentration directly stimulates the adrenal cortex to increase its output of aldosterone, stimulates K^+ secretion by the tubular cells late in the nephron simultaneous to enhancing these cells' reabsorption of Na^+, and vice versa.
- Note that a rise in plasma K^+ concentration directly stimulates aldosterone secretion by the adrenal cortex, whereas a fall in plasma Na^+ concentration stimulates aldosterone secretion by means of the complex renin-angiotensin pathway.
- For this reason, K^+ secretion can be stimulated by Na^+ depletion, the resulting inappropriate loss lead to K^+ deficiency.



Effect of H^+ secretion on K^+ secretion

- The basolateral pump in the distal portions of the nephron can secrete either K^+ or H^+ in exchange for reabsorbed Na^+.
- Normally the kidneys secrete a preponderance أكثرية of K^+, but when the body fluids are too acidic and H^+ secretion is increased, leads to inappropriate K^+ retention in the body fluids.

➢ **Importance of regulating plasma K^+ concentration**

- The kidneys usually exert a fine degree of control over plasma K^+ concentration, because even minor fluctuations in plasma K^+ concentration can have detrimental consequences, in the membrane electrical activity of excitable tissues, can alter the intracellular-to-extracellular K^+ concentration gradient, which in turn can change the resting membrane potential. A rise in ECF K^+ concentration leads to a reduction in resting potential and a subsequent increase in excitability, especially of heart rate and even fatal cardiac arrhythmias.
- Conversely, *a fall in ECF K^+ concentration results in hyperpolarization of nerve and muscle cell membranes, which reduces their excitability*. Its manifestations are muscle weakness, diarrhea and abdominal distension caused by smooth muscle dysfunction, and abnormalities in cardiac rhythm and impulse conduction.

Organic anion and cation secretion helps efficiently eliminate foreign compounds from the body

- The proximal tubule contains two types of carriers: (1) for the secretion of organic anions and (2) organic cations, serve several important functions:

1. Facilitate excretion of theses substances like certain blood-borne chemical messengers such as prostaglandins, histamine, and norepinephrine, that having served their purpose.
2. Organic ions are poorly soluble in water, they are extensively but not irreversibly bound to plasma proteins. It cannot be filtered through the glomeruli. A small percentage of the ion always exist in free or unbound form in the plasma. Removal of this free organic ion by secretion permits “unloading” of some of the bound ion, which is then free to be secreted.
3. The organic ion systems can secrete a large number of different organic ions, both those produced endogenously (within the body) and those foreign organic ions that have gained access to the body fluids, including food additives, environmental pollutants (for example, pesticides), drugs, and other nonnutritive organic substances that have entered the body.

* Many foreign organic chemicals are not ionic in their original form. The liver converts these foreign substances into an anionic form that facilitates their secretion by the organic anion system and thus accelerates their elimination. Such as penicillin and NSAIDs, eliminated by means of the proximal tubule organic-ion secretary systems.

Summary of reabsorptive and secretory processes

- Table 14-3.
- To generalize, the proximal tubule dose most of the reabsorbing, transfers much of the filtered water and needed solutes back into he blood in unregulated fashion.
- The distal and collecting tubules then determine the final amount of H_2O, Na^+, K^+ and H^+ by "fine-tuning" the amount of Na^+ and H_2O reabsorbed and the amount of K^+ and H^+ secreted, depending on the body's momentary needs.

▲ TABLE 14-3
Summary of Transport across Proximal and Distal Portions of the Nephron

Proximal Tubule	
Reabsorption	**Secretion**
67% of filtered Na^+ actively reabsorbed; not subject to control; Cl^- follows passively	Variable H^+ secretion depending on acid–base status of body
All filtered glucose and amino acids reabsorbed by secondary active transport; not subject to control	Organic ion secretion; not subject to control
Variable amounts of filtered PO_4^{3-} and other electrolytes reabsorbed; subject to control	
65% of filtered H_2O osmotically reabsorbed; not subject to control	
50% of filtered urea passively reabsorbed; not subject to control	
Almost all filtered K^+ reabsorbed; not subject to control	

Distal Tubule and Collecting Duct	
Reabsorption	**Secretion**
Variable Na^+ reabsorption, controlled by aldosterone; Cl^- follows passively	Variable H^+ secretion, depending on acid–base status of body
Variable H_2O reabsorption, controlled by vasopressin	Variable K^+ secretion, controlled by aldosterone

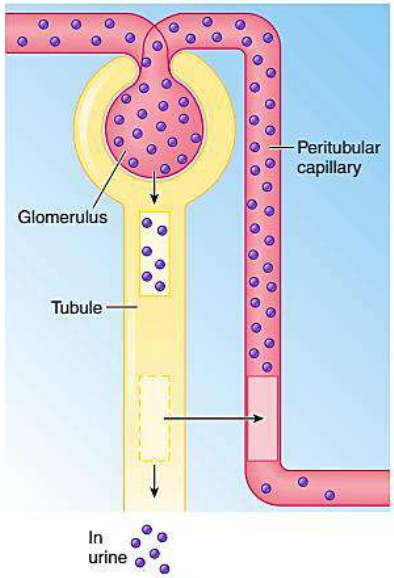
Urine excretion and plasma clearance

- Of the 125ml/min filtered in the glomeruli, normally only 1 ml/min remains in the tubules to be excreted as urine.
- A relatively small change in the quantity of filtrate reabsorbed can bring about a large change in the volume of urine formed.
- Only wastes and excess electrolytes not wanted by the body are left behind, dissolved in a given volume of H_2O to be eliminated in urine.

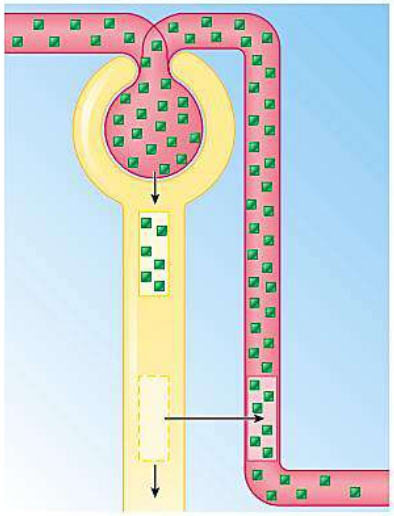
➢ **Plasma clearance is the volume of plasma cleared of a particular substance per minute**

- The **plasma clearance** of any substance is defined **as the volume of plasma completely cleared of that substance by the kidneys per minute**, *not the amount of the substance removed*.
- Plasma clearance is actually a more useful measure than urine excretion.

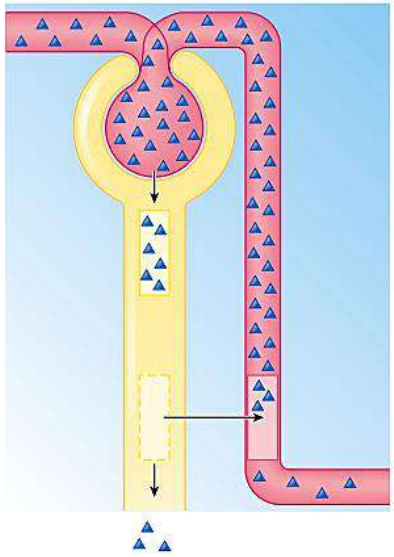
$$\text{clearance rate of a substance (ml/min)} = \frac{\text{urine conc. Of the substance} * \text{urine flow rate (ml/min)}}{\text{plasma conc. Of the substance}}$$



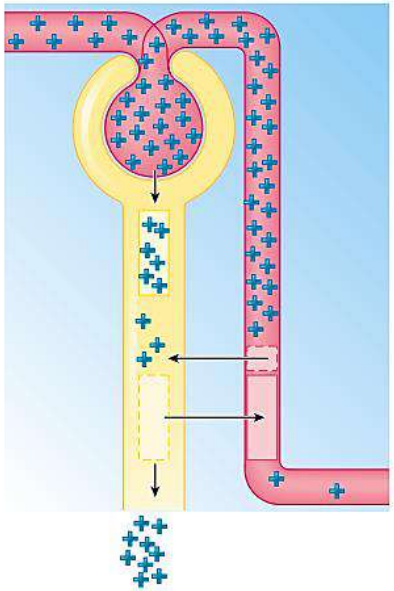
(a) For a substance filtered and not reabsorbed or secreted, such as inulin, all of the filtered plasma is cleared of the substance.



(b) For a substance filtered, not secreted, and completely reabsorbed, such as glucose, none of the filtered plasma is cleared of the substance.



(c) For a substance filtered, not secreted, and partially reabsorbed, such as urea, only a portion of the filtered plasma is cleared of the substance.



(d) For a substance filtered and secreted but not reabsorbed, such as hydrogen ion, all of the filtered plasma is cleared of the substance, and the peritubular plasma from which the substance is secreted is also cleared.

Figure 14-23 Plasma clearance for substances handled in different ways by the kidneys.

If a substance is filtered but not reabsorbed or secreted, its plasma clearance rate equals the GFR

- Assume that a plasma constituent, substance X, is freely filterable at the glomerulus but is not reabsorbed or secreted. As 125 ml/min of plasma are filtered and subsequently reabsorbed, thus 125 ml of plasma are cleared of substance X each minute (fig14-26a), e.g. **inulin**, produced by Jerusalem artichokes.

Clearance rate for inulin $= \frac{\text{30 mg/ml urine} \times \text{1.25 ml urine/min}}{\text{0.30 mg/ml plasma}} = \text{125 ml plasma/min}$

- **If a substance is filtered and reabsorbed but not secreted its plasma clearance rate is always less than the GFR**, (fig. 14-26 b,c).
- **If a substance is filtered and secreted but not reabsorbed, its plasma clearance rate is always greater than the GFR**
- H^+, not only is filtered plasma cleared of nonreabsorbable H^+, but the plasma from which H^+ is secreted is also cleared of H^+. For example, if the quantity of H^+ secreted is equivalent to the quantity of H^+ present in 25 ml of plasma, the clearance rate for H^+ will be 150 ml/min at the normal GFR of 125 ml/min (fig.14-26d).

- **Para-aminohippuric acid (PAH),** can be used to measure renal plasma flow, it is freely filterable and nonreabsorbable. It differs than inulin that all the PAH in the plasma that escapes filtration is secreted from the peritubular capillaries by means of the organic anion secretory pathway in the proximal tubule.
- So, the plasma clearance for PAH is a reasonable estimate of the rate of plasma flow through the kidneys.
- Typically, renal plasma flow averages 625 ml/min, for a renal blood flow of 1,140 ml/min over 20% of the cardiac output.

➢ **Filtration fraction**

- You can easily determine the filtration fraction; the fraction of the plasma flowing through the glomeruli that is filtered into the tubules:

$$\text{filtration fraction} = \frac{\text{GFR (plasma inulin clearance)}}{\text{renal plasma flow (plasma PAH clearance}} = \frac{125 \text{ ml/min}}{625 \text{ ml/min}} = 20\ \%$$

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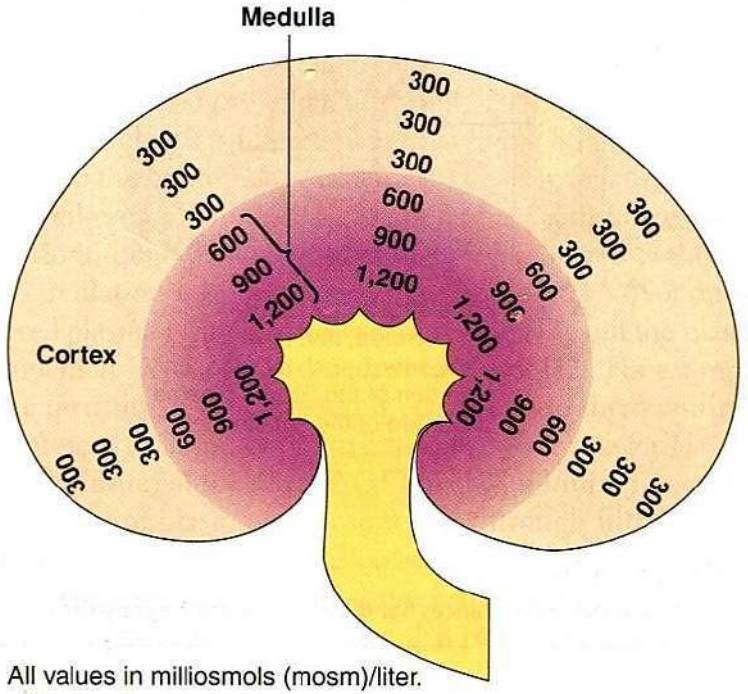
* A large **vertical osmotic gradient** is uniquely maintained in the interstitial fluid of the medulla of each kidney. The concentration increases from the cortical boundary down through the depth of the renal medulla until it reaches a maximum of 1,200 mosm/L, (fig.14-27)

- When the body is overhydrated, the kidneys can produce a large volume of dilute urine (up to 25 ml/min and hypotonic at 100 mosm/L), thus eliminating the excess H_2O in the urine. Conversely, the kidneys can put out a small volume of concentrated urine (down to 0.3 ml/min and hypertonic at 1,200 mosm/L) when the body is dehydrated (too little H_2O), thus conserving H_2O for the body.
- This variable reabsorption is made possible by a vertical osmotic gradient ranging from 300 to 1,200 mosm/l in the modularly interstitial fluid, established by the long loops of Henle of the juxtamedullary nephrons by means of the countercurrent system.

● FIGURE 14-27

Vertical osmotic gradient in the renal medulla
The osmolarity of the interstitial fluid throughout the renal cortex is isotonic at 300 mosm/liter, but the osmolarity of the interstitial fluid in the renal medulla increases progressively from 300 mosm/liter at the boundary with the cortex to a maximum of 1,200 mosm/liter at the junction with the renal pelvis.



The medullary vertical osmotic gradient is established by countercurrent multiplication

- By the end of the proximal tubule about 65% of the filtrate has been reabsorbed, but the 35% remaining in the tubular lumen still has the same osmolarity as the body fluids. Additional 15% of the filtered H_2O is obligatorily reabsorbed from the loop of Henle during the establishment and maintenance of the vertical osmotic gradient.

➢ **Properties of the descending and ascending limbs of along Henle's loop**

- ***The descending limb:***

1. Is highly permeable to H_2O.
2. Does not actively reabsorb Na^+. It is the only segment of the entire tubule that does not do so.

- ***The ascending limb:***

1. Actively transports NaCl out of the tubular lumen.
2. Is always impermeable to H_2O.

Benefits of countercurrent multiplication

Such a mechanism offers two benefits;

First, it establishes a **vertical osmotic gradient** in the medullary interstitial fluid, used by the collecting ducts to concentrate the tubular fluid so that a urine *more concentrated than normal body fluids can be secreted.*

Second, the fact that the fluid is hypotonic as it enters the distal portions of the tubule enables the kidneys to excrete a urine *more dilute* than normal body fluids. ***HOW??***

Vasopressin-controlled, variable H_2O reabsorption occurs in the final tubular segments

20% of the filtered H_2O remains in the lumen to enter the distal and collecting tubules for variable reabsorption that is under hormonal control, 20% × GFR (180 L/day) = 3 liters per day ((13 times the amount of plasma H_2O)).

The (100 mosm/l) fluid leaving the loop of Henle enters the distal tubule surrounding by isotonic (300 mosm/l) interstitial fluid of the renal cortex then empties into the collecting tubule, which is bathed by progressively increasing concentrations (300 to 1,200 mosm/l) of surrounding interstitial fluid as it descends through the medulla.

Role of vasopressin

- For H_2O absorption to occur two criteria must be met: (1) an osmotic gradient across the tubule, and (2) the tubular permeable to H_2O. The distal and collecting tubules are *impermeable* to H_2O except in the presence of **vasopressin**, as **antidiuretic hormone (ADH)**.
- Vasopressin is produced by the *hypothalamus,* then stored in the *posterior pituitary gland*. In negative-feedback fashion, vasopressin secretion is stimulated by a H_2O deficit, when the ECF is too concentrated and vice versa.
- Vasopressin reaches the basolateral membrane with receptors specific for it .
- Vasopressin influences H_2O permeability only in the distal and collecting tubules.

It has no influence over the 80% of the filtered H_2O that is obligatorily reabsorbed without control in the proximal tubule and loop of Henle.

The ascending limb of Henle's loop is always impermeable to H_2O, even in the presence of vasopressin.

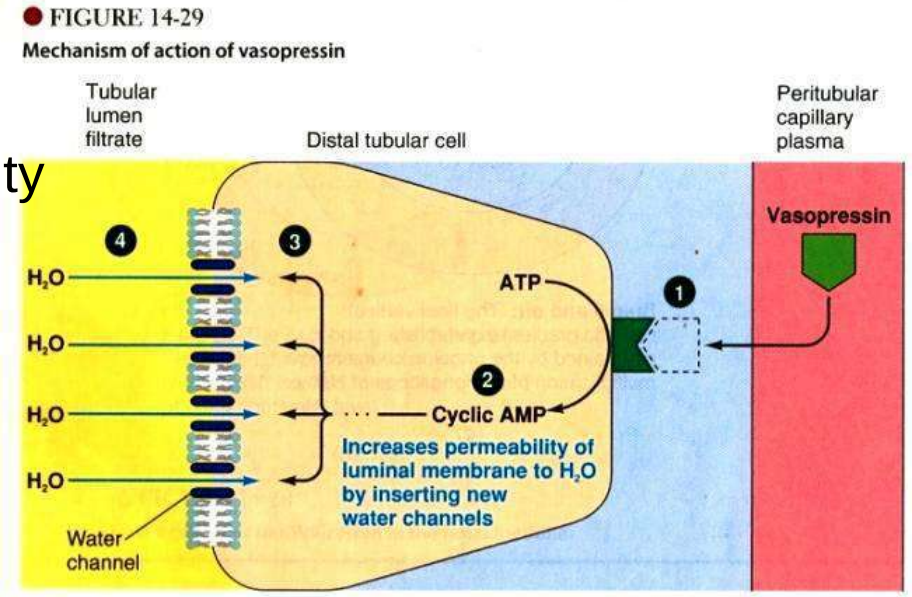
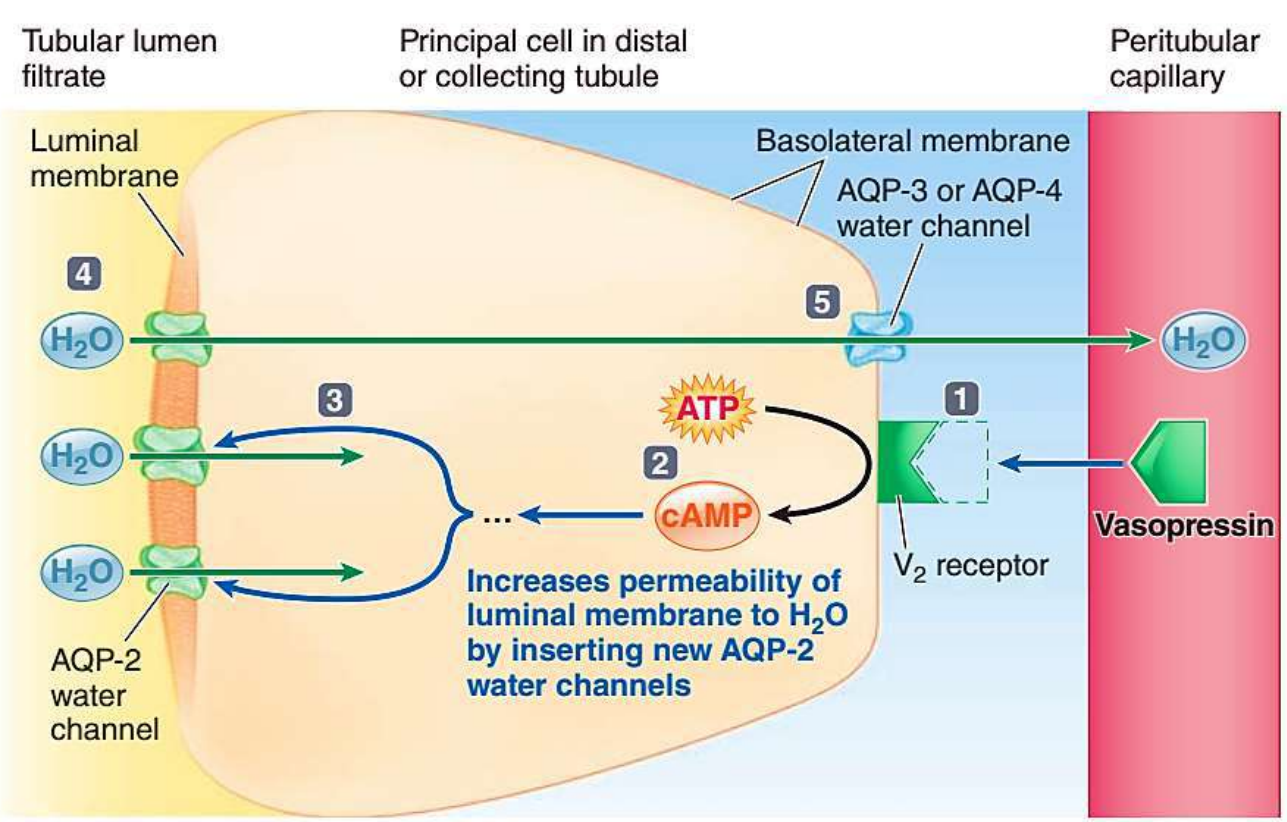


FIGURE 14-29
Mechanism of action of vasopressin

1. Blood-borne vasopressin binds with its receptor sites on the basolateral membrane of a distal or collecting tubule cell.
2. This binding activates the cyclic AMP second-messenger system within the cell.
3. Cyclic AMP increases the opposite luminal membrane's permeability to H_2O by promoting the insertion of water channels in this membrane. This membrane is impermeable to water in the absence of vasopressin.
4. Water enters the tubular cell from the tubular lumen through the water channels and subsequently enters the blood, in this way being reabsorbed.



1 Blood-borne vasopressin binds with its receptor sites on the basolateral membrane of a principal cell in the distal or collecting tubule.

2 This binding activates the cyclic AMP (cAMP) second-messenger pathway within the cell.

3 Cyclic AMP increases the opposite luminal membrane's permeability to H_2O by promoting the insertion of vasopressin-regulated AQP-2 water channels into the membrane. This membrane is impermeable to water in the absence of vasopressin.

4 Water enters the tubular cell from the tubular lumen through the inserted water channels.

5 Water exits the cell through different, always open water channels (either AQP-3 or AQP-4) permanently positioned at the basolateral border, and then enters the blood, in this way being reabsorbed.

Figure 14-26 Mechanism of action of vasopressin.

Function of the renin-angiotensin-aldosteron system

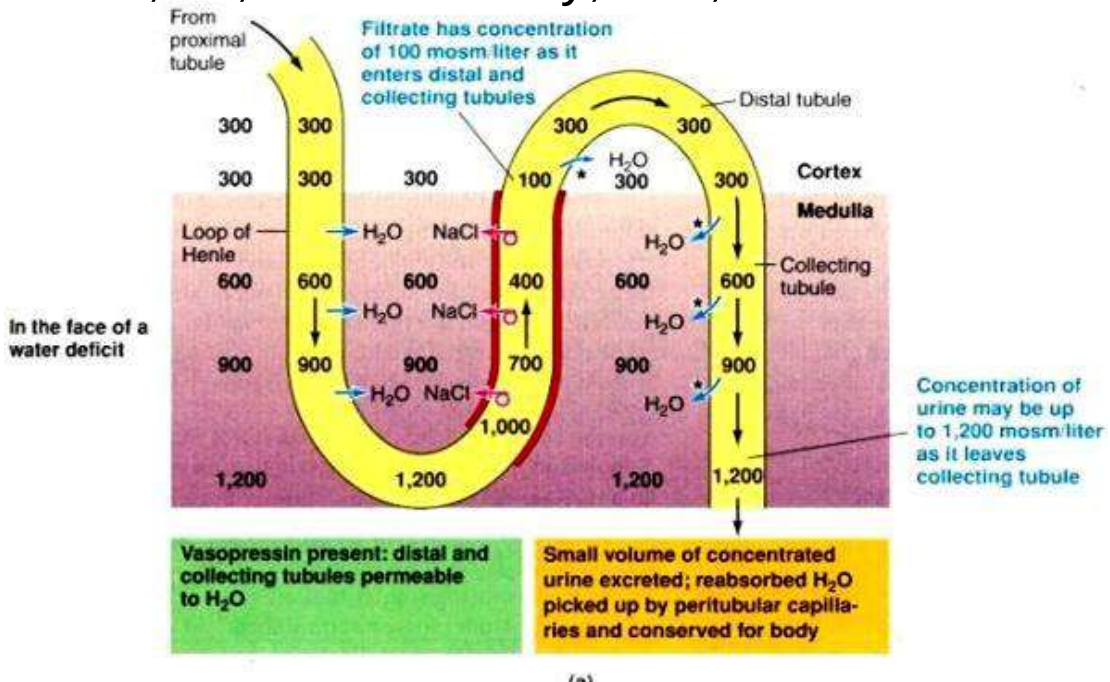
- *Aldosterone* increases Na^+ reabsorption by the distal and collecting tubules, by promoting the insertion of additional Na^+ channels into the luminal membranes and additional Na^+-K^+ ATPase carriers into the basolateral membranes of he distal and collecting tubular cells.
- The renin-angiotensin-aldosteron system thus promotes salt retention and a resultant H_2O retention and elevation of arterial blood pressure (-ve feedback fashion).
- In addition to **(1)** aldosterone secretion **(2)** is also a potent constrictor, thereby increasing total peripheral resistance, **(3)** it stimulates thirst and **(3)** stimulates vasopressin.
- The opposite situation exists when the Na^+ load, ECF and plasma volume, and arterial blood pressure are above normal, this nonreabsorbed Na^+ is lost in urine. An average salt consumer typically excretes about 10g/day, a heavy salt consumer excretes more, and someone who has lost considerable salt during heavy sweating excretes less urinary salt.

➢ **Role of the renin-angiotensin-aldosteron system in various diseases**

- some cases of hypertension are due to abnormal increases in renin-angiotensin-aldosterone activity, also it is responsible in part for the fluid retention and edema accompanying congestive heart failure.
- Na^+ excretion may fall to virtually zero despite continue salt ingestion and accumulation in the body, producing edema and exacerbates the congestive heart failure because the weakened heart cannot pump the additional plasma volume.

Regulation of H_2O reabsorption in response to a H_2O deficit

- The hypotonic tubular fluid entering the distal tubules can lose progressively more H_2O by osmosis into the interstitial fluid as the tubular fluid first flows increasing osmolarity of the medullary interstitial fluid as it plunges toward the renal pelvis (fig. 14-30a). As little as 0.3 ml of urine may be formed each minute, less than one-third the normal urine flow rate of 1 ml/min.
- Vasopressin cannot completely halt urine production, because a minimum volume of H_2O must be excreted with the solute wastes. Collectively, the waste products and other constituents eliminated in the urine average 600 mosm each day. Because the max. urine concentration, is 1,200 mosm/l , the minimum volume of urine that is required to excrete these wastes is 500 ml/day (600 /1,200 = 0,5 L, or 500 ml/day, or 0,3 ml/min.



- The kidneys' ability to tremendously concentrate urine to minimize H_2O loss when necessary is possible only because of the presence of the osmotic gradient in the medulla. If this gradient did not exist, the kidneys could not produce a urine more concentrated than the body fluids no matter how much vasopressin was secreted, because the only driving force for H_2O reabsorption is a concentration differential between the tubular fluid and the interstitial fluid.

Regulation of H_2O reabsorption in response to a H_2O excess

- The excess H_2O must be removed from the body without simultaneously losing solutes that are critical for maintaining homeostasis, so no vasopressin is secreted, so the distal and collecting tubules remain impermeable to H_2O(fig.14-30).
- Urine flow may be increased up to 25ml/min in the absence of vasopressin, compared to the normal urine production of 1ml/min.
- Therefore, the loop of Henle, by simultaneously establishing the medullary osmotic gradient and diluting the tubular fluid before it enters the distal segments, plays a key role in allowing the kidneys to excrete urine that ranges in concentration form 100 to 1,200 mosm/ml.

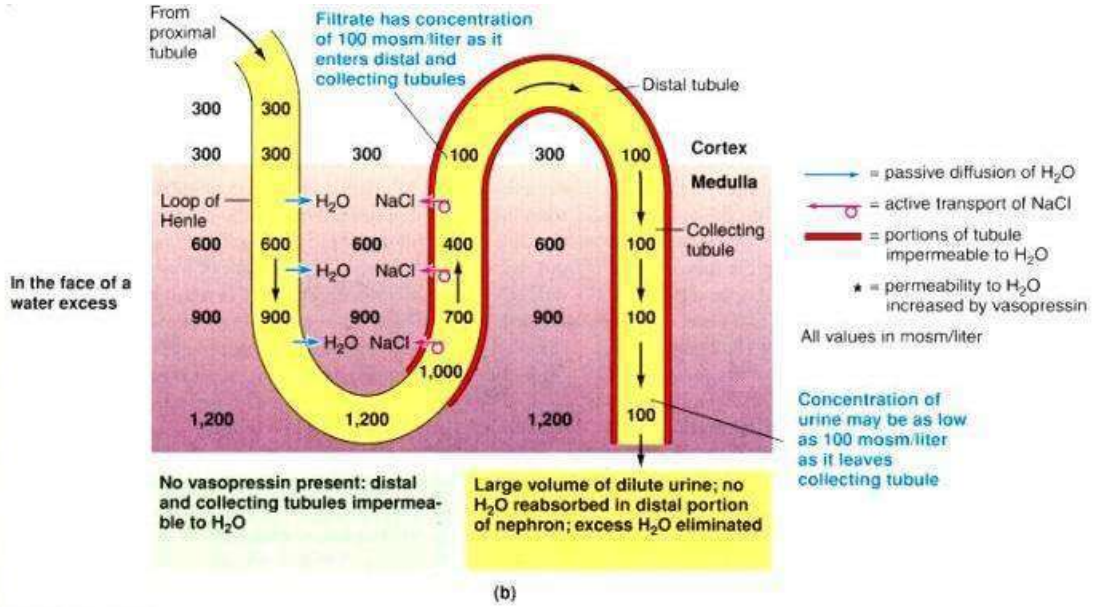


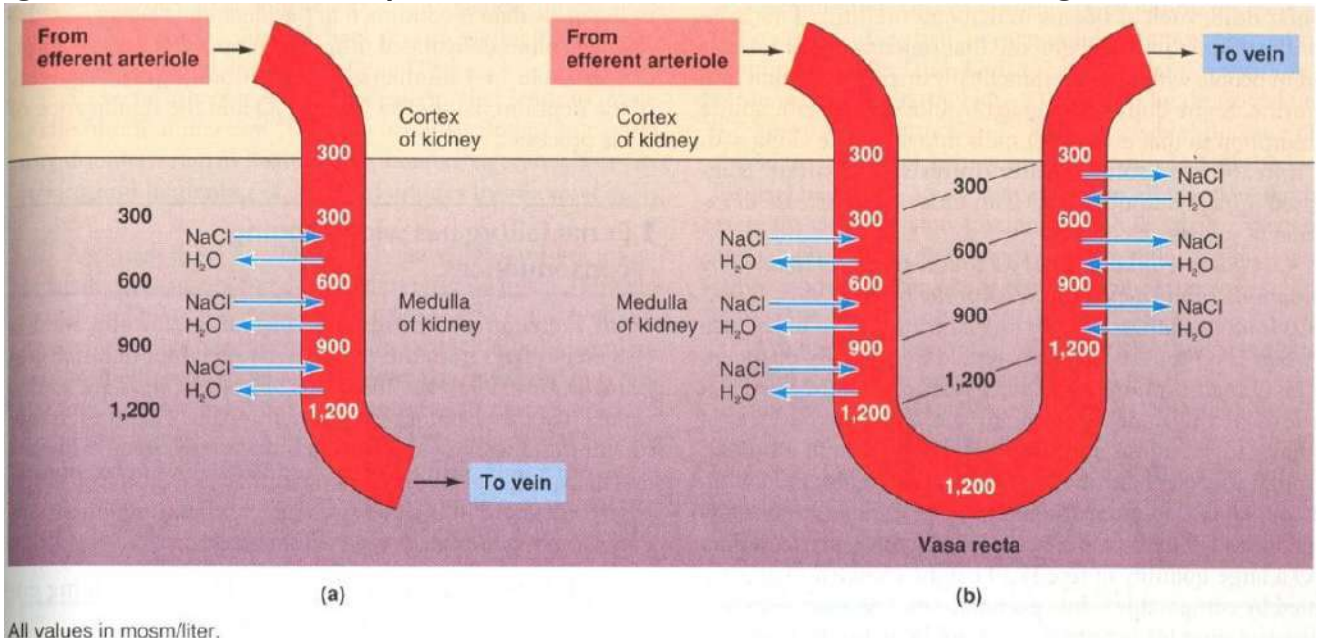
FIGURE 14-30

Excretion of urine of varying concentration depending on the body's needs

Countercurrent exchange within the vasa recta conserves the medullary vertical osmotic gradient

The renal medulla must be supplied with blood to nourish the tissues in this area as well as to transport water that is reabsorbed back to the general circulation. In doing so, its important that it disturb the vertical gradient of hypertonicity. If blood were to flow straight from the cortex to the inner medulla and then directly into the renal vein (fig.14-31a). Because capillaries are freely permeable to NaCl and H_2O, the blood would progressively pick up salt and lose H_2O through passive fluxes down concentration and osmotic gradients. It would be impossible to establish and maintain the medullary hypertonic gradient, because the NaCl would continuously be carried away by the vasa recta (fig.14-31b).

This passive exchange of solute and H_2O between the two limbs of the vasa recta and the interstitial fluid is known as **countercurrent exchange**. It does not *establish* the concentration gradient, rather it *prevents the dissolution* of the gradient.



Water and solute reabsorption versus excreting are only partially coupled

- *In the tubular segments that are permeable to H_2O, solute reabsorption is **always** accompanied by comparable H_2O reabsorption because of osmotic consideration.* therefore, the total volume of H_2O reabsorbed is determined by the total mass of solute reabsorbed (especially of NaCl).
- *Solute excretions is **always** accompanied by comparable H_2O excretion because of osmotic considerations,* e.g. the obligatory excretion of at least a minimal volume of H_2O and osmotic diuresis.
- There are two types of diuresis: **(1) osmotic diuresis** , involves increases excretion of both H_2O and solute caused by excess unreabsorbed solute in the tubular fluid, such as occurs in diabetes mellitus. Some diuretic drugs act by blocking specific solute reabsorption so that extra H_2O spills into the urine along with the unreabsorbed solute, and **(2) water diuresis**, is increases urinary output of H_2O with little or no increase in excretion of solutes.
- *A loss or gain of pure H_2O that is not accompanied by comparable solute deficit or excess in the body that leads of changes in ECF osmolarity*, through the combined effects of vasopressin secretion and the medullary osmotic gradient. Water diuresis is normally a compensatory response to ingestion of too much H_2O, accompanies alcohol ingestion, as alcohol inhibits vasopressin secretion .

Table 14-4 summarizes how various tubular segments of the nephron handle Na^+ and H_2O and the significance of these processes

▲ TABLE 14-4
Handling of Sodium and Water by Various Tubular Segments of the Nephron

	Na^+ Reabsorption		H_2O Reabsorption	
Tubular Segment	Percentage of reabsorption in this segment	Distinguishing features	Percentage of reabsorption in this segment	Distinguishing features
Proximal Tubule	67	Active; uncontrolled; plays a pivotal role in the reabsorption of glucose, amino acids, Cl^-, H_2O, and urea	65	Passive; obligatory osmotic reabsorption following active Na^+ reabsorption
Loop of Henle	25	Active, uncontrolled; Na^+ along with Cl^- reabsorption from the ascending limb helps establish the medullary interstitial vertical osmotic gradient, which is important in the kidneys' ability to produce urine of varying concentrations and volumes, depending on the body's needs	15	Passive; obligatory osmotic reabsorption from the descending limb as the ascending limb extrudes NaCl into the interstitial fluid (that is, reabsorbs NaCl)
Distal and Collecting Tubules	8	Active; variable and subject to aldosterone control; important in the regulation of ECF volume and long-term control of blood pressure; linked to K^+ secretion and H^+ secretion	20	Passive; not linked to solute reabsorption; variable quantities of "free" H_2O reabsorption subject to vasopressin control; driving force is the vertical osmotic gradient in the medullary interstitial fluid established by the long loops of Henle; important in regulating ECF osmolarity

Renal failure has wide-ranging consequences

- **Renal failure**; when the functions of both kidneys are so disrupted that they cannot perform their regulatory and excretory functions sufficiently to maintain homeostasis.
- Among the causes are the following:

1. *Infectious organisms.*
2. *Toxic agents*, such as lead, arsenic, pesticides, or even long-term exposure to high doses of aspirin.
3. *Inappropriate immune responses*, such as *glomerulonephritis*, which occasionally follows streptococcal throat infections as antigen-antibody complexes leading to localized inflammatory damage are deposited in the glomeruli.
4. *Obstruction of urine flow by kidney stones*, tumors, or an enlarged prostate gland, with back pressure reducing glomerular filtration as well as damaging renal tissue.
5. An *insufficient renal blood supply* that leads to inadequate filtration pressure, secondary to heart failure, hemorrhage, shock or renal arteries atherosclerosis.

Regardless of cause, renal failure can manifest itself either as *acute renal failure* characterized by a sudden onset with a rapid reduction in urine formation or *chronic renal failure*, characterized by slow, progressive insidious loss of renal function.

Table 14-4 will give you an idea of the broad effects that kidney impairment can have, considering the central role the kidney play in maintaining homeostasis

TABLE 14-4 Potential Ramifications of Renal Failure

Uremic toxicity caused by retention of waste products

- Nausea, vomiting, diarrhea, and ulcers caused by a toxic effect on the digestive system
- Bleeding tendency arising from a toxic effect on platelet function
- Mental changes—such as reduced alertness, insomnia, and shortened attention span, progressing to convulsions and coma—caused by toxic effects on the central nervous system
- Abnormal sensory and motor activity caused by a toxic effect on the peripheral nerves

Metabolic acidosis caused by the inability of the kidneys to adequately secrete H^+ that is continually being added to the body fluids as a result of metabolic activity (*among most life-threatening consequences of renal failure*)

- Altered enzyme activity caused by the action of too much acid on enzymes
- Depression of the central nervous system caused by the action of too much acid interfering with neuronal excitability

Potassium retention resulting from inadequate tubular secretion of K^+ (*among most life-threatening consequences of renal failure*)

- Altered cardiac and neural excitability as a result of changing the resting membrane potential of excitable cells

Sodium imbalances caused by inability of the kidneys to adjust Na^+ excretion to balance changes in Na^+ consumption

- Elevated blood pressure, generalized edema, and congestive heart failure if too much Na^+ is consumed
- Hypotension and, if severe enough, circulatory shock if too little Na^+ is consumed

Phosphate and calcium imbalances arising from impaired reabsorption of these electrolytes

- Disturbances in skeletal structures caused by abnormalities in deposition of calcium phosphate crystals, which harden bone

Loss of plasma proteins as a result of increased "leakiness" of the glomerular membrane

- Edema caused by a reduction in plasma-colloid osmotic pressure

Inability to vary urine concentration as a result of impairment of the countercurrent system

- Hypotonicity of body fluids if too much H_2O is ingested
- Hypertonicity of body fluids if too little H_2O is ingested

Hypertension arising from the combined effects of salt and fluid retention and vasoconstrictor action of excess angiotensin II

Anemia caused by inadequate erythropoietin production

Depression of the immune system caused by toxic levels of wastes and acids

- Increased susceptibility to infections

Urine is temporarily stored in the bladder, from which it is emptied by micturition

- Once formed, urine is propelled by peristaltic contractions through the ureters from the kidneys to the urinary bladder for temporary storage.
- The ureters penetrate the wall of the bladder obliquely, coursing through the wall several centimeters before they open into the bladder cavity, prevents backflow of urine. As the bladder fills, the ureteral ends within its wall are compressed closed.
- **Role of the bladder**
- Both the epithelium and the smooth muscle actively participate in the bladder's ability to accommodate large fluctuations in urine volume.
- Membrane-enclosed cytoplasmic vesicles are inserted by exocytosis into the surface area during bladder filling; then the vesicles are withdrawn by endocytosis to shrink the surface area following emptying. As is characteristic of smooth muscle, bladder muscle can stretch tremendously without building up bladder wall tension. In addition, the highly folded bladder wall flattens out during filling.
- The bladder smooth muscle is richly supplied by parasympathetic fibers, stimulation of which causes bladder contraction.
- The exit from the bladder, however, is guarded by two sphincters, *the internal urethral sphincter and the external urethral sphincter*.

Role of the urethral sphincters

- A **spincter** is a ring of muscle that, when contracted, closes off passage through an opening. The **internal urethral sphincter** which is composed of smooth muscle is under involuntary control.
- Farther down the passageway, the urethra is encircled by a layer of skeletal muscle, the **external urethral sphincter**. This sphincter is reinforced by the entire **pelvic diaphragm**, a skeletal muscle sheet that forms the floor of the pelvis and helps support the pelvic organs (fig. 14-2) the motor neurons that supply the external sphincter and pelvic diaphragm fire continuously at a moderate rate unless they are inhibited, under voluntary control, they can deliberately tightened to prevent urination from occurring even when the bladder is contracting and the internal sphincter is open.

Micturition reflex

- **Micturition** or **urination** is governed by two mechanisms;

(1) the micturition reflex; is initiated when stretch receptors within the bladder wall are stimulated (fig.14-32, 33).

- Afferent fibers from the stretch receptors carry impulses into the spinal cord and eventually, by interneurons, stimulate the parasympathetic supply to the bladder to contract, and inhibit the motor neuron supply to the external sphincter to relax.
- Change in the shape of the bladder during contraction mechanically pull the internal sphincter open. This micturition reflex governs bladder emptying in infants.

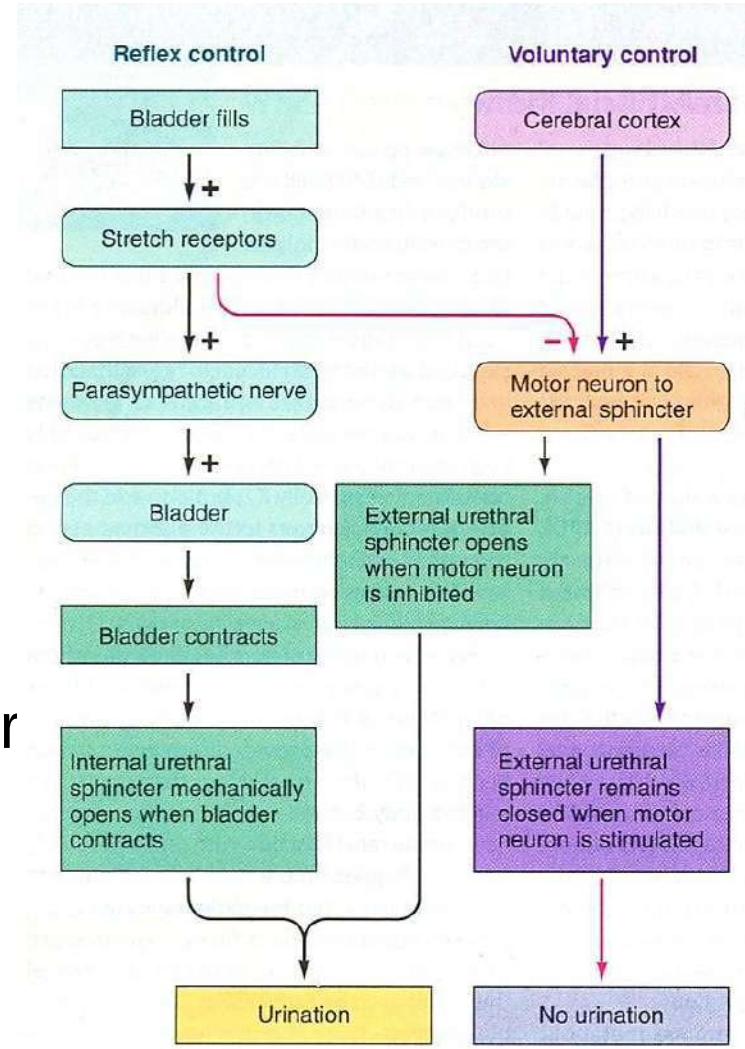


FIGURE 14-32
Reflex and voluntary control of micturition

- **(2) voluntary control of micturition**, the perception of bladder fullness appears before the external sphincter reflexly relaxes, the person can voluntarily prevent bladder emptying by deliberate tightening the external sphincter and pelvic diaphragm. Voluntary excitatory impulses from the cerebral cortex override the reflex inhibitory input from the stretch receptors to the involved motor neurons (the relative balance of EPSPs and IPSPs), keeping these muscles contracted so that no urine is expelled.
- Urination cannot be delayed indefinitely. As the bladder continues to fill, reflex input from the stretch receptors increases with time.
- Micturition can also be deliberately initiated, by voluntarily relaxing the external sphincter and pelvic diaphragm. Lowering of the pelvic floor allows the bladder to drop downward, which simultaneously pulls open the internal urethral sphincter and stretches the bladder wall, may be further assisted by contracting the abdominal wall and respiratory diaphragm.
- The resultant increase in intra-abdominal pressure “squeezes down” on the bladder to facilitate its emptying.

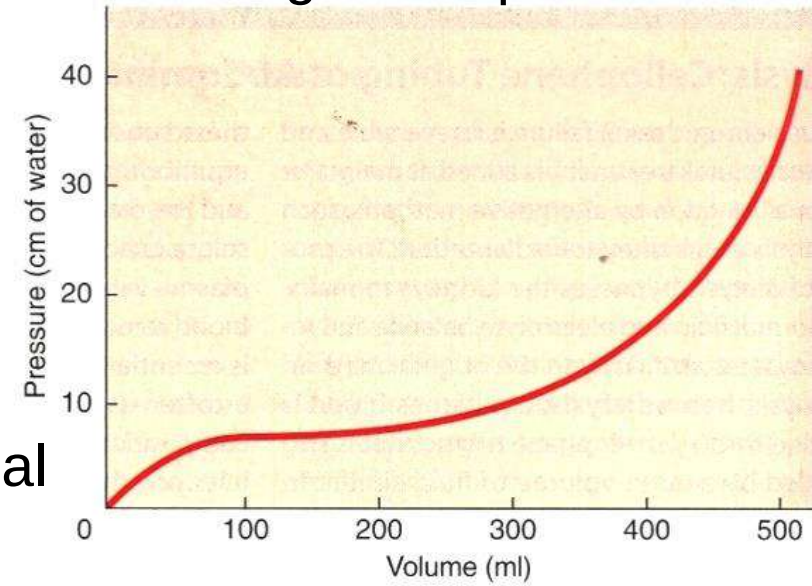


FIGURE 14-33

Pressure changes within the urinary bladder as the bladder fills with urine

Urinary incontinence

- **Urinary incontinence**, or inability to prevent discharge of urine, occurs when descending pathways in the spinal cord that mediate voluntary control of the external sphincter and pelvic diaphragm are disrupted, as in spinal cord injury.
- Bladder emptying becomes governed by an uncontrollable spinal reflex, as in infants. A lesser degree of incontinence, such as during coughing or sneezing, can result from impaired sphincter function.
- This is common in women who have borne children or in men whose sphincters have been injured during prostate surgery.

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